

How to diagnose neuropathy in diabetes mellitus?

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ABSTRACT

Diabetic neuropathy is a common problem and can present various clinical presentations such as cranial neuropathy, radiculopathy, plexopathy, mononeuropathy, polyneuropathy and autonomic neuropathy. Clinical evaluation and use of scoring systems for the evaluation of diabetic polyneuropathy is an important step to get correct diagnosis. New informations about the diagnosis of diabetic neuropathy continue to emerge, which will lead to correct diagnosis and treatment as well. Diabetic length-dependent sensorimotor polyneuropathy (DSPN) and carpal tunnel syndrome are the most common seen problems. While acute and painful situations with motor weakness are mostly transient, sensory fibres are predominantly involved in chronic ones. Nerve conduction studies are needed to confirm diagnosis of any type of diabetic neuropathy, but they are normal in cases with small fiber involvement. The early diagnosis is crucial because it is well-known that subclinical diabetic neuropathy may be reversed or significantly improved with diabetes control. Because neuropathy at the stage in which only small fibers are affected can be reversed, it is important to diagnose DSPN in these stages. Skin biopsy taken from the dermatomal area of sural nerve, laser-doppler-imager flare technique, corneal confocal microscopy are used to assess small fibre dysfunction. The aim of the present review was to evaluate evidence-based diagnosis for any type of neuropathy seen in the patients with diabetes mellitus.

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Introduction

Neuropathy developing secondary to diabetes is not only a late complication but also can develop at any time during the course of the disease. It should be evaluated carefully because neuropathy symptoms are associated with poor quality of life [1]. The neuropathies developing in patients with diabetes are heterogeneous and may be separated into generalized and focal/multifocal varieties [2-4]. Onset of

symptoms is also variable and may be acute, subacute, or chronic in forms. Symmetric or generalized neuropathies usually present as chronic neuropathies and asymmetric ones present as acute forms with more prominent pain [2-4]. Diabetic neuropathy diagnosis needs exclusion of other causes for peripheral neuropathy and it is also increasingly recognized in patients with prediabetes who are at high risk of

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developing diabetes mellitus (DM). As it was seen Figure.1, there are different types of neuropathy seen in diabetes. The most commonly seen and typical form is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy and is thought to be the most common variety [5]. The second most commonly problem seen in the patients with diabetes is carpal tunnel syndrome [6]. Distal symmetric polyneuropathy (DSPN) may be associated with retinopathy and nephropathy for which total hyperglycemic exposure is perhaps the most important risk covariate [7, 8]. Autonomic dysfunction and neuropathic pain may develop over time as well [7]. Chronic inflammatory demyelinating polyradiculopathy (CIDP) is another problem which may be seen in diabetic patients. It is well known that similar patterns of DSPN may occur in patients

without diabetes, but with other toxic or metabolic causes [7]. Although many neuropathic problems were reported in the literature, there is not any diagnostic algorithm. The presence of atypical polyneuropathies, which are different from DSPN in several important features, is another problem to be evaluated. In this report, we will test to review the old advances and present some practical clues about the diagnosis of neuropathies in patients with diabetes mellitus.

Prevalence of any Case of Neuropathy in Diabetes

Both type I and type II diabetes are the most usual cases of neuropathy worldwide. The prevalence of neuropathy changes from 50% to 90%, depending on the criteria and methods used [5, 9-11]. Almost one and half of the diabetics had classical symmetric polyneuropathy, 25% had carpal tunnel syndrome,

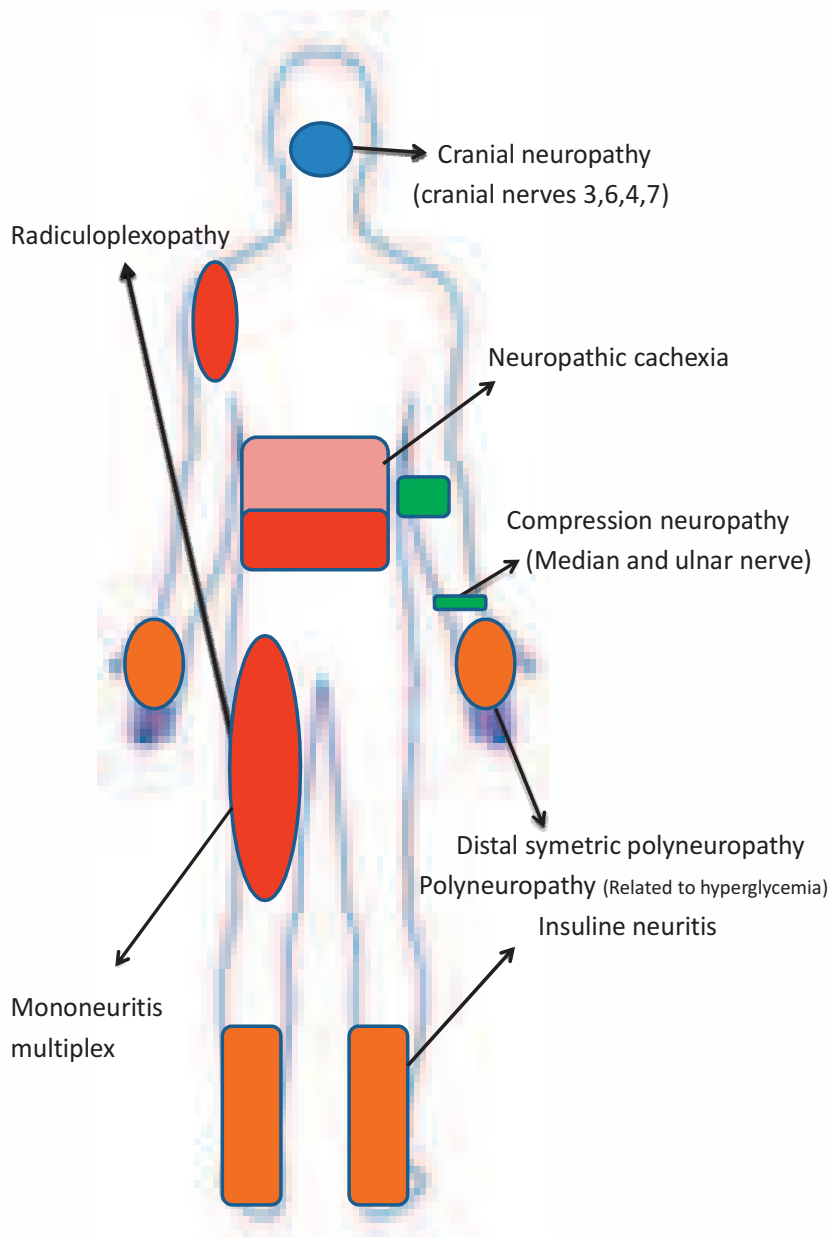


Figure 1. Types of neuropathy seen in diabetes.

about 5% had autonomic neuropathy and 1% had asymmetric proximal neuropathy [6]. The occurrence of any type of neuropathy correlates with the duration of diabetes, poor glycemic control and with the presence of retinopathy and nephropathy [5]. In patients with neuropathy associated with impaired glucose tolerance, controlled diet and exercise may lead to re-innervation [12]. Findings from subclinical neuropathy studies suggest that intensive control of glycemia may result in improved nerve conduction

[13]. Neuropathic pain is a very popular and an important problem causing discomfort in patients with diabetes. Neuropathic pain is a pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [14]. Bilateral thalamus, spinal cord, left parietal lobe and subcortical located deep nuclei are involved in pain generation in diabetes patients [15]. The etiology of neuropathic pain is broad, and diabetes is a significant and widely seen cause [4, 14, 15]. Neuropathic pain is also one of the

Table1. The diagnostic approaches in the patients with suspicion of diabetic neuropathy.

DIAGNOSTIC PROCEDURES	WHEN THE PROCEDURE SHOULD BE USED
Neurological Examination	<ol style="list-style-type: none"> 1- Sensory examination: response to light touch, temperature, painful stimulus, vibration and proprioception. 2- Motor examination: testing muscle tone and strength, reflexes and coordination. 3- Autonomic findings: examining changes in colour, temperature, sweating and swelling.
Diabetic neuropathy examination (DNE) score	<ol style="list-style-type: none"> 1- In any type of diabetic polyneuropathy
Diabetic symptom score (DNS)	<ol style="list-style-type: none"> 1- In distal symmetric polyneuropathy (DSPN)
Nerve conduction studies	<ol style="list-style-type: none"> 4- In atypical cases with superimposed nerve entrapments or inflammatory demyelinating neuropathy such as CIDP 5- In neuropathy cases with asymmetrical symptoms 6- In cases with involvement of the upper limbs 7- In any period of DSPN (To confirm diagnosis)
Screening laboratory tests	<ol style="list-style-type: none"> 1- Serum glucose, HbA1C ve glucose tolerance test 2- For differential diagnosis in DSPN cases Blood sugar, blood count, ESR, anti-HIV Ab, anti-Lyme Ab, Liver and renal function tests, serum vitamin B₁₂, serum protein electrophoresis, vasculitis profile, paraneoplastic markers, thyroid function tests
Two-hour glucose tolerance testing	<ol style="list-style-type: none"> 1- In patients with an otherwise idiopathic neuropathy 2- In patients with chronic idiopathic axonal polyneuropathy
Vibration sensation (Halux of great toe)	<ol style="list-style-type: none"> 1- In early diagnosis of neuropathy 2- In large-fiber involved cases in diabetes 3- In all cases of other types of polyneuropathy
The Semmes-Weinstein 1-10 gram monofilament examination (SWME)	<ol style="list-style-type: none"> 1- In early diagnosis of neuropathy 2- In large-fiber involved cases in diabetes
Genetic testing	<ol style="list-style-type: none"> 1- In patients only with a history of hereditary neuropathy and cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype
Neuroimaging (MRI)	<ol style="list-style-type: none"> 1- In oculomotor nerve involved cases with pupillary involvement or absence of pain 2- In radiculopathy or plexopathy cases
Skin biopsy from the dermatomal area of sural nerve	<ol style="list-style-type: none"> 1- In early diagnosis of DSPN to assess small-fiber function 2- In evaluation of NP development risk
Laser-Doppler-imager flare technique	<ol style="list-style-type: none"> 1- In early and reversible stage of DSPN to assess small-fiber function (in whom results of conventional quantitative sensory tests and skin biopsy results are normal)
Neuropathic pain assessment	<ol style="list-style-type: none"> 1- In any polyneuropathy patients to identify and quantify neuropathy
Corneal confocal microscopy	<ol style="list-style-type: none"> 1- In early diagnosis of DSPN to assess small-fiber function 2- In evaluation of severity of neuropathy and NP development risk

Table 2. Toronto clinical neuropathy scoring system for the evaluation of diabetic polyneuropathy.

Symptom scores	Reflex scores	Sensory test scores
Foot	Knee reflexes	Pinprick
Pain	Ankle reflexes	Temperature
Numbness		Light touch
Tingling		Vibration
Weakness		Position
Ataxia		
Upper-limb symptoms		

Recording of scores (Symptom scores: present = 1; absent = 0. Reflex scores: absent = 2; reduced = 1, normal = 0. Sensory test score: abnormal = 1. normal = 0).

most common presentations not only in diabetes, but also in impaired glucose tolerance and impaired fasting glucose [4, 12, 14]. While the relationship between diabetes and neuropathic pain is well documented, the occurrence rate of neuropathic pain is still underdiagnosed and difficult to quantify [11, 15]. Neuropathic pain occurs in 7.5% to 35% of patients with DM [11, 15].

Neurological Examination and Diagnostic Procedures

Any toxic, metabolic or systemic inflammatory diseases resulting in distal type axonal neuropathies, small fiber neuropathies, demyelinating neuropathy especially CIDP, multifocal neuropathies and radiculopathies or plexopathies may mimic neuropathy seen in diabetes. Neurologic examination focuses on the recognition of clinical signs of neuropathy. Patients are asked to report whether they experienced gait problems (difficulty in walking or climbing, ataxia), thermal allodynia (e.g. When they have a bath) and/or pain in the feet. For evaluation of diabetic neuropathy, neurological examination should include cranial nerve examination, assessment of muscle force, sensations of pinprick, touch, temperature, joint position and vibration. It is also tried to identify the presence and distribution (e.g. length or non-length dependent) of any type of sensory loss and pain. At the second step, symptoms and signs of dysautonomy are recorded. Dysautonomic symptoms (e.g. pupil abnormalities, impotence, impaired bladder function, constipation or diarrhea, early satiety and gastric fullness, abnormal sweating, flushing, skin discoloration, xerostomia and xerophthalmia, orthostatic hypotension) are recorded. The examination clicks, and diagnostic processes are summarized below and some diagnostic clues are presented on Table 1. They are also detailed in the

following section named as “classification and diagnostic work-up in diabetic neuropathies”.

In the algorithm, a patient with neuropathy should be assessed in order mentioned below.

1. Evaluation of neuropathic symptoms and signs:

The patients are assessed by the Toronto Clinical Scoring System for Diabetic Polyneuropathy, a validated instrument reflecting the presence and severity of DSPN as measured by sural nerve morphology and electrophysiology [16]. Sensory testing was performed on the first toe. Total scores range from normal = 0 to a maximum of 19. Mild DSPN was defined from a score of 5 onwards, and severe neuropathy as a score of 10 (see Table 2). Diabetic neuropathy examination (DNE) score, which is a modification of the Neuropathy Disability Score of Dyck is another scoring and identification way of neuropathy in which neurological examination was carried out and the neurological signs were recorded [17]. The DNE consists of eight items (Extension of the knee and dorsiflexion of the foot, Sensitivity to pinpricks at index finger and great toe, Ankle reflex, Sensitivity to touch, Vibration perception and Sensitivity to joint position). More than three abnormal results in these exams indicate presence of polyneuropathy. A third way of evaluation DSPN is to record diabetic symptom score (DNS). The DNS score has the following items: (1) unsteadiness in walking, (2) pain, burning or aching in the legs or feet, (3) prickling sensations in the legs or feet, and (4) numbness in legs or feet. Presence is scored 1, absence 0, maximum score 4 points. The DNS is valid in cases of diabetic polyneuropathy, and is fast and easy to perform in clinical practice [18].

2. Examining muscle power and deep tendon

reflexes:

Motor and reflex exams are more important in the evaluation of other neuropathies such as radiculo/plexopathies developed secondary to diabetes. Although ankle reflex is a powerful screening tool, a combination of ankle reflex and vibration sense has superior sensitivity and specificity compared with either of them done alone for the detection of DSPN in clinical settings [19]. Muscle strength was graded using the Medical Research Council (MRC) score. Positive Romberg's sign and gait abnormalities were recorded. Ankle reflexes are obtained at both ankles. The examiner gently dorsiflex the foot and strike the achilles tendon briskly with the reflex hammer. Deep tendon reflexes were graded as normal, decreased (with reinforcement) or absent. It may be normal to have reduced or absent ankle reflexes in some elderly people, although the frequency and significance of this is disputed [20, 21]. It should be also remembered that the isolated loss of a reflex can point to a radiculopathy affecting that segment e.g. loss of ankle jerk if there is an S1 disc prolapse.

3. *Quantitative sensory testing:*

It is an important title meaning an objective index of neurologic functional status in the assessment of neuropathy in diabetes. The normal ranges of these tests vary systematically according to the age of the patients. These tests require the patient to be alert and cooperative for reliable results because quantitative sensory testing is a psychophysical test and lacks the objectivity of nerve conduction studies. Another problem is the weak correlation between these tests indicating the need to apply more than one test in screening for diabetic neuropathy [22].

a) *Touch and pain sensation:* Touch sensation examination is performed by using cotton gauze (to test light touch and dynamic mechanic allodynia). Disposable safety needle (to test hypoalgesia, pinprick hyperalgesia) is applied for evaluation of pain sensation. Sensory loss and positive sensory signals (evoked and spontaneous pain, paresthesias) are recorded for both types of sensory modalities. Superficial pain sensation may be conducted using a sterile Neurotip (Owen Mumford, Oxford, U.K.) and it is applied at the eponychium of the first toe and it is repeated in an arrhythmic manner to the three sites described for the SWME at next paragraph and one side for the Neurotip. The superficial pain threshold is defined as the total number of times the application of the pain sensation is not perceived, with scores

varying from 0 to 8 [23, 24].

b) *The Semmes-Weinstein monofilament examination (SWME):* It is a noninvasive, lowcost, rapid (takes less time, <5 minutes), and practical test often used in clinical testing of pressure sense [25, 26]. The 5.07/10 g Semmes Weinstein monofilament assesses the integrity of Merkel touch domes and Meissner's corpuscles and their associated large diameter fibers [27]. The variability in the methodology of SWME (weight of the filament, the number of sites, location of sites, and the diagnostic threshold) limits the effectiveness of the test as a diagnostic tool. In general, nine plantar sites (distal great toe, third toe, and fifth toe; first, third, and fifth metatarsal heads; medial foot, lateral foot, and heel) and one dorsal site were examined. The monofilaments are applied to the test site perpendicularly until they bend for about one second. Patients are instructed to say "yes" each time they sense the monofilament on their foot. If patients fail to sense the monofilament after it twists, the test site is thought to be insensate [28, 26]. It was repeated four times on both feet in an arrhythmic manner. The SWME threshold was defined as the total number of times the application of 10-g monofilament was not perceived by the patient, and it varies according to the number of placed. Patients unable to detect one or more sites should be classified as at risk in order to maximize sensitivity [26]. The quantitative analysis of the 16 studies with sufficient data revealed that SWME is both fairly sensitive and highly specific when compared with the gold standard of NCS. While the use of 5.07/10 g SWME is widespread and generally accepted, data show biothesiometry and the use of finer monofilaments (1 g) may improve detection rates of abnormality [29-31].

c) *Vibration sense:* Examining vibration sensation reflects large fiber involvement and it is performed by using 128 Hz Rydel-Seiffer tuning fork (vibration at the first metatarsal joints, ankles, knees, first metacarpal joints, elbows). For the best result, a 128-Hz tuning fork is applied to the halux bilaterally situated at the lateral side of the first toe [32]. The on-off method or the timed method is used in testing of vibration. It is recorded whatever the patient reports about the perception of both the start of the vibration sensation and the cessation of vibration. The testing is conducted twice on each toe, and correct responses are recorded [23, 33, 34]. The vibration can be felt for 10 to 15 seconds. Patients are asked initially, and after 5 seconds, whether they perceive vibration. Patients who felt vibration both initially and after 5 seconds are

scored as normal. Vibration not perceived at all is scored as absent, and vibration perceived initially but not at 5 seconds is scored as abnormal. The vibration test is reproducible and accurate test. It provides a quantitative assessment of DSPN and can document severe neuropathy, even in the presence of a normal result with the 10-g monofilament test [33]. The risk of foot ulcers is associated with diminished vibratory sensation and can be detected earlier and more accurately with the great toe vibration test. It is accepted that great toe vibration test should replace the 10-g monofilament test as the recommended technique for detection of DSPN [33].

d) Thermal sensory testing: Quantitatively testing of warm and cold is one of the tests currently being used for early detection of diabetic neuropathy such e. g. DSPN (This test is performed by using glass tubes filled with cold and hot water (thermal sensation, allodynia test, aftersensation test). Sensory loss and positive sensory signs (evoked and spontaneous pain, paresthesias) are recorded [22, 35]. Nowadays, pain and temperature sensation thresholds are measured by some devices for the evaluation of small nerve fiber dysfunction [36].

e) Pain-related evoked potentials: It is elicited by a nociceptive electrical stimulation of the skin and may contribute to the early detection of diabetic sensory neuropathy [37]. This method is one of the easiest and most reliable of the neurophysiological methods for assessing function of nociceptive pathways (mainly A delta fibers) [25].

f) Position sense: Sense of movement and position of toes and hand fingers were evaluated. Position sense was assessed at the interphalangeal joint of each great toe for a position change. The toe was held at both sides of proximal phalanx with one hand while using the other hand to move the distal phalanx up or down. After three trials of exam for each foot, the patient was asked to choose "up or down?" and the three responses per foot were scored as correct or incorrect [38].

4. *Electromyography:*

Nerve conduction studies (NCSs) are the most frequently used diagnostic tool for evaluation of any case of neuropathy in the patients with diabetes.

5. *Corneal confocal microscopy:*

It is a new sensitive non-invasive examination, which may be used to detect early small fiber nerve damage in patients with small nerve fiber neuropathy. Corneal nerve parameters are assessed and it allows

quantification of corneal nerve morphology. Cornea nerve damage correlates with the severity of pain and autonomic neuropathy [39, 40].

6. *Skin biopsy:*

Nowadays it is included in the diagnostic work-up of patients with suspected small-fiber neuropathy [41]. This technique is used to show that small fibers degenerate early in the course of neuropathies associated with diabetes and it confirms the diagnosis when clinical and neurophysiologic examinations are not informative for diabetic neuropathy [42, 43]. A skin biopsy is also important to say about pain. Information from the literature suggest that a more serious loss of intraepidermal nerve fiber density increases the hazard to develop neuropathic pain, whereas intraepidermal nerve fiber density regeneration can be linked with a reduction in pain intensity [44]. Skin biopsy shows a diagnostic efficiency of 88.4%, clinical examination of 54.6% and quantitative sensory tests about 46.9% in patients with small fiber neuropathy [22, 35, 41].

7. *Laser-Doppler-imager (LDI) flare technique:*

LDI flare may represent a novel method for detecting early small-nerve-fiber changes in people with diabetes. The LDI flare easily detects small-fiber dysfunction before the occurrence of potentially irreversible structural loss of nerve fibers and can demonstrate abnormal C-fiber function in subjects with symptomatic DSPN in whom the results of conventional quantitative sensory tests are normal and in whom there is no significant reduction in nerve fiber density NFD [24]. In this non-invasive technique, axon reflex mediated vasodilatation in response to skin heating is measured and C-fiber dysfunction is detected in type 2 diabetes before small-fiber neuropathy can be discovered by other currently available noninvasive methods [24, 45]. Skin proximal to the first and second metatarsal heads on the dorsum is heated with a circular skin heater (diameter 1.0 cm; Moor Instruments) to 44°C for 20 min. An area of surrounding the heated skin was scanned with the LDI immediately after careful removal of the heater probe [24, 45]. On the flux image, the region of interest demarcated by the edge of the flare is drawn, and the area of the LDI flare is calculated and expressed in square centimeters [24].

8. *Neuropathic pain assessment:*

Although only some patients with nerve lesions develop neuropathic pain, it is a significant issue

because neuropathic pain is associated with poor quality of life and in that respect is no recognized objective gold standard for assessing neuropathic pain. Clinical assessment and diagnosis of neuropathic pain, a clinical history of pain and sensory exam are established to confirm nervous system involvement. Standardized screening tools which are often applied to distinguish and quantify neuropathy provide a full clinical record for follow-up of the patients with any case of neuropathy [46]. The diagnostic accuracy of neuropathic pain screening and assessment tools varies across patient populations. The DN4 may be more universally applicable than other creatures (e.g. The Leeds assessment of neuropathic symptoms and signs, PD-Q, and Neuropathic Pain Questionnaire) in general [47]. In DN4 scoring system, the presence of neuropathy symptoms (1 - Burning, 2 - Painful cold, 3 - Electric shocks, 4 - Tingling, 5.- Pins and needles, 6 - Numbness, 7 - Itching) and examination findings (1 - Hypoesthesia to touch, 2 - Hypoesthesia to prick, 3 - Allodynia by brushing) are evaluated. The total score is calculated as the sum of the 10 items and the cutoff value for the diagnosis of neuropathic pain is a total score of 4/10.

Classification and Diagnostic Work-up in Diabetic Neuropathies

A. Chronic symmetric neuropathies

Diabetic sensorimotor polyneuropathy

The most common complication is peripheral neuropathy and distal symmetric polyneuropathy (DSPN) occurring in up to 50% of patients is the most common presentation of neuropathy in diabetes [48-50]. Chronic inflammatory demyelinating neuropathy which has similar sensory findings as seen in DSPN of diabetes is also more common in diabetic than in non-diabetic patients [51]. Typical DSPN is defined as a “chronic, symmetrical, length dependent sensorimotor polyneuropathy” [50, 52]. It is a commonly seen polyneuropathy with small and large fibre sensory, motor and autonomic involvement in various combinations. Diagnosis of DSPN is primarily clinical and needs a good history taking and neurological examination [50, 52]. A minimum of two abnormalities (from symptoms, signs, nerve conduction abnormalities, quantitative sensory tests, or quantitative autonomic tests) is needed in diagnosis [53]. In other words, documenting an abnormal sensory and motor examination of feet and great toe, and Aschille tendon reflex is sufficient to diagnose

neuropathy with appropriate symptoms in a diabetic patient. Because of this reason, the use of monofilaments to assess touch-pressure sensation should not be forgotten as well as the Rydell-Seifert semi-quantitative tuning fork [54, 55]. New diagnostic techniques (including measurement of nerve fiber density using corneal confocal microscopy, and nociceptive evoked potentials) may contribute to the diagnostic work-up [53-56]. In the examination of the most serious complications such as foot ulcers, Charcot foot abnormalities and small injuries, they are checked visually [56]. To assess peripheral vascular disease as a possible cause of foot problems, peripheral pulses are checked as well.

Symptoms and signs: Sensory symptoms are more prominent, and the neuropathy symptoms start in the feet and spread proximally in a stocking glove distribution with increasing duration or severity of diabetes [57]. Both “positive” (tingling, burning, and other abnormal sensations) and “negative” (sensory loss, weakness, numbness, and unsteady gait) sensory symptoms may be seen [50, 52, 57, 58]. Small fibers are firstly effected and manifests with the impairment of pain, temperature and autonomic functions. Patients may report superficial burning pain or deep aching pain, tingling and numbness in their toes [11, 59]. They feel that their feet are persistently cold. Progression of sensory symptoms predisposes the patients to falls, development of foot ulcers and decreased quality of life [58]. Upwards to 50% of patients may experience neuropathic pain symptoms worse at night and disturb sleep [60]. What a pity, as up to 50% of the patients may be asymptomatic, a diagnosis may simply be made on examination and the patient presents with a painless foot ulcer in some cases [56, 60]. Small fiber neuropathies may be experienced even in the patients with impaired glucose tolerance and motor and reflex tests are normal during that stage [11, 48, 59]. Subsequently, the large nerve fibers are damaged and then gait disturbance due to impaired proprioception, mild distal weakness such as weakness of big toe and autonomic symptoms (pallor alternating with rubor, cyanosis, and mottling) may be seen [11, 57, 58]. Examination of the lower limb reveals distally located signs such as loss of pinprick, temperature, touch and vibration sense with reduced or absent ankle jerks and loss of great toe position sensation [60, 64]. Distal weakness occurs only in the most severe instances, so testing of the Achilles tendon reflex often indicating DSPN even in mild or asymptomatic cases is significant. In a typical DSPN

case, monophasic or fluctuating course and asymmetric or proximal symptoms as well as motor involvement may be seen. Acute neuropathic pain localized distally is another atypical characteristic of DSPN cases and pain may come in even prediabetes cases [61-63]. Any two of the following: neuropathy symptoms, decreased distal sensation, or decreased/absent ankle reflexes make DSPN diagnosis probable. For a definite diagnosis, it should be confirmed by abnormal nerve conduction study [64].

Differential diagnosis: Any variation of clinical findings such as acute, asymmetric, proximal, or motor involvement suggests an atypical neuropathy. In cases with sensory ataxia or profound distal upper and lower extremity weakness, an evaluation for other causes of neuropathy i.e. CIDP is recommended [65]. It should be also remembered that progression of DSPN is usually quite slow except the unusual cases of severe sensory and autonomic neuropathy that can occur in the first several months after the onset of Type 1 diabetes [65, 66]. The severe proprioceptive problem occurs when there is prominent large fiber involvement. These patients develop sensory ataxia and autonomic manifestations with impotence, bladder atony, and pupillary changes and thus have been called the pseudotabetic form of diabetic neuropathy. The presence of proprioception deficits and ataxia should lead to a search for other possible etiologies (syphilis, B12 deficiency, paraneoplastic or Sjogrens syndrome sensory neuropathy, CIDP) [66, 67]. Nevertheless, it is thought that the pseudosyringomyelic, pseudotabetic, and the early onset neuropathy described by Said et al. [66], all are severe variants of diabetic DSPN and probably not distinct forms of neuropathy [65-67]. Finding electrophysiologic changes that fulfill demyelinating criteria superimposed on axonal degeneration in a diabetic should be assessed with care. Likewise progressive polyradiculoneuropathy with a presentation similar to CIDP in diabetes may be seen, CIDP can develop in diabetic patients, too [67-69]. The clinical presentation of progressive poly-radiculoneuropathy is dominated by painful progressive motor weakness, with or without exacerbation of sensory symptoms. The weakness involves all limbs, but is often asymmetric. These symptoms and signs are important in differential diagnosis from classical DSPN. Electrophysiology of polyradiculoneuropathy may be predominantly axonal similar to DSPN, and CSF may show increased protein similar to CIDP cases [69]. Because nerve conduction studies and nerve biopsy

are not helpful in differential diagnosis, the clinical features of gradually progressive, usually painless, proximal and distal symmetric weakness and numbness in the arms and legs should be sufficient to distinguish CIDP from the typical symmetric and asymmetric diabetic neuropathies [65].

Screening tools: Utah Early Neuropathy Scale examining great toe dorsiflexion, pin sensation, great toe vibration and joint position, allodynia, and deep tendon reflexes is a sensitive and reproducible clinical measure of sensory and small-fiber nerve damage and may be useful in early diagnosis of diabetic neuropathy [70]. On the other hand, several examination scales focusing on large-fiber function have been risen to establish DSPN diagnosis. The Michigan Neuropathy Screening Instrument (MNSI) is a good screening tool for diabetic neuropathy and the Michigan Diabetic Neuropathy Score (MDNS) having higher concordance with nerve conduction studies provides a simple support to confirm this diagnosis [71, 72]. In the evaluation of neuropathic pain in diabetes, DN4 questionnaire or LANSS easily identifies potential patients with neuropathy, particularly by non-specialists, but it should be remembered that they cannot replace careful clinical judgement [73].

Electrophysiological tests: Nerve conduction studies (NCSs) are the most frequently used diagnostic tools for DSPN and used for confirmation. The main feature of DSPN is reduced distal lower extremity sensory nerve action potential amplitudes [74]. In early cases, nerve conduction velocity studies are usually normal when only small-diameter fibers are damaged. Although NCSs have limited utility in diagnosing small-fiber neuropathy in the early period of neuropathy related to diabetes, it is a reliable procedure to exclude any other etiology (superimposed nerve entrapments or inflammatory demyelinating polyneuropathies, neuropathies with asymmetrical symptoms or involvement of the upper limbs etc.) [52, 75]. Despite much study reports that the underlying process is axonal degeneration and/or demyelination, axonal degeneration is the primary process [76]. Follow-up changes in peroneal motor conduction velocity or sural sensory amplitude have often been used as primary progression measures in diabetic neuropathy trials because they are objective, repeatable, and continuously variable [52, 75-77].

Laboratory tests: Small fiber predominant

neuropathy presenting with pain and dyesthesias in the feet is usually an early manifestation of the typical DSPN in diabetes. To show decreased intra-epidermal nerve fiber density by Laser-evoked potentials and skin biopsy is very helpful because the clinical examination and nerve conduction studies may be normal in the early period [73, 78, 79]. Histological analysis of tissue taken from the distal part of the leg, within sural area 10 cm above the lateral malleolus in cases of suspected DSPN shows degenerated small-diameter sensory fibers. A low intraepidermal nerve fiber density below the fifth percentile is usually considered confirmatory for a diagnosis of early cases of DSPN [42, 43]. Screening laboratory tests providing the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine) and serum protein immunofixation electrophoresis in the patients with DSPN. Metformin interferes with the absorption of cobalamin and may contribute to vitamin deficiency. Vitamin B12 deficiency should be certainly evaluated because it can lead to progressive deterioration of nerve tissue frequently misdiagnosed as diabetic peripheral neuropathy [80-82]. On the other hand, functional deficiency of vitamin B12 (ie, normal cobalamin but elevated MMA levels) is another problem with a tripling of neuropathy frequency in type 2 diabetes patients (regardless of metformin use) [80-82]. Infections (e.g., Lyme disease, HIV, Hepatitis), vasculitis, alcohol use, cancer and related paraneoplastic syndromes should also be assessed in order to exclude other etiologies of polyneuropathy. Furthermore, diabetic neuropathy may be associated with demyelination, and diabetes mellitus, multifocal motor neuropathy and CIDP may have elevated CSF protein [83]. Because of this diagnostic problem, we should consider all possible causes of neuropathy in order to properly treat the diabetes patients [48]. Genetic testing may be considered in patients only with a history of hereditary neuropathy and cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype [84].

B. Transient symmetric neuropathies (Acute, painful, sensory predominant)

1. Diabetic neuropathic cachexia (DNC)

It is an uncommon syndrome and symmetric sensory peripheral neuropathy is associated with “weight loss up to 60% of total body weight, symmetric painful dyesthesias over the limbs and trunk which is typically affecting trunk” [48, 85, 86].

It is not associated with weakness similar to DSPN. Patients may experience neuropathic pains tending to be worse at night or during periods of relaxation. The patients complain very severe pain, but sensory impairment associated with the DNC is usually minimal. The pain resolves with weight gain. Depression is one of the hallmarks of the syndrome [48]. The DNC is reversible with adequate diabetic control over weeks to months, unlike other symmetric diabetic neuropathies. Most reported patients are adult males, ordinarily in the sixth or seventh decades of lifetime. The DNC can occur in both types of diabetes patients and are associated with poor glucose control [48, 55, 56].

2. Hyperglycemic neuropathy

It is likewise a secret and mostly transient state. Hyperglycemic neuropathy can occur at the time of diagnosis or may follow an episode of ketotic coma, and the symptoms rapidly subside once the diabetes is controlled. Distally located sensory paresthesias and pain have been declared but not proved to be due to hyperglycemia in these patients. The relationship between hyperglycemia and neuropathy is still not definite because the neuropathy can regress in these patients despite poor glucose control [48].

3. Insulin neuritis

The insulin neuritis is usually characterized by symmetric neuropathy with acute onset of severe distal limb pain and autonomic dysfunction in relation to intensive glycemic control following the institution of insulin or intake of oral hypoglycemic agents (predominantly small-fiber neuropathy manifesting with pain and paresthesia) [48, 87-89]. Typical cases occur after several episodes of protracted hypoglycemia with mostly insulinoma [48]. A classic patient may complain of distal paresthesia similar to DSPN. Although insulin neuritis involves the upper extremities more than the lower extremities, footdrop is also common [48]. Neuropathic symptoms such as hyperalgesia and allodynia which are refractory to medications persist for weeks or months and regress after control of hypoglycemia [47, 48].

C. Transient asymmetric neuropathies (Acute, painful, sensory-motor type)

1. Diabetic radiculoplexus neuropathies

They are acute or subacute forms of neuropathy and presents commonly with abrupt onset of pain followed by weakness and primarily affect patients

with mild diabetes [1]. The symptoms progress, then stabilizes and gradually improve over a few weeks. There are three types of radiculoplexus neuropathy named according to location.

a- Cervical radiculoplexus neuropathy: It is a very uncommon form of the radiculoplexus neuropathy.

b- Thoracic radiculoneuropathy: It typically presents with abrupt onset severe pain (burning, stabbing or belt like) with contact hyperesthesia along the thoracic spine, chest, rib cage or upper abdominal wall. Popping out of the abdominal wall may come because of muscle weakness. Truncal radiculoneuropathy can be symmetrical and involve multiple dermatomes, so it may be confused with intra-abdominal or thoracic disease or herpes zoster [1, 4, 90]. Needle EMG findings include fibrillations in the paraspinous or abdominal wall muscles [65].

3- Lumbar radiculoplexopathy: It causes the most morbidity and known by different names, including diabetic amyotrophy, Bruns-Garland syndrome, diabetic mononeuritis multiplex, diabetic polyradiculopathy, proximal diabetic neuropathy, and others [1, 90]. Motor involvement is predominant and weakness and wasting in the thigh are seen after unilateral severe pain to be more severe at night in the anterior thigh, buttock, lumbar area or knee. The distal muscles of the leg are rarely involved. Knee jerk is absent [1, 90].

2. Diabetic mononeuritis multiplex

Mononeuritis multiplex (MNM) is a syndrome of painful, unilateral or asymmetrical, asynchronous sensory and motor multiple neuropathies at least 2 separate nerve areas [90, 92]. The areas affected by MNM depend on the underlying cause of the condition. This case of neuropathy tends to occur in older patients with relatively mild cases of diabetes. After the abrupt onset of pathology because of occlusion of the vasa nervosum in one nerve, multiple nerves are affected in a random distribution. As the condition worsens, it becomes less multifocal and more symmetrical. Individuals with diabetes typically present with acute onset of severe, unilateral thigh pain that is followed rapidly by weakness and atrophy of the anterior thigh muscles and loss of the knee reflex (see diabetic amyotrophy) [1, 90]. As mononeuropathy multiplex or multifocal neuropathy can occur with diabetes mellitus, it can be also associated with many different conditions such as infections,

rheumatological disorders, cancer-related conditions and hematological conditions. In electrodiagnostic studies, a reduction in the motor and sensory nerve action potential amplitudes and minimal alterations in nerve conduction velocity are seen in the patients with MNM [92]. In diabetic multifocal motor neuropathy, mild inflammatory infiltrates and loss of axons may be observed in addition to conduction blocks [48, 92]. The needle electrode examination findings can vary and acute and chronic denervation may be seen depending on the severity and time course of the disorder. Nerve biopsy may be required as part of the diagnostic evaluation in cases with vasculitis which is usually treatable with immunosuppressive medications [48]. Any condition with asymmetrical polyneuropathy is considered in the differential diagnosis of MNM. As last words, the usual causes need to be pursued (vasculitis, infections, and hereditary) if a diabetic patient develops a true MNM [65].

3. Cranial neuropathy

The upper cranial nerves are affected (third, sixth, rarely fourth and seventh in order of frequency) [48, 93]. Diabetic third nerve palsy presents acute ophthalmoplegia with abrupt onset of pain behind or above the eye, followed by double vision, unilateral ptosis, paresis of the oculomotor innervated muscles and sparing of the pupil which is the hallmark of diabetic third nerve palsy [48, 93]. Cranial neuropathy is attributed to presumed microvascular ischemia of nerve [93, 94]. If there is pupillary involvement or absence of pain, there is concomitant autonomic nerve involvement or aneurysm which must be excluded by neuroimaging [93, 94]. Typically, cranial neuropathies in diabetes mellitus improve and settle within 2 to 3 months [48, 93, 94]. Imaging studies may be required to rule out stroke in some shells. Nevertheless, history alone without additional testing is sufficient in the bulk of these patients [65]. Pupillomotor function impairment (e.g., decreased diameter of dark adapted pupil) and Argyll-Robertson pupil abnormality can be seen as a result of autonomic dysfunction [1].

4. Mononeuropathies

Mononeuropathies often emerge during periods of transition in the diabetic illness, or when there has been rapid weight loss and nerve entrapment seems to be more common than nerve infarction [89, 90]. The nerves most frequently affected are the femoral, sciatic and peroneal ones in that order. Patients with diabetes are also at increased risk of entrapment

mononeuropathy. A higher prevalence of compressive neuropathies of median or ulnar nerves exists in patients with diabetes in comparison to the general population [48]. The second most commonly seen neuropathy in the patients with diabetes is carpal tunnel syndrome, which is 3 times more common in comparison to normal population [6, 89, 90]. The mononeuropathies are easily can be diagnosed using electromyography.

D. Diabetic autonomic neuropathy (DAN)

All organs are susceptible to autonomic dysfunction because vasomotor, visceromotor, and sensory nerve fibers innervate every organ. DAN is a widespread disorder and may be manifested by dysfunction of one or more organ systems. DAN typically affects both parasympathetic and sympathetic parts of the autonomic nervous system, so it results in cardiovascular, gastrointestinal, urination, sweating, pupils, and metabolic disturbances [48, 95]. Clinical symptoms of DAN generally do not occur in early phases of diabetes and it manifests first in the vagus nerve which is the longest of the ANS nerves. The cardinal signs of DAN are orthostatic/postural hypotension, orthostatic bradycardia and orthostatic tachycardia, resting tachycardia, exercise intolerance, decreased hypoxia-induced respiratory drive, impaired heart rate variability, heart rate unresponsiveness to respiration and abnormal blood pressure regulation. [48, 96]. Because of all these problems mentioned above, DAN may be linked to increased incidence of asymptomatic ischemia, myocardial infarction, and decreased rate of survival after myocardial infarction [95, 96]. Age, duration of diabetes, obesity, smoking, and poor glycemic control are risk factors increasing DAN prevalence [96]. What a pity, most of the cases with DAN have subclinical forms without the presence of signs and symptoms and they are detectable only by tests [48, 96]. Subclinical forms of DAN may be detected within 1 year of diagnosis with type 2 diabetes and within 2 years of diagnosis with type 1 diabetes [48, 96, 97]. Although cardiovascular autonomic neuropathy (CAN) is the most clinically important and easily-studied form of DAN, DAN involving other organ systems should also be viewed in the optimal care of patients with diabetes.

1. Cardiovascular Autonomic Neuropathy (CAN)

There is a problem of autonomic control of the cardiovascular system in CAN and the earliest manifestations of autonomic neuropathy in diabetes

tend to be associated with parasympathetic denervation because of vagal involvement which represents the longest fibers [48, 95]. Reduced heart rate variation is the earliest indicator of CAN and it increases mortality rate because of myocardial infarction or malignant arrhythmia [95, 97].

Symptoms and signs: Unexplained tachycardia or bradycardia, orthostatic hypotension and poor exercise tolerance should be assessed for the presence of CAN [48].

Tests: Nowadays it is possible to objectively identify early stages of CAN with the usage of different autonomic function tests. Screening tests should be performed particularly in the patients with DSPN, poor glycemic control, cardiovascular risk factors, and vascular diabetic complications [52]. In comparison of a variety of simple, validated, and noninvasive tests (e.g., Valsalva maneuver, Handgrip test, Heart rate response to deep breathing and standing, and blood pressure response to standing), valsalva maneuver and heart rate variation tests are more common than others [52, 95-97].

a- Exercise intolerance: When you begin to exercise, your heart rate increases rapidly to the level necessary to meet the metabolic needs of increased activity. Diabetic patients who are likely to have CAN show a reduced response in heart rate and blood pressure during exercise and it is called as exercise intolerance [95]. Degrees of exercise intolerance can vary and it can exhibit itself after the mildest exertions or require more sustained effort to be recognized. Fatigue, cyanosis, muscle cramps, insufficient heart rate, blood pressure changes and depression are the most common signs of exercise intolerance [95-96].

b- Orthostatic hypotension: Orthostatic hypotension is defined by consensus as a fall in blood pressure of at least 20 mmHg systolic and/or 10 mmHg diastolic within three minutes in an upright position. Blood pressure and heart rate are measured after 5 min supine and at 1 and 3 min after standing; patients unable to stand may be assessed while sitting upright. Hypotension without a compensatory increase in heart rate (< 10 beats/min) suggests autonomic impairment. Faintness, light-headedness, dizziness, confusion, or blurred vision with postural changes is seen. Symptoms occur within seconds to a few minutes of standing and resolve rapidly on lying down. Exercise or a heavy meal may exacerbate symptoms [96]. Questionnaires may be used to investigate orthostatic symptoms and their severity in

dysautonomic conditions [1, 96].

c- Heart rate variability (HRV): Heart rate variability (HRV) is the physiological phenomenon of variation in the time interval between heartbeats. When the autonomic system is intact, heart rate increases in response to inspiration. Autonomic function can be evaluated with bedside cardiac monitoring. The autonomic evaluation consisted of measuring HRV for 30 min in supine position in absence of any physical, sensory, or pharmacological stimuli. R-R variation between supine and standing position is measured. If R-R supine/R-R standing is lower than 1.03, it is accepted as abnormal [95, 98, 99]. Patients with abnormal R-R intervals or with autonomic symptoms or signs require further evaluation for diabetes [95, 98, 99].

2. Gastrointestinal Autonomic Neuropathy (GAN)

It is difficult to evaluate gastrointestinal autonomic function in humans. Gastroparesis is the most debilitating complication of GAN [1, 99]. The diagnosis of GAN is often one of exclusion, because many of the gastrointestinal symptoms related to sympathetic and parasympathetic nervous systems may be seen [52, 96]. GAN symptoms are associated with poor glycemic control, malnutrition, abnormal postprandial regulation of blood pressure, poor quality of life, and a high rate of hospitalization in the patients [52, 100].

Symptoms and signs: Nausea, bloating, dysphagia and chest pain secondary to esophageal dysmotility, constipation and abdominal pain secondary to gastroparesis, diarrhoea, and fecal incontinence may be seen. Up to 75% of patients with diabetes can experience these symptoms mentioned [100].

Tests: Objective gastric emptying measurement may be used for the diagnosis of gastroparesis. To quantify gastrointestinal symptoms, the Diabetes Bowel Symptom Questionnaire is applicable [52].

3. Erectile Dysfunction

Erectile dysfunction or impotence is the inability to develop or maintain an erection of the penis during sexual activity. The most important organic causes are aging (>60 years of age), cardiovascular disease and diabetes. Adverse or unanticipated drug interactions, obesity, sex (hypogonadism and prolactinoma), medical causes (groin hernia, trauma from prostatectomy surgery, multiple sclerosis, kidney

failure), drugs (SSRIs and nicotine), alcohol use, tobacco use and psychosocial causes (anxiety, mental disorders, stress) are potential risks [52]. Erectile dysfunction affects 30-40% of diabetic men and is an early marker of cardiovascular risk because of endothelial dysfunction [1]. The use of validated questionnaires such as the international index of erectile function or quality of erection questionnaire is the most appropriate method to evaluate the erectile dysfunction symptoms [52, 101, 102]. In practice, the problem is likely to be physiological if the patient never has an erection; it could be physiological or psychological if sometimes (however rarely). Duplex ultrasound exam, the bulbocavernosus reflex test, nocturnal penile tumescence assessment and cavernosography are the most commonly used investigations to determine erectile dysfunction. Specific testing may be recommended in patients not responding to phosphodiesterase-5 inhibitor which is the first effective oral treatment available for erectile dysfunction [52]. In female with genitourinary autonomic neuropathy, loss of lubrication is seen [95, 99]. Retrograde ejaculation due to neuropathy of the bladder sphincter is another complication of diabetes [99].

4. Diabetic Sudomotor Dysfunction

Loss of thermoregulatory sweating in a 'glove and stocking' distribution that can extend to the upper parts of the limbs and the anterior abdomen, confirms the length dependency of diabetic neuropathy. Not only anhidrosis but also hyperhidrosis can be seen as a sign of DAN [1, 103]. Abnormal production of sweat that appears over the upper part of the body after consumption of even non-spicy foods, occurs in occasional cases [103]. The quantitative sudomotor axon reflex test is capable of detecting distal small-fiber polyneuropathy with a sensitivity of 75% [52].

5. Diabetic Bladder Dysfunction

In patients with diabetes and bladder dysfunction, sensory and autonomic nerve fibers are affected [104]. Patients often remain asymptomatic in early stages and impaired bladder sensation is usually the first manifestation of lower urinary tract involvement [1]. The usual symptoms are straining, hesitation and weakness of stream [52, 104]. Impaired sensation of bladder fullness leads to overstretched bladder, reduced bladder contractility, increased residual urine and impaired outflow in the patients with diabetic bladder dysfunction [104].

Conclusion

DSPN and carpal tunnel syndrome are commonly experienced problems in the patients with diabetes. Clinical evaluation and use of scoring systems for the evaluation of diabetic polyneuropathy is an important step to get a correct diagnosis. NCSs confirm the diagnosis of DSPN, entrapment neuropathies, MNM or radiculoplexopathy. SWME (1-10 g), vibrating test and ankle reflex can be used confidently for annual screening of diabetic neuropathy in diabetic patients. By using both the SWME and vibration tests, it can be differentiated non-diabetic control subjects from subjects with diabetes, as well as subjects with diabetes with and without neuropathy. The DN4 questionnaire is utilized for the evaluation of neuropathic pain. The primary advantage of this screening instrument which is comfortable to use and delivers a good diagnostic performance is to identify potential patients with neuropathy, especially by non-specialists. Because neuropathy at the stage in which only small characters are affected can be annulled, it is important to diagnose DSPN in early phases. Skin biopsy taken from the dermatomal area of the sural nerve, laser-doppler-imager flare technique, corneal confocal microscopy are used to assess small fiber dysfunction in these patients with peripheral neuropathy, with the aim to demonstrate specific findings for diagnosing small fiber neuropathy.

Conflict of interest

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