

ASSESSING THE PERIPHERAL SENSITIVITY OF NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS PATIENTS USING CASEIVSYSTEM AND CLASSIC METHODS

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Abstract

Background and Aims: A complete evaluation of complications should be done each time a new case of Type 2 Diabetes Mellitus (T2DM) is diagnosed. A good screening of complications will be the background of an oriented treatment. Our aim was to assess the vibratory and thermal sensitivity using a Computer Aided Sensory Analyzer (CASEIVSystem) in newly diagnosed T2DM patients and to compare it with the threshold determined by classical methods. **Material and Methods:** We sequentially enrolled 260 patients with newly diagnosed T2DM. The threshold of peripheral vibratory and thermal sensitivity was comparatively assessed using CASEIVSystem and classic tools. Other neurological scores were obtained from patients. **Results:** The vibratory threshold was abnormal in 56.92% (hand) and respectively 75.00% (foot) of subjects. Altered perception for the thermal threshold was registered in 76.15% and, respectively, 76.92% of subjects for the same sites. The 10g-monofilament exam was positive for 28.46% and the 128Hz-tuning-fork exam was positive for 20.38% of the examined patients. Mean time for a complete CASEIVSystem exam was around 27.23±9.34min vs. 3.21±0.24min ($p<0.05$) for a classic exam. **Conclusions:** In our study, CASEIVSystem allowed the assessment of the vibratory and thermal thresholds. The time needed for investigation renders this tool difficult to use in a time effective manner.

key words: CASEIVSystem, neuronal sensitivity, vibratory threshold, thermal/cold threshold, type 2 diabetes mellitus

Background and Aims

All patients with diabetes should be tested for the presence of diabetic neuropathy. In patients with type 2 diabetes (T2DM), since the diagnosis of diabetes, and in patients with type 1

diabetes, usually 5 years after diabetes diagnosis, examination of tendon reflexes and sensory function should be performed at least once a year if not more often using simple tests [1-3]. Nevertheless, electrophysiological testing is rarely needed, except in situations where the

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clinical features are atypical. Decreased thermal and pain perception in the extremities results in increased risk of skin breakdown, infection and Charcot joint destruction. However, studies have shown that moderate-intensity walking may not lead to increased risk of foot ulcers or reulceration in those with peripheral neuropathy [4,5]. All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open sore should be restricted to non-weight-bearing activities [1].

The diabetic neuropathies are heterogeneous, with diverse clinical manifestations. They may be focal or diffuse. The most common are chronic sensorimotor diabetic peripheral neuropathy (DPN) and autonomic neuropathy. Although DPN is a diagnosis of exclusion, complex investigations to exclude other conditions are rarely needed.

Pathogenesis of diabetic neuropathy remains incompletely elucidated but the main cause seems to be represented by the metabolic effect of hyperglycemia. Another pathogenic pathway could be represented by the ischemia of peripheral nerves [6]. In addition, impaired neurotrophic factors and some immunological mechanisms may also have a role in neuropathy pathogenesis [7,8]. Hyperglycemia produces a range of metabolic disorders such as: altered polyol pathway, non-enzymatic glycosylation of proteins, altered lipid metabolism, axonal function abnormalities. Polyol pathway activity leads to the conversion of glucose to sorbitol and fructose, their accumulation leading to reduced intracellular myoinositol and taurine [9]. All of these metabolic changes and other structural changes are already present when T2DM is diagnosed, and – at the same time – they affect all neurological structures.

The early recognition and correct treatment of neuropathy in patients with diabetes are important for a number of reasons: 1) non-

diabetic neuropathies may be present in patients with diabetes and may be treatable; 2) there are several treatment options for symptomatic diabetic neuropathy and a clear diagnosis will be helpful in choosing the right solution; 3) up to 50% of DPN may be asymptomatic and patients are at risk for insensate foot injury, while a diagnosis will warn the patient against it.

Importantly, in patients with neuropathy, particularly when severe, causes other than diabetes should always be considered, such as neurotoxic medications, heavy metal poisoning, alcohol abuse, vitamin B12 deficiency (especially in those taking metformin for prolonged periods), renal disease, chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis [9].

Specific treatment for the underlying nerve damage is currently not available, other than improved glycemic control, which may modestly slow progression [6] but not reverse neuronal loss. Effective symptomatic treatments are available for some manifestations of DPN [7,8].

Subjects with diabetes should be screened at diagnosis and then annually for DPN using tests such as pinprick sensation, vibration perception (using a 128Hz tuning fork), 10g-monofilament pressure sensation at the distal plantar aspect of both great toes and metatarsal joints, and assessment of ankle reflexes. Combinations of more than one test have 87% sensitivity in detecting DPN. Loss of 10g-monofilament perception and reduced vibration perception predict foot ulcers [10,11].

The Computer Aided Sensory Analyzer (CASEIVSystem) is a laboratory grade device for the automated thermal and vibration threshold detection, providing sensitive, specific and reproducible measurements. Automated testing and analysis eliminate bias. Using the CASEIVSystem proved to have a positive impact on neuropathy diagnosis [12,13]. In addition, the CASEIVSystem has been used to

study the neurological effects of a variety of compounds in several large trials [12].

The aim of our study was to assess the vibratory and thermal (cold) sensitivity using the CASEIVSystem in newly diagnosed T2DM patients, compared with some classical methods, such as 10g-monofilament, tuning fork, Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS), and to determine the possible correlation between these tests.

Material and Method

Between February 2008 – July 2012 we performed a cross-sectional study on a group of 260 patients with newly diagnosed T2DM in the "Prof NC Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases and "Carol Davila" Central Military Emergency Hospital. Prior to inclusion, patients signed the informed consent form and the Helsinki Declaration was respected. We used the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Signed informed consent (agree with their participation in this study);
2. Newly diagnosed T2DM (ADA 2008 criteria) [14];
3. Agreement to provide some personal data;
4. Agreement to be interviewed about their current conditions and other previous conditions;
5. Agreement to be interviewed about a number of conditions that may be present in the members of their family (those who know that their appearance would have a hereditary component);
6. Agreement to undergo tests for peripheral sensitivity level;
7. Able to follow the instructions given by the investigator.

Exclusion Criteria:

1. Secondary iatrogenic diabetes (eg post pancreatectomy);

2. Presence of conditions that, in the opinion of the investigator, would prevent the patient from participating in the study till its end (including alcohol and drug abuse, psychiatric disorders, skin disorders);

3. Presence of conditions that would limit/reduce patient's ability to execute certain requirements (ophthalmologic, musculoskeletal disorders);

4. Investigator decision during tests; presence of a neurological condition or others that could influence test results (stroke, peripheral artery disease, mononeuropathies, etc).

After being selected and included in the study, the patients were required to fill in a form containing the following personal and clinical data: personal information regarding age, place of residence, height, weight and (Body Mass Index) BMI. Clinical data refer to the presence of specific symptoms of diabetic neuropathy: fatigue, paresthesia, numbness, pain in the legs, muscle cramps. Laboratory data were collected to assess the metabolic status of patients. The analyses include: blood glucose, HbA1c, total Cholesterol, HDL and LDL cholesterol, blood count (etc.). Laboratory data were collected entirely from the official records of the Diabetes Clinics.

In addition, each patient data sheet contained a special section designed for the grading values obtained during the test procedure and the time needed to perform it. Peripheral sensory status was evaluated using the CASEIVSystem.

All patients included filled in specific questionnaires containing Neuropathy Symptom Score (NSS) which is the number of symptoms from a predetermined list of symptoms encountered in a patient with neuropathy. Neuropathy Disability Score (NDS) was calculated by one of the authors. NDS is a summated score of graded assessment of the deficits of selected items from the neurologic

examination. Neuropathic status was standardized using the EASD staging of diabetic neuropathy, too [15-17].

Testing procedure

The testing procedure was drawn up following manufacturer's recommendations [10]. Briefly, the qualified personnel presented the vibration and thermal stimulator, the display and the remote control. The procedure was explained. Four tests were performed: (1) two tests to determine the sensitivity to vibration, one in one hand and one in one foot and (2) two tests for determining the sensitivity to cold, also for one hand and one foot. On completion of the test, results were displayed on the computer screen and saved in the database.

The test for determining the vibration sensitivity of the hand was performed as follows: the patient was asked to sit comfortably and lay the hand on the table with the fingers spread and stretched. The vibration stimulator was placed on the second phalanx of the medius. The stimulator was adjusted so as to lie horizontally. The patient was encouraged not to move his hand during the test.

The test for determining the vibratory threshold in the foot was performed in the same way, the only differences being that the foot was placed in the most comfortable position for the patient and the arm of the Vibration Stimulator positioned on the distal phalanx of the hallux.

Tests for determining the thermal (cold) perception threshold were generally held similarly to the vibration tests. To determine the thermal sensitivity threshold in the leg the same methodology was followed, with two exceptions: the foot was clad in a special sock to limit interference of heat from the environment (eg. air currents in the room) and the thermal stimulator was placed in the dorsal face of the foot.

All vibratory and thermal thresholds calculated by computer were expressed in JND

(Just Noticeable Difference), which represents the smallest difference (between stimuli) presented to the patient. The program contains 25 levels of JND and JND test starts at level 13. Increasing or decreasing the JND value during the test is done by an exponential function. For example, temperature pulses at predefined rates and to predetermined levels can then be fashioned by computer software. In Case IV, 25 discrete steps or stimulus magnitudes are available which range from step 1 (the smallest) to step 25 (the largest). For vibratory threshold, 25 discrete levels of stimulation magnitude are provided, ranging from 0.1 to 576 μ m of displacement. These levels were based on estimates of just noticeable difference. The threshold is defined as the mean of the observed turnaround levels, but only those where single stepping was employed [12]. Hypo/Insensitive site or hyper/supersensitive site could be defined. Normal values were provided by testing healthy subjects (people who did not have diabetes or any other neurological disorder). Patients who had a threshold value below the lowest normal range were classified into the hypersensitive category, and those values which were higher than the highest value of the range of normality were classified in the hyposensitive category [12,13].

After testing and data centralization, patients were assigned to each type of sensitivity, grouped into three categories depending on the sensitivity threshold. The results of vibration susceptibility testing were first divided according to the site where the testing was performed and then grouped into 3 categories:

1. For upper limb testing, subjects were divided into: Hypersensitive (<5JND); Normosensitive (5 to 9.5JND); and Hyposensitive (>9.5 JND);

2. For lower limb testing, subjects were divided into: Hypersensitive (<7JND); Normosensitive (7 to 13.5JND) and Hyposensitive (>13.5 JND).

For the thermal sensitivity threshold, the same 3 categories were established (both for upper limb and lower limb): Hypersensitive (<7.5 JND); Normosensitive (7.5 to 12.5); and Hyposensitive (>12.5 JND)

In addition, classic screening of diabetic neuropathy was done using the 10g Semmes-Weinstein monofilament and 128Hz tuning fork. The filament was placed perpendicular to the skin and some pressure was applied until the filament buckled with a contact time of 1.5-2.0 sec. The examiner applied the monofilament and the patient had to recognize the place of application. The monofilament was applied to the plantar surface of the halux and at the base of first, third, and fifth metatarsals of both feet. Areas affected by ulceration or thick callus formation were omitted. Inability to perceive the sensation at any of the sites was considered abnormal.

Assessment of vibration sensation was done with a 128Hz tuning fork applied at the distal plantar surface of halux in both legs. The response was considered abnormal when the patient lost vibratory sensation while the examiner still perceived it.

Statistical analysis

The statistical package SPSS-PC 10.0.07 (Chicago) was used to compute the descriptive statistics, factor analysis, Pearson's and Spearman's correlation coefficient r , and Student-t test. Mean, standard deviations, minimum and maximum are given. The number of 260 patients is sufficient to detect an r of 0.3 with a power of 90 % and $p < 0.05$.

Results

Patients' characteristics are presented in [Table 1](#). The mean age of the patients was 54.72 ± 8.36 years, the youngest patient being 18 and the oldest 79 years old.

Table 1. Characteristics of studied patients.

Age	54.72±8.36
Glycemia (mg/dl)	212.58±5.28
Hb A1c (%)	8.84±1.89
Total Cholesterol (mg/dl)	244.9±126.47
HDL -cholesterol (mg/dl)	38.9±10.37
Triglycerides (mg/dl)	303.84±460.73
Uric acid (mg/dl)	5.43±1.90
Urea (mg/dl)	50.9±25.2
Creatinine (mg/dl)	1.09±0.51
TGO (U/l)	34.31±44.45
TGP (U/l)	35.89±24.9
Hemoglobin (g/dl)	14.56±1.43

Testing of the vibration and thermal perception thresholds with the CASEIVSystem gave the following results (as also depicted in [Figure 1](#)):

1. Hand vibratory testing:
 - **88** patients were graded as hypersensitive; 112 patients were normosensitive; **60** patients were graded as hyposensitive;
2. Foot vibratory testing:
 - **47** were hypersensitive patients; 68 patients were classified as normosensitive; **145** patients were classified as hyposensitive;
3. Hand sensitivity to cold:
 - **144** patients were classified as hypersensitive; 62 patients were classified as normosensitive; **54** patients were classified as hyposensitive;
4. Foot sensitivity to cold:
 - **90** patients were classified as hypersensitive; 60 patients were classified as normosensitive; **110** patients were classified as hyposensitive;

The assessment of the vibratory threshold by CASEIVSystem suggested the presence of diabetic neuropathy in 56.92% considering hand, respectively 74.84% considering foot as a site of determination. Regarding the thermal (cold) threshold, 76.15% (for hand) and 76.92% (for foot) were the estimations of altered perception in our study group.

Neuropathy Symptoms Score (NSS) was positive for 55% of the patients. Neuropathy Disability Score (NDS) was positive for 54.23%

of the patients. EASD classification Score distributed the patients into: STAGE 0/1 – 155

patients, STAGE 2 – 80 patients, STAGE 3 – 25 patients.

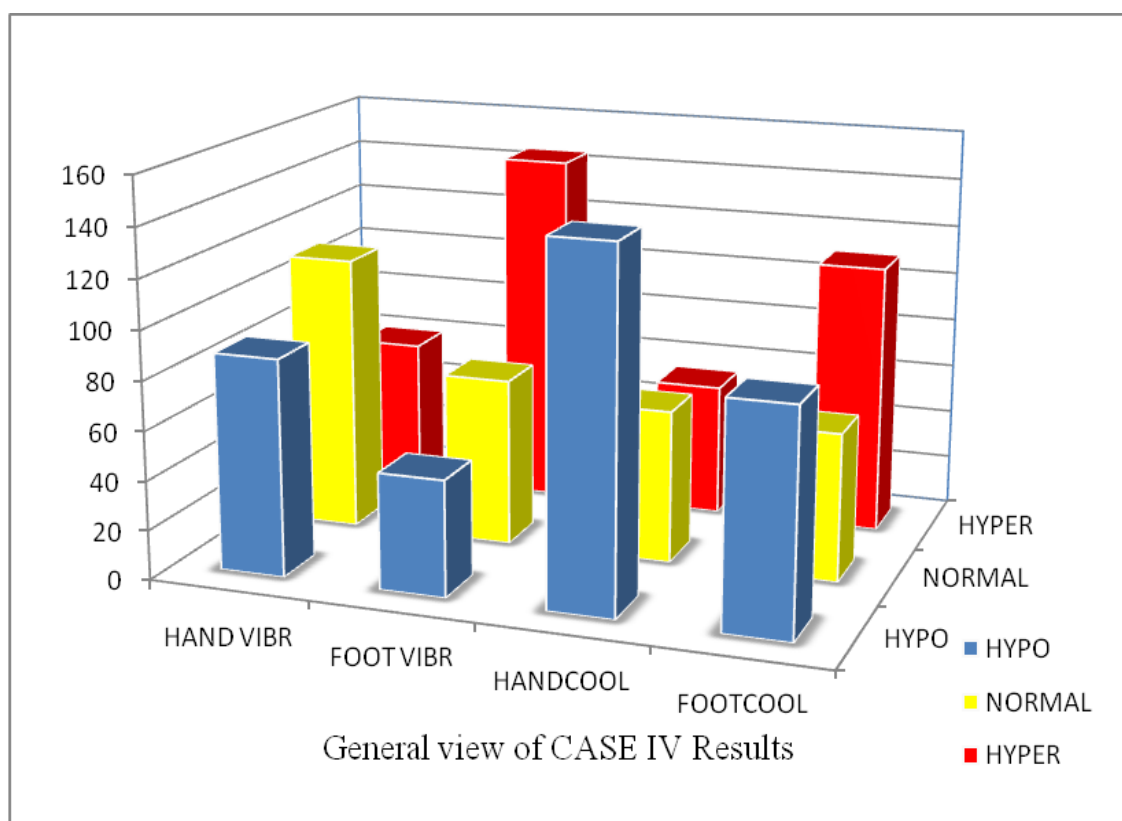


Figure 1. Vibration and thermal perception assessed with the CASEIVSystem.

Table 2. Correlation coefficients between results of various tests.

	Association with NSS	Association with NDS	Association with 10g filament	Association C with Tuning fork
VIBRATION PERCEPTION TEST				
HAND				
88 (hypersensitive)	0.292	0.343	0.211	0.192
112 (normosensitive)	0.112	0.253	0.123	0.095
60 (hyposensitive)	0.236	0.357*	0.155	0.311*
TOE				
47 (hypersensitive)	0.354	0.232	0.343	0.288
68 (normosensitive)	0.155	0.133	0.145	0.178
145 (hyposensitive)	0.364*	0.478*	0.398*	0.544*
THERMAL PERCEPTION TEST				
HAND				
144 (hypersensitive)	0.164	0.166	0.188	0.157
62 (normosensitive)	0.177	0.210	0.214	0.155
54 (hyposensitive)	0.254	0.453*	0.477*	0.486*
TOE				
90 (hypersensitive)	0.155	0.163*	0.165	0.175
60 (normosensitive)	0.175	0.176	0.164	0.165
110 (hyposensitive)	0.366*	0.214	0.484*	0.388*
NSS	-	0.511*	0.523*	0.577*
NDS	-	-	0.518*	0.323*
10g monofilament	-	-	-	0.428*
Tuning fork	-	-	-	-

*p<0.05, for all other values p>0.05

The 10g-monofilament exam was positive for 28.46% and the tuning fork exam was positive for 20.38% of the examined patients.

Mean time for a complete CASEIVSystem exam was around 27.23±9.34min vs. 3.21±0.24min (p<0.05) for a classic exam.

We also analyzed the correlation between the results of the CASEIVSystem evaluation and those of the classic (monofilament, tuning fork, NSS, NDS) evaluations. For this we used two methods:

1. First we used an approach using the correlation coefficients for these associations

(Table 2). With some exceptions, the results of one test were associated with those of another test and often to highly significant degree (p<0.05).

2. In the second approach we calculated the associations determining the percentage of patients showing abnormality among different tests by number of abnormal tests per patient (Table 3). Impaired peripheral sensitivity was present in the absence of neurological type symptoms. There are 28 with normal tests and 8 with all tests abnormal. The 50% boundary is indicated by a line.

Table 3. Rate (percentage) of abnormality among different evaluations by number of abnormal evaluations per patient.

No. of abnormal evaluation per patient	Abnormal (%)						
	No. of patients	Vibratory Detected Threshold (FOOT)	Cool/Thermal Detected Threshold (FOOT)	NSS	NDS	10g monofilament	128 Hz tuning fork
0	28	0	0	0	0	0	0
1	37	47	46	36	35	11	7
2	48	76	87	49	46	26	10
3	51	92	92	54	68	26	16
4	44	94	98	61	76	31	35
5	44	100	97,5	100	81	51	32
6	8	100	100	100	100	100	100

Discussion

Since peripheral sensory neuropathy is a pivotal element in the causal pathway to both foot ulceration and amputation, selecting a quick, inexpensive, and accurate instrument to evaluate the high-risk patient is essential to make clinical relevant decisions. So, apart from CASEIVSystem, we also assessed monofilament, tuning fork, NNS and NDS scores for evaluation of peripheral neuropathy. In clinical practice diagnosis of neuropathy is not so difficult to make, but as for other diabetic complications, it is not a simple matter to detect its degree of severity [18,19].

In our study we observed that more than half of the newly diagnosed patients had changes in

sensitivity, regardless of the type of sensitivity test or anatomical region where it was performed. Changes in sensitivity mean not only hyposensitivity. They also mean hypersensitivity, but for the identification of this status, the regular tests (10g-monofilament and 128Hz tuning fork) are not helpful. Some of the investigators consider that modified detection thresholds reflect metabolic disturbances at diagnosis and not the presence of neuropathy. This statement is sustained by the anatomic sites (hand without neuropathic symptoms) and the rapid improvements following metabolic correction.

We could say that our study has some limitations: (1) highly selected population, considering the sites of selection (National

Institute of Diabetes and a Diabetes Department in an Emergency Hospital). This situation could have a great impact on results, so it should be necessary a study in sites with general practice, where patients are presented with less metabolic disorders at diagnosis of diabetes mellitus; (2) transversal design – we don't have an image after correction of acute metabolic disorders (glucotoxicity).

In our study we detected a high percentage of patients with abnormal Vibratory Detected Threshold (VDT) and Cool/Thermal Detected Threshold (CDT) and the metabolic disturbances at diagnosis of diabetes mellitus could be an explanation. VDT and CDT can be evaluated in hypersensitive patients, representing a particular category of abnormal results (hypersensitivity). The classic methods cannot provide this kind of results. Vibratory Detection Threshold and Cool/Thermal Detection Threshold using CASEIVSystem are precise, quantitative evaluation methods. By comparison, NSS, NDS, 10g-monofilament and 128Hz tuning fork tests are less standardized or validated and there could be more variability among evaluators. CASEIVSystem seems to be an effective method in detecting modification of VDT and CDT,

even in preclinical stages, compared to classical methods. However, using CASEIVSystem is a time consuming method to assess the diabetic neuropathy. If more sites are to be tested for perception thresholds, the time will increase considerably. Despite of this consideration, CASEIVSystem seems to be a reliable method to diagnose modifications of VDT and CDT for scientific research area [18,19].

Conclusion

In conclusion, a good correlation between CASEIVSystem score and 128Hz tuning fork, 10g-monofilament, NSS and NDS shows that simple bed side tests are useful in clinical practice, even in those subjects with newly diagnosed type 2 diabetes mellitus. CASEIVSystem allowed the assessment of the vibratory and thermal thresholds. However, the time needed for investigation renders this tool difficult to use in a time effective manner.

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