

The Evaluation of Small Nerve Fiber Dysfunction with Quantitative Sensory Testing in Patients with Type II Diabetes Mellitus without Large Fiber Neuropathy, and Normal Values for Thermal Thresholds

Geniş Lif Nöropatisi Olmayan Tip II Diabetes Mellituslu Hastalarda İnce Lif Hasarının Kantitatif Duyusal Test ile Değerlendirilmesi ve Termal Eşik Normal Değerleri

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ABSTRACT

Objective: Quantitative sensory testing (QST) thermal threshold evaluation is used in order to determine small fiber neuropathy, and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale is used in diagnosing neuropathic pain. The aim of this study is to find out the normal QST thermal threshold values, and to compare the QST values of normal controls and patients with type II diabetes mellitus, who do not have large fiber neuropathy. With this comparison, the study also aims to determine whether QST abnormalities are present in patients without neuropathic pain.

Methods: A total of one hundred normal subjects between the ages of 20 and 69, and 50 patients with type II diabetes mellitus aged 40 to 69 years with no sign of large fiber neuropathy were recruited. The normal subjects were divided into 5 subgroups according to their ages. The mean values of the QST thermal detection and thermal pain thresholds were determined. Sixty normal subjects between the ages of 40-69 were defined as a control group for comparison with the diabetic group. The patients were divided into subgroups according to their LANSS points and their data were compared with the data of age-matched controls.

Results: The mean ages of total normal subjects and the control group were 44.8±14.4 and 57.4±8.4, respectively. In diabetic group, according to LANSS, 10 patients (mean age, 55.1±8.5 years) scored above 12 (14.6 ± 3.5), and 40 patients (mean age, 55.5±8.4 years) scored under 12 points (6.8±3.4). In the LANSS>12 group, the least abnormality rate was 100 %, and the most frequently detected abnormality was in the foot cold pain threshold (70%). In the LANSS<12 group, the least abnormality rate was 67.5%, and the most frequently detected abnormality was in the hand cold pain threshold (45%).

Conclusion: It was demonstrated that QST was successful in determining thermal detection abnormalities in all patients with probable neuropathic pain according to LANSS Pain Scale. QST is a test, which gives reliable and reproducible results in the diagnosis of small fiber sensory neuropathy. Because of its subjectivity and inefficacy in differentiation of peripheral and central causes, QST findings should be evaluated together with findings of neurological examination and nerve conduction studies. (*Archives of Neuropsychiatry* 2010; 47: 223-9)

Key words: Quantitative sensory testing; Neuropathic pain; Diabetes Mellitus Type II; Small fiber neuropathy; LANSS

ÖZET

Amaç: Kantitatif duyuşal test (QST) termal eşik değeriendirilmesi ince lif nöropatisinin tespitinde, LANSS skalası da nöropatik ağrı tanısında kullanılmaktadır. Bu çalışmada kalın lif nöropatisi olmayan tip II diyabetes mellituslu olgularda iki inceleme birlikte yapılarak, uyumlu sonuçlar verip vermedikleri, birbirlerine üstünlüklerinin olup olmadığının araştırılması ve laboratuvarımızın değışik yaş gruplarına ait QST termal eşik değeriendirilmesinin tespiti amaçlanmıştır.

Yöntemler: 20-69 yaş arası kadın ve erkek 100 normal birey ve kalın lif nöropatisi saptanmayan 50 tip II diyabetes mellituslu hasta çalışmaya alınmıştır. 20-69 yaş arasında 5 normal grup belirlenmiş ve normal QST termal algı ve termal ağrı algısı ortalamaları saptanmıştır. 40-69 yaş arasında 60 normal birey, diyabetik grupla karşılaştırmak üzere kontrol grubu olarak kullanılmıştır. LANSS skalasına göre nöropatik ağrı tanısı alanlar ve almayanların verileri, yaşları uyumlu kontrol grubu verileri ile karşılaştırılmıştır.

Bulgular: Normal bireylerin ve kontrol grubunun yaş ortalamaları 44.8±14.4 ve 57.4±8.4'dür. Diyabetik grupta yaş ortalaması 55.1±8.5 olan 10 kişi LANSS skalasında>12'nin üzerinde puan almış (14.6 ± 3.5), yaş ortalaması 55.5±8.4 olan 40 kişinin LANSS puanı 12'nin altında kalmıştır (6.8±3.4). LANSS>12 grubunda, en az bir anormallik saptanma oranı % 100 bulunmuş, en fazla anormallik ayak soğuk ağrı algısında saptanmıştır (% 70). LANSS<12 grubunda en az bir anormallik saptanma oranı % 67.5 olarak belirlenmiş ve en fazla anormallik el soğuk ağrı algısında bulunmuştur (% 45).

Sonuç: QST, LANSS skalası ile 12'den fazla puanı olan büyük olasılıkla nöropatik ağrı tanısı alanlarda termal algı anormalliklerinin varlığını göstermekte başarıyla bulunmuştur. QST, ince lif nöropatisi ve nöropatik ağrı tanısında güvenilir ve tekrar edilebilir sonuçlar veren bir testtir. Subjektivite içermesi, periferik ve santral sebepleri ayırmadaki yetersizlikleri nedeniyle nörolojik muayene ve ileti incelemeleri ile birlikte değeriendirilmelidir. (*Nöropsikiyatri Arşivi* 2010; 47: 223-9)

Anahtar kelimeler: Kantitatif duyuşal test; nöropatik ağrı; Diabetes mellitus tip II; ince lif nöropatisi; LANSS

Introduction

International Association for the Studies of Pain (IASP) (1) defines neuropathic pain as a pain induced by a dysfunction in or damage to the nervous system. The definition covers the cases of burning, stabbing, tingling, prickling sensations and disturbing sensation or pain to the innocuous stimulation of normal skin. The most frequent reason of small fiber neuropathy is diabetes mellitus alongside with many other causes (2, 3). In correct diagnosis, the first step is to identify fundamental complaints caused by small fiber neuropathy and neuropathic pain. A battery of tests based on medical history and simple examination methods were described to diagnose neuropathic pain. Leeds Assessments of Neuropathic Symptoms and Signs (LANSS) Pain Scale is the most widely-used test among others and its Turkish validation study has been established previously (4, 5).

Small nerve fibers, thin myelinated A delta and unmyelinated C fibers can not be examined by routine electromyography (6). Quantitative sensory testing (QST) is required to determine and to follow small fiber neuropathy (7,8,9). It has been first used by Frustofor in 1976 (10) and still maintains its place as an important and objective method in the assessment of neuropathic pain (11). Different modalities such as vibration perception threshold, warm-cold detection thresholds and heat-cold pain thresholds are evaluated by this method. QST brings important contributions in evaluating small fiber neuropathy by presenting relatively objective and reproducible results with computerized measurements that provide thermal and thermal pain assessment (7,8,9). Its sensitivity rate has been reported as 60-85 % in many studies (12,13,14,15), and it has been noted that many factors including age, gender, educational background, sociocultural environment, motivation, ethnic and racial differences, technical factors, and the testing area are important in evaluation (9,16,17,18,19).

This study aims to make an early diagnosis of neuropathy and neuropathic pain by assessing small fiber involvement using both QST and LANSS concurrently in patients with type II diabetes mellitus without large fiber neuropathy. The study is designed to define normal QST thermal threshold values and to compare the QST values of the normal controls and the patients with type II diabetes mellitus who do not have large fiber neuropathy. The aim of the comparison is to determine whether there are QST abnormalities in patients without neuropathic pain.

Method

A total of 50 patients (31 women and 19 men) aged between 40-69 years, with type II diabetes mellitus who were referred to our Neurology Department from Endocrinology Section. Neurological examination and electromyography revealed no finding of large fiber neuropathy and they were thus included into the study.

50 men and 50 women, a total of 100 normal subjects aged 20-69 were also enrolled into the study. Control group was composed of normal subjects who were within the same age interval (40-69 years) of the diabetic patients. Normal subjects were divided into 5 subgroups each consisting 10 women and 10 men according to their ages (20-29, 30-39, 40-49, 50-59, 60-69 years).

Patients were neurologically examined and interviewed whether they had neuropathy or neuropathic pain complaints. LANNS was applied and QST thermal and thermal pain threshold measurements were obtained for each patient. Normal controls were also neurologically examined and QST thermal and thermal pain threshold measurements were done for each subject.

The Inclusion and Exclusion Criteria

The inclusion criteria for patients with type II diabetes mellitus: 1. 40 - 69 years interval, 2- Type II diabetes mellitus <diagnosis according to ADA (American Diabetes Association) (20) criteria, 3- Normal neurological examination findings and normal electromyography.

The exclusion criteria for patients with type II diabetes mellitus: 1. Chronic disease other than diabetes mellitus and hypertension, 2. Psychiatric illness such as somatisation, conversion, 3. Central nervous system disease, nerve lesion, entrapment neuropathy, radiculopathy or plexopathy, 4. Chemotherapy or radiotherapy history.

The inclusion criteria for control subjects

1. 40 – 69 year interval, 2. Normal neurological examination findings. The exclusion criteria for control subjects: 1. Chronic disease other than hypertension, 2. Psychiatric illness such as somatisation, conversion, 3. Any disease of peripheral or central nervous system, 4. Complaints of neuropathic pain.

Patients were scored between 0-24 points according to LANNS (4, 5). The features and history about diabetes mellitus were interrogated in a detailed way. Nerve conduction studies were carried out with Nihon Kohden 9100 EMG device; tibial, peroneal nerve motor, sural nerve sensory, median and ulnar nerve motor and sensory measurements were performed. Biochemical and hematological analysis, 24 hour urine protein measurements were done. Ophthalmologic evaluations were also performed.

Neurosensory Analyzer (Model TSA-II 2001) was used in QST analysis. Measurements were done in a silent room with 22-24°C temperature. Cold and warm detection and cold and heat pain thresholds were assessed in centigrades (°C) with 16x16 mm thermal probe. In the assessment, basal temperature was 32°C, increasing/ decreasing rate of the temperature and returning rate to baseline were 1 °C/s for cold and warm detection. These rates were arranged as 1.5 °C/s and 10 °C/s subsequently for cold and heat pain thresholds. The lower and upper limits of the temperature were 0°C and 50°C for the neurosensory analyzer. Cold and warm detection measurements were repeated four times and 10 second breaks were given in between each session; cold and heat pain thresholds measurements were repeated three times and 15-seconds breaks were given in between sessions. Averaged values were calculated. Measurements were bilaterally performed from the C6 dermatom, palmar/thenar area in hands and S1 dermatom, lateral dorsal area region in feet.

QST details and knowledge about the applications were given to all subjects. Initially, the test was performed with the instructions given by the physician and when the subjects learned the application, the exact testing procedure initiated.

This study was approved and reviewed by the Regional Ethics Committee. Informed consent was obtained from each subject and the study was performed in accordance with the principles of the Declaration of Helsinki.

In statistical analysis, the distribution properties were assessed with normal distribution curves and with the Kolmogorov Smirnov test. The data of the right and left side, women and men were compared with independent student t test. Patient groups and normal control groups were compared with one way ANOVA. Correlation analysis of the QST values with the LANSS points, age, gender, cigarette smoking, and with all diabetic parameters were also performed.

Results

The mean age of the normal subjects was 44.8 ± 14.4 . The mean ages of the patients with type II diabetes mellitus and the control group with the same age range with the patient group were 55.4 ± 8.4 and 54.7 ± 8.4 years. The mean of the illness duration was 76 ± 7 months.

The members of the control group did not have any serious systemic or metabolic disease, peripheral or central nervous system disease. Also, they do not have any complaints about neuropathy or neuropathic pain. Their neurological examinations

were normal. The neurological examinations of the patients with type II diabetes mellitus were also normal. They did not display any findings in favor of large fiber neuropathy. All patients were evaluated and scored based on LANSS. In 10 (8 women and 2 men) out of 50 diabetic patients, the LANSS point was higher than 12 (LANSS > 12). These patients were accepted as probably having neuropathic pain. The remaining 40 patients (23 women and 17 men) had lower LANSS points (<12), and they were accepted as not having neuropathic pain.

The mean of the fasting and postprandial glucose level, HbA1C and insulin level were as follows (respectively): 156 ± 53 mg/dl, 255 ± 89 mg/dl, 8.1 ± 1.6 (%), 19.4 ± 20 mU/L. QST cold and warm detection, cold and heat pain threshold mean values of normal subjects in five subgroups (20-29, 30-39, 40-49, 50-59 and 60-69 age intervals) are given in Table 1. There was not any significant difference between right and left sides for all age intervals. In the comparison of the whole group according to the gender, there was not any prominent difference, thus the normal values for both sides and for both genders have been evaluated together.

Table 1. The united data of women and men's QST thermal thresholds of the hands and feet (Centigrade, C°) for separate normal age groups (Mean $\pm$ SD (SE) [range])

	N	20-29	30-39	40-49	50-59	60-69
Mean Age	20	25 ± 3.4	35 ± 2.8	44.8 ± 2.5	54.8 ± 3	64.5 ± 3
F+M		(0.8)	(0.6)	(0.6)	(0.7)	(0.7)
		[20-29]	[30-39]	[40-49]	[50-59]	[61-69]
Hand						
HCD	20 (R+L)	29.3 ± 0.89	29.5 ± 0.75	28.7 ± 0.9	28.5 ± 0.8	28 ± 0.84
		(0.14)	(0.12)	(0.14)	(0.13)	(0.13)
		[26-31]	[28-31]	[26-30.5]	[27-30]	[26-30]
HWD	20 (R+L)	34.9 ± 0.6	35.8 ± 1.1	35.8 ± 1.1	35.8 ± 0.9	36.3 ± 1.1
		(0.1)	(0.18)	(0.18)	(0.15)	(0.18)
		[34-36]	[34-38]	[34-38]	[34-38]	[35-39]
HCP	20 (R+L)	21 ± 1.9	20 ± 2.7	18.7 ± 3.2	17.2 ± 2.1	16.3 ± 2.4
		(0.3)	(0.44)	(0.51)	(0.33)	(0.37)
		[16-24.5]	[12-26]	[11-26.5]	[11.8-21]	[11.3-21]
HHP	20 (R+L)	41.4 ± 1.6	42 ± 1.6	42.3 ± 1.1	42.2 ± 0.7	42.2 ± 0.94
		(0.25)	(0.26)	(0.18)	(0.12)	(0.15)
		[37-46]	[38-46]	[38.5-45]	[40-44]	[40-45]
Foot						
FCD	20 (R+L)	28.2 ± 1	28.2 ± 1.1	27.1 ± 1.26	26.6 ± 1.2	25.5 ± 1.5
		(0.16)	(0.17)	(0.2)	(0.19)	(0.23)
		[25.5-30]	[26-31]	[24-30]	[26-29]	[24-28]
FWD	20 (R+L)	37.4 ± 1.7	37.9 ± 1.8	39.3 ± 2.2	39.3 ± 2.4	39.8 ± 2.2
		(0.27)	(0.28)	(0.35)	(0.38)	(0.37)
		[34-41]	[34-42.5]	[35-44]	[35.5-42.3]	[35-43.4]
FCP	20 (R+L)	22.7 ± 1.8	22 ± 2	19.8 ± 2.9	18.4 ± 3.3	16.2 ± 3.4
		(0.29)	(0.32)	(0.45)	(0.52)	(0.54)
		[19-27]	[18-26]	[14-25]	[10.5-24]	[10-22.3]
FHP	20 (R+L)	42.6 ± 1.3	42.9 ± 2	43.9 ± 1.8	43.5 ± 1.9	44.15 ± 1.8
		(0.2)	(0.32)	(0.29)	(0.3)	(0.29)
		[40-45]	[38-47]	[40-47]	[40-46.7]	[40-47.6]

HCD: Hand cold detection, **HWD:** Hand warm detection, **HCP:** Hand cold pain, **HHP:** Hand heat pain

FCD: Foot cold detection, **FWD:** Foot warm detection, **FCP:** Hand cold pain, **FHP:** Foot heat pain.

Table 2. The mean values of cold and warm detection, cold and heat pain thresholds (Centigrade, C°) of normal men and women (Mean±SD (SE) [range]), and correlations with age (coefficients and p values)

50F+50M (1.4) Mean age: 44.8±14.4 [20-69]	Gender	N	Mean ±SD (SE) [range]	W+M (R+L) N = 100 Age Corellation
HCD	F	50 (R+L)	28.7±1 (0.1) [26-31]	0.516, - p:0.000
	M	50 (R+L)	28.9±1 (0.1) [26-31]	
HWD	F	50 (R+L)	35.5±1 (0.1) [34-39] p:0.01	0.389 p:0.000
	M	50 (R+L)	35.9±1.1 (0.1) [34-39]	
HCP	F	50 (R+L)	17.7±3.1 (0.3) [11-26] p:0.000	-545 p:0.000
	M	50 (R+L)	19.5±2.6 (0.26) [12-26]	
HHP	F	50 (R+L)	42.3±1.4 (0.14) [37-44] p:0.008	0.174 p:0.014
	M	50 (R+L)	41.8±1.1 (0.1) [37-44]	
FCD	F	50 (R+L)	27.1±1.7 (0.17) [24-31]	-0.629 p:0.000
	M	50 (R+L)	27.1±1.4 (0.14) [24-30]	
FWD	F	50 (R+L)	38.4±2.4 (0.2) [34-44]	0.429 p:0.000
	M	50 (R+L)	39±2.1 (0.2) [35-43]	
FCP	F	50 (R+L)	19.4±3.8 (0.38) [10-27]	-0.658 p:0.000
	M	50 (R+L)	20.2±3.4 (0.34) [12-26]	
FHP	F	50 (R+L)	43.3±2 (0.2) [38-47.6]	0.318 p:0.000
	M	50 (R+L)	43.5±1.7 (0.2) [38-47]	

HCD: Hand cold detection, **HWD:** Hand warm detection, **HCP:** Hand cold pain, **HHP:** Hand heat pain

FCD: Foot cold detection, **FWD:** Foot warm detection, **FCP:** Hand cold pain, **FHP:** Foot heat pain.

Thermal detection and thermal pain threshold mean values in the LANSS>12 and LANSS<12 subgroups, and normal control group are shown in Table 2. There was not any significant correlation between QST values and HbA1c, insulin, postprandial glucose levels, hypertension and renal functions.

Hand and foot cold detection and cold pain threshold values were negatively, hand and foot warm detection and foot heat pain threshold values were positively correlated (weakly) with the age in normal controls (Table 2). Hand cold detection, hand heat pain threshold, foot cold detection, foot warm detection, foot cold pain threshold, foot heat pain threshold values correlated with the age also in the patients with type II diabetes mellitus (-0.301/p:0.02, 0.297 / p:0.03, -0.386 / p:0.00, 0.271 / p:0.06, -0.283 / p:0.004, 0.397 / p:0.000 respectively).

Hand warm detection and hand heat pain threshold, foot cold detection, foot warm detection, foot heat pain threshold values were weakly correlated with male gender (0.325 / p:0.01, 0.256 / p:0.01, -0.272 / 0.06, 0.300/ p:0.002, 0.341 / p:0.01, respectively). Smoking was very weakly correlated with hand cold detection, foot cold detection, foot warm detection (-0.218 / p: 0.029, -0.299 p: 0.02, 0.227/ p: 0.023, respectively). Fasting glucose levels were weakly correlated with foot warm detection, foot heat pain threshold values (0.304 / p: 0.02, 0.267/0.007, respectively). The duration of the disease and hand cold detection values were weakly correlated (0.313 /0.002). Foot warm detection, foot heat pain threshold values were weakly correlated with retinopathy (0.284/p:0.04, 0.255/ p: 0.01, respectively).

In diabetic patients, there was a weak correlation with LANSS and hand cold detection values (0.229 / p: 0.022). However

there was not any significant correlation between LANSS and other QST values in the LANSS>12 group. In this group, the least abnormality rate was 100%, and the most detected abnormality was in the foot cold pain threshold (70%). Hand cold pain threshold (60%), hand heat pain threshold (50%), foot heat pain threshold (40%), hand warm detection (30%), foot cold detection (10%) abnormalities followed respectively. In the LANSS<12 group, the least abnormality rate was 67.5%, and the most detected abnormality was in the hand cold pain threshold (45%). Foot cold pain threshold (42.5%), hand heat pain threshold (22.5%), hand warm detection (10%), foot heat pain threshold (7.5%) and foot warm and cold detection abnormalities (5%-5%) followed respectively.

The mean values of cold and warm detection, cold and heat pain thresholds of patients and normal control subjects are given in Table 3. When we compared the patients with higher

and lower LANSS points with normal controls, the mean values of hand warm detection, hand heat pain threshold and foot heat pain threshold were significantly different and they were higher in the LANSS>12 group than the control and LANSS<12 groups. The mean of the hand heat pain threshold in the LANSS<12 group was also higher than the control group. The mean of the foot cold pain threshold was lower in the LANSS>12 group than the control and LANSS<12 groups. The mean of the foot cold pain threshold in the LANSS<12 group was also lower than the control group (for all p values see Table 3).

Discussion

It has been demonstrated that an increase in the warm detection and heat pain threshold and a decrease in the cold detection and cold pain threshold occur with aging. The cause

Table 3. The mean values of cold and warm detection, cold and heat pain thresholds of patients and normal control subjects (Centigrade, C°) (Mean ± SD (SE) [range]). Comparisons between groups (p values).

	Control mean±SD (SE) [range]	LANSS > 12 mean±SD (SE) [range]	LANSS < 12 mean±SD (SE) [range]
N (F+W)	60 (R+L)	10 (8W/2M; R+L)	40 (23W/17M; R+L)
Mean Age	54.7±8.4 (1.1) [40-69]	55.1±8.5 (2.7) [45-69]	55.5±8.4 (1.4) [40-69]
Hand			
HCD	28.4±0.9 (0.1) [26-30]	28.7±1 (0.23) [27-30]	28.9±0.9 (0.1) [27-31]
HWD	35.9±1.1 (0.1) [34-39]	36.4±1.9 (0.43) [34-40]	35.9±1.8 (0.21) [33-45]
HCP	17.4±2.8 (0.25) [11-26]	10.2±4.6 (1) [1-18] p:0.000 Lh - C*	12.1±5.2 (0.6) [2-22] p: 0.000 Ls - C
HHP	42.2±1 (0.1) [38-45]	44±1.3 (0.29) [42-47] p:0.000 Lh - C p:0.008 Lh - Ls	42.9±2 (0.22) [38-49] p: 0.006 Ls - C
Foot			
FCD	26.4±1.4 (0.13) [23-30]	26.4±1.2 (0.27) [24-29]	26.6±1.9 (0.22) [18-30]
FWD	39.5±2.3 (0.21) [35-44]	40±1.9 (0.42) [37-43]	39.3±2.5 (0.28) [36-49]
FCP	18.1±3.5 (0.32) [10-25]	7.5±6 (1.3) [1-19] p:0.000 Lh - C p:0.002 Lh - Ls	11.6±6 (0.67) [1-22] p:0.000 Ls - C
FHP	43.9±1.9 (0.17) [40-48]	45.8±1.9 (0.24) [42-48] p:0.000 Lh - C p:0.035 Lh - Ls	44.6±2.2 (0.24) [39-50] p: 0.051 Ls - C

*Lh : LANSS higher (>12), Ls: LANSS smaller (<12), C: control

HCD: Hand cold detection, **HWD:** Hand warm detection, **HCP:** Hand cold pain, **HHP:** Hand heat pain

FCD: Foot cold detection, **FWD:** Foot warm detection, **FCP:** Hand cold pain, **FHP:** Foot heat pain

of the thermal detection and pain threshold changes with increasing age has been explained in a study by Goransson et al. (21), which showed that intraepidermal nerve fiber (IENF) decreases with advancing age. In tune with this conclusion, it is important to select normal controls properly on the basis of age. For the comparison with the diabetic group, the control group has been selected from the subjects in the same age range with the enrolled patients in the current study.

Hegander et al. (22) have demonstrated that hands are more sensible than feet for thermal detection. They have also demonstrated that thermal thresholds are not affected from the skin temperature. In this study, we have used the same thermal analyzer that was used in their study. In the current study, for the same age range, the controls had slightly lower cold detection values, slightly higher warm detection values, higher cold pain thresholds and similar warm pain thresholds.

QST German Neuropathic Pain research group (23) studied the QST parameters in 180 healthy subjects between 17-77 ages. They showed that younger subjects were more sensible than the ones older than 40 years of age. The mean of the cold pain thresholds were also lower in the study of Rolke et al. which was similar to the study of Hegander et al. (22). The reason for this discrepancy may relate to several factors. In this current study, all of the QST measurements were made by the same researcher, and at least one assay about QST thermal analysis was made before the exact measurement, and it has been assumed that it was clearly understood by the subject. Another reason may be due to racial or ethnical differences. Multicentered design of German research study and the existence of several researchers can explain the wide range for the upper and lower limits of thermal pain thresholds obtained in the mentioned study. On the other hand, the decrease in sensation with advancing age was similar in all three studies.

LANSS is a valuable test in diagnosis of the neuropathic pain that appears due to nerve injury that may relate to several different reasons (4). It is aimed to make differential diagnosis by interrogating the features of neuropathic pain as a subjective phenomenon. The validation studies of this scale have been done for many languages including Turkish (5,24,25,26).

In the study conducted in Belgium (26), LANSS has been performed in 2480 patients with pain. Among them, 1163 patients had higher LANSS points (>12), accordingly diagnosed as the most probable neuropathic pain. Mean LANSS point has been found as 14.4 in the patients with diabetes mellitus. In this current study, mean LANSS points were 14.6 and 6.8 in patients with the higher and lower LANSS points.

It was suggested that QST is an objective and a useful test in discriminating the small fiber neuropathy in diabetic patients with or without any symptoms (27). Vinik et al. presented 78% abnormality in the warm perception and 77% abnormality in the cold perception in 81 patients with diabetic polyneuropathy (28). In another study, Navarro et al. demonstrated thermal abnormality in 26 patients, EMG abnormality in 15 patients among 46 diabetic patients with normal neurological examination (29). In a study conducted in Turkey, 9.1% abnormality in warm detection, 15.9% abnormality in cold detection, 56.8% abnormality in warm and cold detection; 4.6% abnormality in heat pain threshold, 63.6% abnormality in cold pain threshold, 15.8% abnormality in heat and cold pain threshold were demonstrated

in patients with diabetes mellitus which had normal EMG (30). Although, any significant correlation between LANSS point level and QST results could not be established in our study, QST abnormality rate was higher and there was at least one abnormality in all patients with higher LANSS points. QST abnormalities also could be found in more than half of the patients with lower LANSS points. This finding of the patients without apparent neuropathic pain, made us think that there exists some small fiber damage even in these patients, however neuropathic pain mechanisms are yet to be settled.

Kramer et al. (31) found a decrease in the C nociceptor mediated neurogenic activity in the patients with diabetic polyneuropathy. In another study by the same authors (32), they affirmed that there were significant differences in cold and warm detections in 30 patients with diabetes mellitus and polyneuropathy and among them, 15 had neuropathic pain. They asserted that it was not necessary to have painful neuropathy concomitantly with the thermal detection abnormality. Our findings were also compatible with this assertion, as the existence of the probable small fiber abnormality may not be necessarily occurring together with neuropathic pain. On the other hand, the finding of 100% rate of the least abnormality in patients with higher LANSS points was in favor of the sensitive assessment of the neuropathic pain with LANSS.

It is known that poor glycemic control and duration of disease play important roles in the development of diabetic complications (33, 34). In the current study, QST thermal threshold abnormalities weakly correlated with age, duration of disease, male gender, glysemic regulation and retinopathy in patients. This finding was attributed to the exclusion of the patients with large fiber neuropathy, and to the relative scarcity of the patients with longer duration of illness.

Loseth et al. (35) showed that there were significant relations between intraepidermal nerve fiber amount, QST values and the amplitude decrease of the sural nerve sensory response. They emphasized that these are complementary tests in the diagnosis of the polyneuropathy. In an article on QST published by American Academy of Neurology (16), most of the studies mentioned above are reviewed and QST vibration and thermal threshold measurements are determined as probably effective. In the same article, it was emphasized that QST abnormality could not demonstrate small fiber damage alone and could not differentiate peripheral or central nervous system involvement. It should be evaluated with neurological examination, and should be supported by EMG, skin biopsy and proper imaging studies.

As a result, this study has provided a normative QST data of Turkish population, and has demonstrated that all diabetic patients with higher LANSS points had at least one QST thermal detection abnormality. It has been also shown that, LANSS and QST are complementary to each other. QST thermal detection abnormalities can be found even in diabetic patients with lower LANSS points, so it may not be necessarily related with neuropathic pain. Furthermore, it has been suggested that the patients with the QST abnormality and lower LANSS points should be followed longitudinally. A future study which will compare QST findings with intraepidermal nerve fiber density would explain properly whether there occurs a decrease in intraepidermal nerve fiber density or not in this group of patients.

References

1. Backonja MM. Defining neuropathic pain. *Anesth Analg* 2003; 97:785-90. [Abstract] / [Full Text] / [PDF]
2. Lacomis D. Small-fiber neuropathy. *Muscle Nerve* 2002; 26:173-88. [Abstract] / [Full Text] / [PDF]
3. Gorson KC, Ropper AH. Idiopathic distal small fiber neuropathy. *Acta Neurol Scand* 1995; 92:376-82. [Abstract]
4. Bennett MI, Attal N, Backonja MM et al. Using screening tools to identify neuropathic pain. *Pain* 2007; 127:199-203. [Abstract] / [Full Text] / [PDF]
5. Yücel A, Senocak M, Kocasoy Orhan E et al. Results of the Leeds assessment of neuropathic symptoms and signs pain scale in Turkey: a validation study. *J Pain* 2004; 5:427-32. [Abstract] / [Full Text] / [PDF]
6. Uludağ B. Nöropatik Ağrı Değerlendirmesinde Elektrofizyolojik Yöntemler. *Sendrom* 2008;(Suppl 3):30-6. [Abstract]
7. Neeling JN, Beks PJ, Bertelsmann FW et al. Sensory thresholds in older adults: reproducibility and reference values. *Muscle Nerve* 1994; 17:454-61. [Abstract]
8. Yarnitsky D, Sprecher E, Zaslansky R et al. Heat pain thresholds: normative data and repeatability. *Pain* 1995; 60:329-32. [Abstract] / [PDF]
9. Gelber DA, Pfeifer MA, Broadstone VL et al. Components of variance for vibratory and thermal thresholds testing in normal and diabetic subjects. *J Diabetes Complications* 1995; 9:170-6. [Abstract] / [PDF]
10. Fruhstorfer J, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry* 1976; 39:1071-5. [PDF]
11. Cruccu G, Anand P, Attal N et al. EFNS guidelines on neuropathic pain assessment. *Eur J Neurol* 2004; 11:153-62. [Abstract] / [Full Text] / [PDF]
12. Holland NR, Crawford TO, Hauer P et al. Small-fiber sensory neuropathies: clinical course and neuropathology of idiopathic cases. *Ann Neurol* 1998; 44:47-59. [Abstract]
13. Periquet MI, Novak V, Collins MP et al. Painful sensory neuropathy: prospective evaluation using skin biopsy. *Neurology* 1999; 53:1641-7. [Abstract] / [Full Text] / [PDF]
14. Tobin K, Giuliani MJ, Lacomis D. Comparison of different modalities for detection of small fiber neuropathy. *Clin Neurophysiol* 1999; 110:1909-12. [Abstract] / [Full Text] / [PDF]
15. Novak V, Freimer ML, Kissel JT et al. Autonomic impairment in painful neuropathy. *Neurology* 2001; 56:861-8. [Abstract] / [Full Text] / [PDF]
16. Shy ME, Frohman EM, So YT et al. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003; 60:898-904.
17. Kojo I, Pertovaara A. The effects of stimulus area and adaptation temperature on warm and heat pain thresholds in man. *Int J Neurosci* 1987; 32:875-80. [Abstract]
18. Dyck PJ, Zimmerman I, Gillen DA et al. Cool, warm, and heat-pain detection thresholds: testing methods and inferences about anatomic distribution of receptors. *Neurology* 1993; 43:1500-8. [Abstract]
19. Bartlett G, Stewart JD, Tamblyn R et al. Normal distributions of thermal and vibration sensory thresholds. *Muscle Nerve* 1998; 21:367-74. [Abstract] / [PDF]
20. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2004;7(suppl 1):5-10.
21. Goransson LG, Mellgren SI, Lindal S et al. The effect of age and gender on epidermal nerve fiber density. *Neurology* 2004; 62:774-7. [Abstract] / [Full Text] / [PDF]
22. Hagander LG, Midani HA, Kuskowski MA et al. Quantitative sensory testing: effect of site and skin temperature on thermal thresholds. *Clin Neurophysiol* 2000; 111:17-22. [Abstract] / [Full Text] / [PDF]
23. Rolke R, Baron R, Maier C et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006; 123:231-43. [Abstract] / [Full Text] / [PDF]
24. Spruce MC, Potter J, Coppini DV. The pathogenesis and management of painful diabetic neuropathy: a review. *Diabet Med* 2003; 29:88-98. [Abstract] / [Full Text] / [PDF]
25. Kaki AM, El-Yaski, Yousef E. Identifying neuropathic pain among patients with chronic low-back pain: use of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale. *Reg Anesth Pain Med* 2005; 30:422-8. [Abstract]
26. Hans G, Masquelier E, De Cock P. The diagnosis and management of neuropathic pain in daily practice in Belgium: an observational study. *BMC Public Health* 2007; 7:170. [Abstract] / [Full Text] / [PDF]
27. Levy D, Abraham R, Reid G. A comparison of two methods for measuring thermal thresholds in diabetic neuropathy. *J Neurol Neurosurg Psychiatry* 1989; 52:1072-7. [Full Text] / [PDF]
28. Vinik AI, Suwanwalaikorn S, Stansberry KB et al. Quantitative measurement of cutaneous perception in diabetic neuropathy. *Muscle Nerve* 1995; 18:574-84. [Abstract]
29. Navarro X, Kennedy WR, Fries TJ. Small nerve fiber dysfunction in diabetic neuropathy. *Muscle Nerve* 1989; 12:498-507. [Abstract]
30. Ülger F, Talu GK, Yücel A. İnce Lif Hasarı olan Diabetik Nöropatili hastalarda KDT (Kantitatif Duyusal Test) Değerlendirmesi. *O.M.Ü Tıp Dergisi* 2005; 22:141-5. [PDF]
31. Kramer HH, Rolke R, Bickel A et al. Thermal thresholds predict painfulness of diabetic neuropathies. *Diabetes Care* 2004; 27:2386-91. [Abstract] / [Full Text] / [PDF]
32. Kramer HH, Schmelz M, Birklein F et al. Electrically stimulated axon reflexes are diminished in diabetic small fiber neuropathies. *Diabetes* 2004; 53:769-74. [Abstract] / [Full Text] / [PDF]
33. Perkins BA, Bril V. Diabetic neuropathy: a review emphasizing diagnostic methods. *Clin Neurophysiol* 2003; 114:1167-75. [Abstract] / [Full Text] / [PDF]
34. Stolar M. Glycemic control and complications in type 2 diabetes mellitus. *Am J Med* 2010; 123(Suppl 3):3-11. [Abstract] / [Full Text] / [PDF]
35. Loseth S, Lindal S, Stalberg E et al. Intraepidermal nerve fibre density, quantitative sensory testing and nerve conduction studies in a patient material with symptoms and signs of sensory polyneuropathy. *Eur J Neurol* 2006; 13:105-11. [Abstract] / [Full Text] / [PDF]