Diabetic Neuropathy

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Remark

The DDG's clinical guideline "Diabetic Neuropathy" emerged on the basis of the National Disease Management Guideline "Neuropathy in Adults with Diabetes, Long Version, Version 1.2 of 28 November 2011, based on the version of August 2011: German Medical Association (BÄK), German Association of Statutory Health Insurance Physicians (KBV), German Association of Scientific Medical Organisations (AWMF). National Disease Management Guideline "Neuropathy in Adults with Diabetes– Long Version, Version 1.2, 2011 [cited 1 Aug. 2012]. Available in the Internet at http://www.diabetes.versorgungsleitlinien.de, http://www.versorgungsleitlinien.de, http://www.awmf-leitlinien.de.

Diabetic Sensorimotor Polyneuropathy

Definition, Risk Factors and Comorbidities

Diabetic neuropathy is a clinically manifest or subclinical disease of the peripheral nerves, which occurs as a consequence of diabetes mellitus or other underlying causes. It can affect the somatic and/or autonomic nervous system. The risk of distal symmetric polyneuropathy and autonomic neuropathy increases with the following risk factors, indicators and co-morbidities:

- Duration of diabetes
- Glycaemic control (hyperglycaemia)
- Arterial hypertension
- Peripheral artery disease (PAD)
- Mönckeberg's medial sclerosis
- Diabetic retinopathy and nephropathy
- Depression
- Visceral obesity
- Hyperlipidaemia
- Alcohol and/or nicotine abuse
- Insufficient physical activity
- Demographic factors (age, height, weight)

Distal symmetric sensorimotor polyneuropathy contributes to the aetiology of diabetic foot syndrome in 85-90 % of cases and is thus of paramount significance in the risk constellation for foot ulcers and amputation. In addition, it is deemed an important predictor of cardiovascular morbidity and mortality.

The prevalence of polyneuropathy in patients with manifest type 1 and type 2 diabetes is approximately 30 %. Some 13-26 % of diabetic patients have painful neuropathy.

Course of Disease

Based on clinical criteria, various courses of the disease have been identified:

- Subclinical neuropathy (no symptoms or clinical findings, but pathological quantitative neurophysiological tests)
- Chronic painful neuropathy (frequent)
- Acute painful neuropathy (insulin neuritis) (rare)
- Painless neuropathy (frequent)
- Focal neuropathies, e. g. diabetic amyotrophy (rare)
- As a complication, diabetic neuropathic foot syndrome with foot ulceration, Charcot neuro-osteoarthropathy and amputation.

Screening

Screening for diabetic sensorimotor polyneuropathy should encompass the following data and examinations (always bilateral):

- History with personal basic data and diabetes-specific data (see H3 "Basic Diagnostic Work-Up) as well as risk factors/indicators and clinical correlations for diabetic sensorimotor polyneuropathy
- Assessment of neuropathic positive and negative symptoms (e. g. sensory abnormalities, pain, cramps, numbness), especially patient-reported pain intensity, pain localisation, and pain triggering situations (using validated questionnaires).

Bibliography
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- Inspection and clinical examination (skin colour, trophic changes, foot deformity, foot ulcer, injuries, skin temperature)
- Screening for foot complications and PAD (see national disease management guideline "Type 2 Diabetes Foot Complications").
- Simple neurological examination methods: testing the ankle reflex, vibration sensation (using the 128-Hz tuning fork according to Rydel-Seiffer) as well as assessing the pressure and touch sensation with a 10-g monofilament. If any one of the above three examinations yields pathological findings, a basic diagnostic work-up should be performed.

In people with type 2 diabetes, screening for diabetic sensorimotor and/or autonomic neuropathy should take place at the time of initial diagnosis of diabetes, and in people with type 1 diabetes not later than five years after diabetes diagnosis.

Basic Diagnostic Work-Up

The basic diagnostic work-up includes those examinations conducted by an office-based general practitioner, internist or diabetologist that are absolutely required in order to diagnose diabetic sensorimotor polyneuropathy and to identify risk patients early on. In addition, complications of diabetic neuropathy (e.g. foot complications) should be diagnosed and treated at an early stage. Both legs and feet should be inspected, clinically examined and comparatively evaluated. A diagnostic work-up should be conducted in all symptomatic patients, especially in those with pain of unknown origin or other neuropathic symptoms, as well as in all asymptomatic patients who present with a pathological test result during the screening examination (see "Screening").Inspection of the legs and feet should encompass the following:

- Skin: colour, turgor, fissures, blister formation, subcutaneous haemorrhages;
- Hyperkeratosis and callus formation;
- Healed foot lesions, hypohidrosis / anhidrosis;
- Signs of bacterial and/or fungal infection;
- Foot deformities (e.g. neuro-osteoarthropathy (Charcot arthropathy), hammer toes, claw toes);
- Foot ulcer with exact description of localisation, extent and concomitant infection.

Clinical examination should encompass the following:

- Peripheral pulse status (palpation of the foot pulses in the posterior tibial artery and the dorsalis pedis artery on both sides);
- Checking skin temperature, skin turgor and sweating;
- Orienting assessment of foot deformities as a sign of diabetic neuro-osteoarthropathy (DNOAP or Charcot arthropathy) as well as orienting assessment of muscle and joint function;
- Judgement of the patient's gait, optical and touch control of shoes and inlays (changes to the upper and lining material, excessive wear-out of the soles, footprint on the inlays, wound secretions on the inlays, wear-and-tear of the padding material).

Acute changes to the skin, soft tissue or joints with or without trauma strongly suggest a serious complication. Hence, infection or diabetic neuro-osteoarthropathy (DNOAP or Charcot arthropathy) must be ruled out in such cases. An infection is indicated by the presence of a skin lesion (entry site). For this reason, the skin should be carefully examined for lesions.

Subjective symptoms are clinically evaluated using the Neuropathy Symptom Score (NSS); the severity of sensory deficits is clinically assessed using the Neuropathy Disability Score (NDS).

Minimal criteria for the diagnosis of neuropathy are (**Fig. 1**):

- moderate neuropathic deficits (NDS 6-8 points) with or without symptoms, or
- mild neuropathic deficits (NDS 3-5 points) with moderate symptoms (NSS 5-6 points).

Accordingly, the presence of mild deficits (NDS 3-5 points) alone or in combination with mild symptoms (NSS 3-4 points) does not yet justify a clinical diagnosis of polyneuropathy. Motor function is tested by checking the ability to spread one's toes, stretch one's toes and feet (toe walking), bend one's toes and feet against resistance (make claws), as well as by assessing heel walking.

If present, the intensity of neuropathic pain is recorded using the Numeric Rating Scale (NRS): 11 ratings on a scale of 0 = no pain to 10 = worst pain imaginable. See **Table 1** for simple neurological examination methods for diagnosing diabetic sensorimotor neuropathy.

Follow-Up

The intervals of follow-up examinations and, as appropriate, any necessary advanced diagnostic work-up (see below) are based on the individual risk. If no neuropathy is present, a neuropathy screening should be carried out once a year. If the screening reveals a suspicion of the presence of neuropathy, the diagnosis should be ascertained using the methods of basic diagnostic work-up, possibly by adding advanced diagnostic procedures. In case of suspicion or presence of diabetic neuropathy, at least semi-annual follow-up of neuropathy should take place depending on the individual disease situation. If peripheral arterial disease and/or foot deformities are present in addition, examination intervals of three months are recommended.

Advanced Diagnostic Work-Up

If the suspected diagnosis of diabetic neuropathy based on symptoms cannot be ascertained by the basic diagnostic work-up, specific investigations (electroneurography and particularly quantitative sensory testing, if a so-called small fiber neuropathy is suspected) should be performed. To this end, the patient should be referred to a physician familiar with the aforementioned methods.

In case of aetiologically unclear or treatment-resistant pain, a physician with experience in diagnosing and treating pain should be involved. The pain documentation should preferably contain an indication of the level (intensity) and subjective severity or endurability (tolerability) of pain as well as documentation of the constellations triggering the pain (pain at rest, pain evokable by touch and/or load-dependent pain [standing, walking]). The latter are atypical for painful neuropathy.

Important Differential Diagnoses

Differential diagnosis includes medications (e.g. cytostatic drugs), metals, toxins (e.g. alcohol), kidney disease, PAD, vitamin B deficiency (B1, B6, B12), tumours, paraproteinemias, infections (e.g. HIV, Lyme disease), vasculitides, inherited neuropathies, endocrine disorders (hypothyroidism, acromegaly), immune neuropathies, and impingement syndromes.

The process of diagnostic exclusion should be based on the following minimally required standard battery of laboratory tests: complete blood count, creatinine, ESR, TSH, vitamin B12, folic acid, alanine aminotransferase (ALAT), gamma-GT, immunoelectrophoresis. Referral to a neurologist is indicated if one or more of the following constellations of findings apply:

- Motor deficits predominate over the sensory deficits;
- Rapid development and progression of symptoms;
- Marked asymmetry of the neurological deficits, mononeuropathy and cranial nerve dysfunction;

- Progression of symptoms despite optimisation of glycaemic control;
- Initial symptoms in the upper extremities;
- Other neurological symptoms beyond the diabetic polyneuropathic syndrome;
- Family history of neuropathy.

Referral to a pain management specialist is indicated if the aetiology of pain remains unclear and/or the symptomatic basic pain therapy described below is not sufficiently effective or not tolerated.

General Treatment Strategies and Prevention

Important goals of therapy in patients with type 1 or type 2 diabetes include the improvement in quality of life, increase of competence (empowerment) of the persons concerned in dealing with their disease, the prevention of microvascular (retinopathy, nephropathy) and macrovascular complications, neuropathy and diabetic foot syndrome as well as the prevention and treatment of symptoms of the disease. The goals of therapy should be individualized both in patients with type 1 and those with type 2 diabetes. These goals depend on, among others, (co-)morbidity, age, life expectancy and quality of life of the persons affected.

In all forms and at all stages of neuropathy patients should be advised concerning their lifestyle habits, diabetes therapy and foot care. Depending on the patient's requirement, appropriate therapists and possibly relatives should be integrated in a problem-oriented manner. In patients with type 1 and type 2 diabetes, glycaemic control should be adapted to the individual patient and his comorbidity and risk profile.

Early surveillance of metabolic control and existing risk factors (e.g. smoking, excessive alcohol consumption, arterial hypertension) in people with diabetes may prevent or at least retard or slow down the progression of diabetic neuropathy. Patients with diabetic neuropathy should be recommended to consume alcohol in moderate amounts at most and give up smoking.

Patients with diabetic polyneuropathy and sensory loss with or without foot deformities/disproportions should receive guideline-based shoe provision.

Pain Therapy

If the patients with diabetic sensorimotor polyneuropathy do not feel hampered in their daily lives, it is not necessary to treat their symptoms. Successful individualized pain therapy starts with a pain analysis. Pharmacotherapy provides symptomatic relief. It should be supplemented by non-pharmacological therapeutic modalities. A detailed medication history should be taken before starting medication therapy. Selection of pharmacotherapy for diabetic sensorimotor polyneuropathy should give due consideration to contraindications and frequent co-morbidities. Non-invasive, non-pharmacological therapeutic modalities such as psychotherapy/behavioural therapy, transcutaneous electrical nerve stimulation (TENS), muscle stimulation (*high tone* external *muscle* stimulation) and acupuncture may be included in the multimodal pain management. If a patient does not achieve adequate pain relief after 12 weeks of therapy and the pain has a major negative impact on his/her quality of life, a pain management specialist should be consulted for further therapy.

Principles of Medication Therapy for Painful Diabetic Polyneuropathy

1. Therapy for painful diabetic polyneuropathy offers symptomatic relief; it does not treat the underlying cause.
2. Medical therapy for chronic neuropathic pain associated with diabetes mellitus should begin as soon as possible if the pain negatively impacts the patient's quality of life.
3. Pain therapy should not merely mitigate pain; it should also improve the quality of sleep, mobility and overall quality of life.
4. The medication is selected on the basis of the efficacy and general risk profile of the substances under consideration of known or potential comorbidities.
5. If medications show comparable analgesic efficacy, the medication with the lowest organ toxicity and particularly with the lowest risk for cardiovascular and renal side effects should be selected.
6. Consequently, substances with increased renal and cardiovascular long-term risks (e.g. NSAIDs, coxibs) are not indicated for therapy of diabetic neuropathic pain.
7. Analgesic efficacy should be tested individually.
8. The required dose should be titrated individually to the lowest effective dose, whereby the maximum allowed dose should not be exceeded.
9. The efficacy of pharmacotherapy should not be assessed earlier than two weeks after an adequate dose has been achieved. Medications without analgesic efficacy should not be further prescribed.
10. Analgesic combination therapy is recommended only if the combination improves the effectiveness of each individual component and/or lowers the risk by reducing the doses of the individual components.
11. Psychotropic drugs without analgesic potency are not indicated for pain therapy. Combination preparations with caffeine, benzodiazepines or muscle relaxants are not indicated and carry a risk of abuse and dependency.

The following realistic objectives of medication therapy for neuropathic pain should be aimed at:

1. Pain reduction of 30-50% on the 11-point Visual Analogue Scale (VAS) or the Numeric Rating scale (NRS);
2. Improvement of sleep quality;
3. Improvement of quality of life;
4. Maintenance of social activities and participation;
5. Maintenance of the ability to work.

The aforementioned therapy objectives must be discussed with the patient both before and during the course of therapy in order to keep the patient's expectations at a realistic level. In this way disappointments are avoided which may result in pain amplification. See also the algorithm for pharmacotherapy of painful diabetic sensorimotor neuropathy (**Fig. 2**).

Diabetic Autonomic Neuropathy

Classification and Prognosis

Apart from diabetic sensorimotor polyneuropathy, diabetic autonomic neuropathy (DAN) is the most frequent form of peripheral neuropathy. Only function tests are able to distinguish between symptomatic and asymptomatic manifestations. Generally speaking, DAN can affect any organ supplied by the autonomic nerves. DAN is classified by the organs and functional systems affected, based on clinical criteria (see **Table 2** "Practice Tools").

The pathomechanisms and risk factors discussed for the pathogenesis of DAN are principally the same as for diabetic sensorimotor polyneuropathy.

In light of the current knowledge, DAN undoubtedly has significant negative consequences in terms of reduced life expectancy, increased risk for end-organ damage and impaired quality of life. The risk of mortality within 16 years is 3.5-fold increased in diabetic subjects diagnosed with diabetic cardiovascular autonomic neuropathy (DCAN) by at least 2 tests compared to those without DCAN.

Screening

There are no suitable test procedures available for screening for diabetic autonomic neuropathy. However, the following symptoms can serve as an indication, albeit with low specificity and sensitivity. These symptoms should be recorded at the screening intervals in the context of early detection.

- Resting tachycardia
- Gastrointestinal symptoms (dyspepsia, constipation, diarrhoea, faecal incontinence)
- Disorders of bladder function, sexual dysfunction
- Hypoglycaemia unawareness
- Disordered sweat secretion
- Blood glucose fluctuations that cannot be explained otherwise

The Survey of Autonomic Symptoms (SAS), a simple questionnaire with 12 questions for autonomic symptoms, has recently been validated (Zilliox et al., Neurology 2011; 76: 1099-1105) and translated into German (Jost et al., Diabetologie 2012; 7: 30-32).

Diagnostic Work-Up

The patient should be asked about the symptoms of autonomic dysfunction when the medical history is taken, especially in view of the need to establish a differential diagnosis and the option of choosing a symptomatic, organ-specific therapy. The full-blown clinical picture of symptomatic DAN affecting multiple organs is encountered only rarely. Usually, the clinical picture shows a heterogeneous pattern of symptoms originating from various organ systems. This can lead to erroneous interpretations (see Practice Tools, **Table 2**).

When diagnosing diabetic sensorimotor neuropathy, possible manifestations of DAN should also be considered, as DCAN coexists in some 50 % of the cases. Likewise, there are also correlations between DAN and other chronic complications of diabetes (retinopathy, nephropathy).

The diagnostic approach is basically the same as for sensorimotor neuropathy (see above). In addition, cardiovascular autonomic function tests and organ-specific examinations are performed in collaboration with other specialists (**Table 2**). The basic diagnostic work-up encompasses all examinations carried out by office-based general practitioners, internists, and diabetologists as a minimum standard. Advanced diagnostic work-up is performed by specialists: neurologists/cardiologists for evaluation of syncope, gastroenterologists for gastrointestinal symptoms, and urologists for urogenital disorders.

Diabetic Cardiovascular Autonomic Neuropathy (DCAN)

As an early sign of damage to the vagal nerve, DCAN is manifested as a reduction of heart rate variability (HRV), which is frequently detected before manifestation of clinical symptoms of cardiovascular and other organ systems. Advanced DCAN is characterised by an increase in resting heart rate (primarily vagal lesion) and orthostatic hypotension (primarily sympathetic lesion). According to the recommendations of the *Toronto Consensus* Panel on Diabetic Neuropathy, initial diagnostic work-up and follow-up should include at least two autonomic reflex tests for the detection of DCAN: heart rate variability (HRV) and the orthostatic test. Hence, the basic diagnostic work-up includes measurement of HRV during deep breathing and upon standing up, as well as blood pressure changes during the orthostatic test, with the following diagnostic constellations:

1. One abnormal HRV test: possible or early DCAN, which needs to be confirmed in further course;
2. At least two abnormal HRV tests: definitive or confirmed DCAN;
3. Orthostatic hypotension in addition to abnormal HRV tests: severe or advanced DCAN.

1.) Heart Rate Variability during deep breathing Examination Procedure

To measure HRV during deep breathing, the supine subject breathes at a rate of 6 breath cycles per minute for 1-2 minutes. Each inspiration and each expiration lasts 5 seconds. The "E/I ratio" (R-Rmax / R-Rmin) is computed from the cycle with the longest R-R interval during expiration (R-Rmax) divided by the shortest R-R interval during inspiration (R-Rmin).
Normal values: age: 20-30 yr ≥ 1.12; age: 31-49 yr ≥ 1.11; age 50-69 yr ≥ 1.10; age ≥ 70 yr ≥ 1.09.

2.) Heart Rate Variability in response to standing up Examination Procedure

The supine subject stands up next to the examination couch. The ECG recording is started the moment the subject begins to rise. As a HRV measure the "30:15 ratio" (R-Rmax / R-Rmin) is defined as the longest R-R interval between beats 20 and 40 divided by the shortest R-R interval between beats 5 and 25 after standing up.
Normal values: age: 20-49 yr ≥ 1.10; age: 50-79 yr ≥ 1.09; age ≥ 80 yr ≥ 1.08.

3.) Orthostatic Test Examination procedure

For the orthostatic test, the blood pressure is taken two times within one minute in the supine position and subsequently directly after standing up and thereafter every 30 seconds for 3 minutes. The normal range for the decrease in systolic blood pressure is ≤ 27 mmHg. Other professional societies have recommended that orthostatic hypotension be diagnosed in the presence of orthostatic symptoms when the decrease in systolic blood pressure is ≥ 20 mmHg.

All symptomatic patients in whom a basic diagnostic work-up has not led to a definite abnormal finding undergo further, computer supported tests performed by a specialist. In addition to securing the diagnosis, these tests serve to establish the severity and risk assessment or prognosis of DCAN.

Gastrointestinal Autonomic Neuropathy

Gastrointestinal symptoms occur frequently in patients with diabetes mellitus. They lead to significantly impaired quality of life and require a diagnostic work-up and differential diagnosis. The history recorded during the basic diagnostic work-up should include detailed information about the following signs and symptoms: gastrointestinal symptoms including dysphagia and odynophagia, abdominal pain, nausea, vomiting, feeling of fullness,

bloating, diarrhoea, constipation, faecal incontinence, and blood in stool; duration and possible worsening of gastrointestinal symptoms; presence of B-symptoms (fever, weakness, weight loss) and their impact on quality of life.

Structural and infectious diseases should be excluded for all new-onset complaints which have not yet been adequately diagnosed and which display a progressive course or are accompanied by warning symptoms such as bleeding, anaemia, early satiety, unexplained loss of weight in excess of 10 %, dysphagia or odynophagia, persistent vomiting, family or personal history of gastrointestinal tumours, previous peptic ulcers, enlarged lymph nodes, palpable masses, malnutrition, blood in stool, paradoxical diarrhoea, age> 50 years. When symptoms last longer than 4 weeks and are subjectively troublesome, it should be decided, on the basis of these symptoms, whether to refer the patient to a specialist for further diagnostic work-up immediately or to try therapy first.

It is especially important to exclude relevant differential diagnoses, because numerous serious gastrointestinal disorders can manifest only through mild and/or non-specific symptoms, especially at their early stages. This applies, for example, to all gastrointestinal malignancies as well as disorders such as coeliac disease and peptic ulcer.

Autonomic Neuropathy of the Urogenital Tract

Diabetic cystopathy (neurogenic bladder) is considered to be primarily a neurogenic sensorimotor dysfunction. During basic diagnostic work-up, every patient with diabetes should be regularly asked about micturition symptoms (micturitions per day, residual urine, urinary tract infections, weak urine stream, whether straining/use of abdominal muscles is required when urinating, incontinence) as well as about satisfaction with sexual life. In addition, a medication history should be taken so that undesirable side effects on the urinary tract can be recognised. The basic diagnostic work-up should also include a micturition diary that is kept for 48 hours (frequency of micturition, voided volume and fluid intake volume). Another 48-hour micturition diary should be kept whenever the history information changes. In asymptomatic patients, the history should be taken annually.

In cases of functional sexual disorders, the basic diagnostic work-up consists of targeted history questions directed at the couple. A more thorough work-up is indicated in cases of troublesome sex life. The IIEF5 questionnaire (International Index of Erectile Function-5) is available for men (see Practice Tools, **Table 3, 4**). No suitable questionnaire is currently available for women.

Patients with micturition complaints should be referred to a urologist for further examination if they display increased residual urine (> 20 % of bladder capacity or > 100 mL) or have recurrent urinary tract infections (i. e. more than three urinary tract infections over a period of one year).

Perioperative Care

Patients with DCAN have higher perioperative morbidity and mortality than diabetic patients without DCAN. When elective surgery is to be performed, the following simple preoperative measures should be taken in order to detect any relevant autonomic neuropathies: medical history with basic personal and diabetes-specific data, risk factors/indicators and clinical correlates for diabetic sensorimotor and autonomic neuropathies; physical examination; and assessment of previous findings including previous anaesthesia charts. Extended haemodynamic monitoring in patients with diabetic neuropathy is not mandatory, not even during major surgery. Like patients without neuropathy, those with diabetic autonomic neuropathy are allowed to eat solid meals up to six hours and drink clear liquids up to two hours before anaesthesia induction.

Therapy

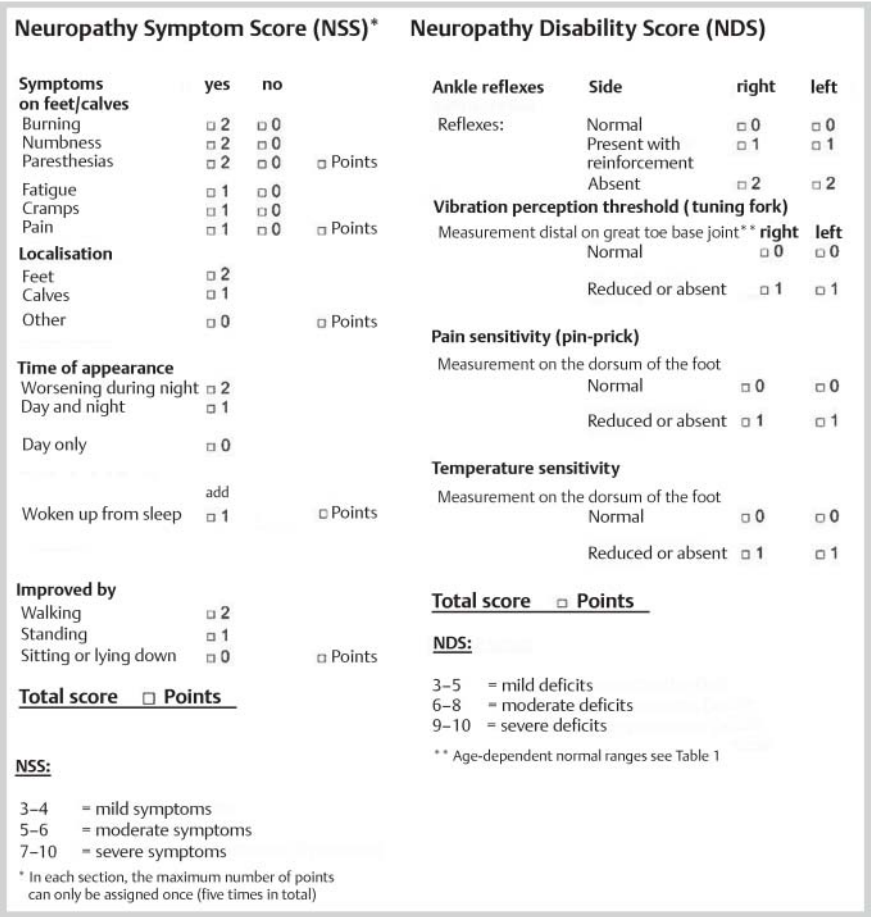
The foregoing principles of general treatment strategies for and prevention of diabetic sensorimotor neuropathy apply to autonomic neuropathies in the same way. However, in respect to pharmacotherapy of symptomatic diabetic autonomic neuropathy, it must be noted that only a few larger controlled studies are available (exception: erectile dysfunction), so that some recommendations are based on additional evidence from studies performed in patients without diabetes who had the corresponding symptoms (see Practice Tools, **Table 2**).

Therapeutic modalities for DCAN that extend beyond physical measures should be conducted only in facilities with competence in treating DCAN. Beta blockers with intrinsic sympathomimetic activity (e. g. pindolol) and tricyclic antidepressants in clinically effective dosage (e. g. amitriptyline, imipramine) should not be administered to patients with DCAN due to their unfavourable influence on HRV and increased risk of cardiac arrhythmias.

Manifest gastrointestinal disorders should be treated symptomatically and by the standards that also apply to patients without diabetes mellitus. However, diabetes specific risks and contraindications should be taken into account. Quantifiable gastrointestinal dysfunction which is not associated with subjective complaints, relevant morphological changes or impaired glycaemic control does not require treatment. Patients with diabetic gastropathy with accelerated gastric emptying should be advised to eat small meals that are distributed over the day and to avoid rapidly absorbed carbohydrates. Patients with diabetic gastroparesis should be advised to modify their diet, i. e. to eat small meals that are distributed over the day, with reduced fat and few fibres. General measures such as chewing thoroughly before swallowing and maintaining upright posture for at least 30 minutes after eating should also be recommended. If symptoms persist, prokinetic agents can be tried. These and other treatment options for symptomatic gastrointestinal disorders are given in **Table 2**.

Treatment of urinary bladder dysfunction (diabetic cystopathy) should address the patient's subjective complaints (e. g. micturition complaints, urinary tract infections). Since some of the possible consequences of diabetic cystopathy (e. g. accumulation of residual urine with subsequent damage to the upper urinary tract) can progress without symptoms or with only very discrete symptoms, a detailed and targeted history is the prerequisite for the recognition of these consequences, prevention of complications and the specific therapy. Behavioural training such as "timed voiding" (by the clock) and "double voiding" (two urinations in rapid succession) can be conducted as initial measures, because improvement of bladder voiding is possible without medication or surgical intervention. Overall,, the symptoms and consequences of diabetic cystopathy can be influenced by drug therapy and surgical interventions only to a limited extent. Urinary tract infections have to be considered as complicated in people with diabetes mellitus, if the metabolic situation is unstable and in presence of manifest diabetic complications. The duration of therapy for complicated urinary tract infections should be at least 7 days. Symptomatic pharmacotherapy of various organ and functional systems (see Practice Tools, **Table 2**) should normally be initiated by appropriate specialists within the interdisciplinary cooperation.

Annex



Neuropathy Symptom Score (NSS)*

Symptoms on feet/calves	yes	no	
Burning	□ 2	□ 0	
Numbness	□ 2	□ 0	
Paresthesias	□ 2	□ 0	□ Points
Fatigue	□ 1	□ 0	
Cramps	□ 1	□ 0	
Pain	□ 1	□ 0	□ Points
Localisation			
Feet	□ 2		
Calves	□ 1		
Other	□ 0		□ Points
Time of appearance			
Worsening during night	□ 2		
Day and night	□ 1		
Day only	□ 0		
	add		
Woken up from sleep	□ 1		□ Points
Improved by			
Walking	□ 2		
Standing	□ 1		
Sitting or lying down	□ 0		□ Points

Total score □ Points

NSS:

3–4 = mild symptoms
5–6 = moderate symptoms
7–10 = severe symptoms

* In each section, the maximum number of points can only be assigned once (five times in total)

Neuropathy Disability Score (NDS)

Ankle reflexes	Side	right	left
Reflexes:	Normal	□ 0	□ 0
	Present with reinforcement	□ 1	□ 1
	Absent	□ 2	□ 2
Vibration perception threshold (tuning fork)			
Measurement distal on great toe base joint**		**right**	**left**
	Normal	□ 0	□ 0
	Reduced or absent	□ 1	□ 1
Pain sensitivity (pin-prick)			
Measurement on the dorsum of the foot			
	Normal	□ 0	□ 0
	Reduced or absent	□ 1	□ 1
Temperature sensitivity			
Measurement on the dorsum of the foot			
	Normal	□ 0	□ 0
	Reduced or absent	□ 1	□ 1

Total score □ Points

NDS:

3–5 = mild deficits
6–8 = moderate deficits
9–10 = severe deficits

** Age-dependent normal ranges see Table 1

Fig. 1 Diagnostic criteria for diabetic sensorimotor polyneuropathy [1, 3].

Table 1 Simple neurological examination methods for the diagnosis of diabetic sensorimotor polyneuropathy (examination to be conducted bilaterally) [1,2]

Function test	Examination	Findings in diabetic sensorimotor polyneuropathy
Pain sensation	– With toothpick, disposable needle or Neurotip – It should be asked: "Is this painful?" (not: "Can you feel the needle?")	Bilateral limb section-wise demarcation (e. g. "stocking-" or "sock"-wise distribution)
Touch sensation	E. g. with cotton-wool swab	Bilateral limb section-wise demarcation (e. g. "stocking-" or "sock"-wise distribution)
Pressure and touch sensation	10 g monofilament on the plantar aspect of the 1st and 2nd metatarsal bone; plantar distal aspect of great toe; in addition, on the basis of the 3rd and 5th metatarsal bone as applicable Caveat: examination should not be carried out on spots with callus	Positive screening test: absent sensation on at least one skin location
Temperature sensation	– With cold metal (e. g. tuning fork), ice water-cooled test tube or TipTherm	Bilateral limb section-wise demarcation (e. g. "stocking-" or "sock"-wise distribution)
Vibration sensation, as measured with the 128 Hz Rydel-Seiffer tuning fork	First at great toe base joint; if no sensation is felt, examination should be carried out at a proximal location (medial malleolus)	Lower limit of normal proximal to great toe base joint: – for age 30 years: 5/8[1] – for age 50 years: 4.5/8[1] – for age 70 years: 4/8[1] Lower limit of normal at medial malleolus: – for age up to 40 years: 6/8[1] – for age above 40 years: 5/8[1]
Proprioceptive reflexes	Ankle reflex and knee reflex	Bilaterally reduced or non-evokable

[1] Lower limit of normal for vibration sensation (Martina et al., J Neurol Neurosurg Psychiat 1998; 65: 743 – 747).

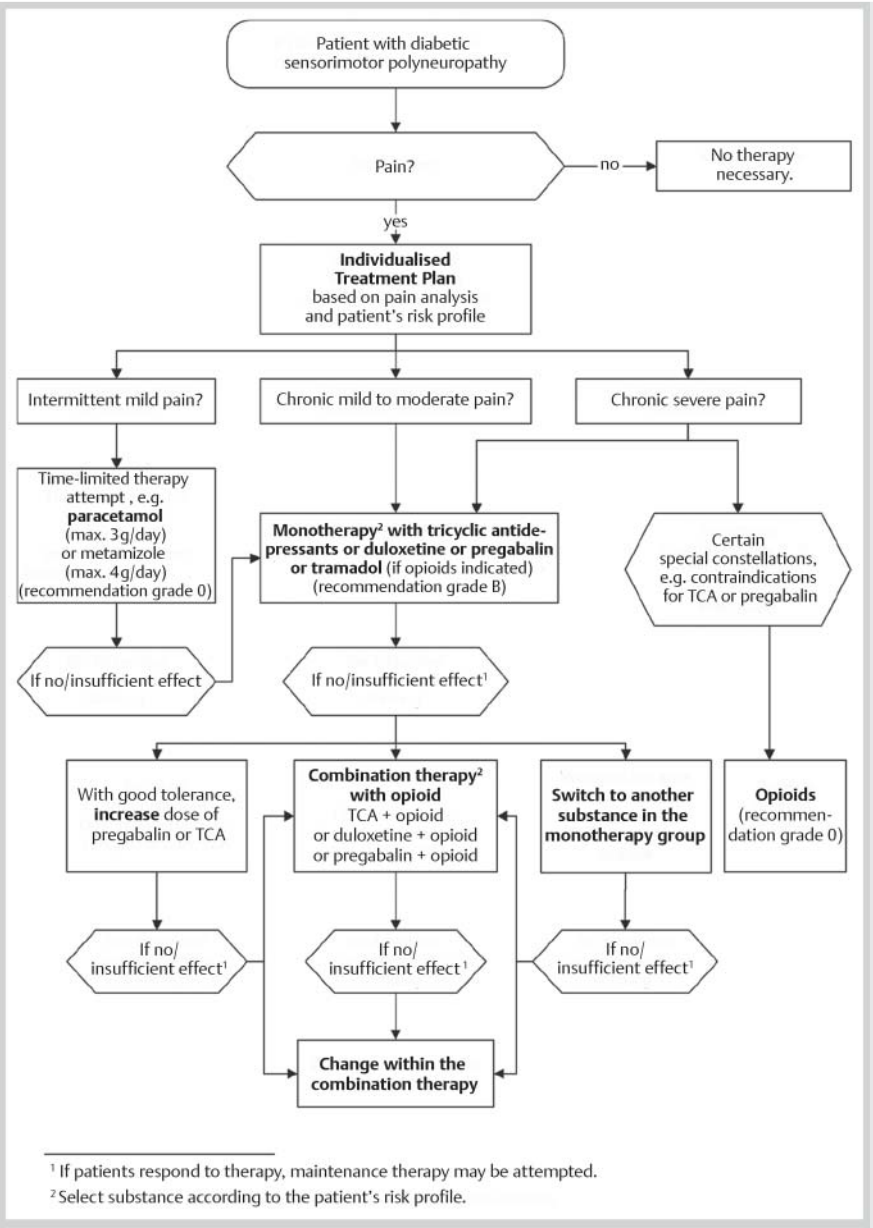


Fig. 2 Algorithm for pharmacotherapy for painful diabetic sensorimotor neuropathy [2].

Table 2 Clinically important manifestations, assigned diagnostic work-up and special therapy for diabetic autonomic neuropathy in patients with diabetes mellitus [2, 4].

Organ manifestations / clinical picture	Examination method	Therapy
Cardiovascular system		
– Resting tachycardia – Reduced heart rate variability – Orthostatic hypotension – Exercise intolerance (inadequate increase in heart rate and blood pressure during physical activity) – Perioperative instability with frequent drops in blood pressure and heart rate – Reduced or absent perception of myocardial ischaemia during physical activity – Silent myocardial infarction or myocardial infarction with few symptoms – Prolongation of the QT interval; – Sudden cardiac death	*Basic diagnostic work-up* – HRV while breathing deeply and after change of posture – Orthostatic test *Extended diagnostic work-up* Autonomic function tests: – Resting HRV (frequency and time domain – E/I ratio while breathing deeply – Max/min 30:15 ratio – Valsalva ratio (Valsalva maneuver) – Orthostatic test 24-hour HRV, syncope work-up	*Cardiovascular autonomic neuropathy* – In general, no special treatment necessary (important: diagnosis and therapy of coronary heart disease and heart failure) – For sinus tachycardia: cardioselective beta receptor blockers *Orthostatic hypotension* – General measures: liberal salt intake, physical training, compression stockings, avoidance of hypotensive medications – Medications with short half-lives that increase blood pressure (midodrine) – Fludrocortisone (start with a low dose)

Table 2 (Continued)

Organ manifestations / clinical picture	Examination method	Therapy
Gastrointestinal tract		
All gastrointestinal manifestations	*Basic GI diagnostic work-up:* – History – Exclusion of structural and infectious diseases	
Dysphagia and reflux disease	*Extended diagnostic work-up:* Stage 1: – Oesophagogastroduodenoscopy – Other imaging, as applicable Stage 2: – Oesophagus manometry – 24-h pH monitoring	*Dysphagia:* General measures Prokinetic agents in individual cases *Reflux:* Proton pump inhibitors
Diabetic gastropathy (dyspepsia, postprandial hypoglycaemia)	Stage 1: – Esophagogastroduodenoscopy – Abdominal sonography – Other imaging, as applicable – Laboratory tests Stage 2: – Gastric emptying scintigraphy – ^{13}C-octanoic acid breath test	Gastroparesis (gastropathy): – Dietary change: frequent, small, low fibre meals with less fat – Adjust injection to meal interval – Prokinetic agents: metoclopramide, domperidone Erythromycin (off-label) For severe refractory symptoms: – Gastric electrical stimulation (“gastric pacemaker”) – Jejunal feeding tube – Parenteral nutrition
Diabetic cholecystopathy	Laboratory tests Abdominal sonography	
Diabetic diarrhoea (enteropathy) and exocrine pancreatic insufficiency	Stage 1: – Endoscopy – Abdominal sonography – Laboratory tests, including examination of stool for pathogenic organisms – Other imaging, as applicable Stage 2: – Lactose, fructose, sorbitol hydrogen breath test – Glucose hydrogen breath test – Faecal elastase-1, as appl. – Lactulose hydrogen breath test, as applicable – D-xylose absorption test, as applicable	Diarrhoea – Bulking agents – Loperamide – Cholestyramine – Clonidine – Octreotide – In case of bacterial overgrowth of the small intestine: broad spectrum antibiotics (e. g. ciprofloxacine, metronidazole and doxycycline one after the other, each for 10 days) with medical yeast (e. g. Perenterol) Severe exocrine pancreatic insufficiency – Pancreatic enzymes
Diabetic constipation (hypomotility of the colon)	Stage 1: – Digital rectal examination – Ileocolonoscopy – Laboratory tests – Abdominal sonography, as applicable – Other imaging, as applicable Stage 2: – (MRI) defaecography – Anorectal manometry – Hinton test – Neurological examinations	Constipation: – Sufficient fluids, fibre and physical activity – Gelling agents (pectins, psyllium preparations) – Fiber-rich foods (e. g. wheat bran, linseed) – Laxatives (e. g. sodium picosulfate, bisacodyl, macrogol, lactulose/lactitol)) Depending on tolerance and efficacy – Biofeedback for rectal emptying disorder, – Prucalopride for delayed transit (a prokinetic agent approved for women who do not respond to laxatives)
Diabetic faecal incontinence	Stage 1: – Digital rectal examination – Rectal endosonography – (MRI) defaecography Stage 2: – Anorectal manometry – Neurological examinations, as applicable	Faecal incontinence: – Antidiarrhoeal medications – Pelvic floor gymnastics – Biofeedback – Sacral nerve stimulation in refractory cases
Urogenital tract		
Diabetic cystopathy (bladder emptying dysfunction)	*Basic diagnostic work-up* – Micturition diary over 48 hours *Extended diagnostic work-up* – Questionnaire (e. g. International Prostate Symptom Score (IPSS)) – Uroflowmetry	Cystopathy – Behavioural changes – Electrical stimulation – Biofeedback – Anticholinergics – Alpha receptor blockers

Table 2 (Continued)

Organ manifestations / clinical picture	Examination method	Therapy
	– Residual urine measurement – Digital rectal examination for men – Urodynamic testing, as applicable	– Antibiotic therapy, as applicable – Bladder neck incision – Self-catheterisation – Suprapubic cystostomy
Erectile dysfunction	*Basic diagnostic work-up* Stage 1: – Sexual history, IIEF-5 – Laboratory tests – Total (free) testosterone, prolactin, FSH, LH Stage 2 (optional) – Test with a PDE-5 inhibitor (sildenafil, vardenafil, tadalafil)	Erectile dysfunction: Avoidance of medication side effects (caused by antihypertensives, tranquillisers, anti-depressants) Stage 1: Phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil) Stage 2: Erection aid system (vacuum pump) Corpus cavernosum auto-injection therapy Stage 3: Corpus cavernosum implant
	Extended diagnostic work-up Stage 3 (only if surgical therapy is planned/ indicated): – Intracavernosal injection test – Doppler/duplex sonography – Cavernosometry / cavernosography – Nocturnal tumescence measurement	Hypogonadism – Testosterone substitution
Neuroendocrine system (endocrine dysfunction)		
Hypoglycaemia-associated autonomic dysfunction – Blunted or absent hormonal counter-regulation – Hypoglycaemia unawareness – Increased glucose threshold for hypoglycaemic symptoms at blood glucose lowering – Decreased catecholamine secretion when standing or upon physical exertion	– Tight blood glucose control (in particular self-monitoring), in particular during the night	– Avoidance of symptomatic and asymptomatic (often nocturnal) hypoglycaemia – Hypoglycaemia awareness training (blood glucose awareness training; BGAT)
Sudomotor and vasomotor systems		
– Dyshidrosis, anhidrosis (“dry feet”) – Gustatory sweating	Sweat tests: QSART: quantitative sudomotor axon reflex test TST: thermoregulatory sweat test SSI: silastic sweat imprint ACHSST: acetylcholine sweatspot test Neuropad: indicator plaster	– Topical agents containing fat or urea – Avoidance of exposure to intense heat – Prophylaxis in case of identified cause of sweating (dietary component) – Anticholinergic drugs, clonidine (low dose) – Topical glycopyrrolate cream – In focal hyperhidrosis, botulinum toxin can be tried
Pupillomotor system		
– Myosis – Defective pupillary reflexes – Reduced dark adaptation	– Clinical examination – Infrared pupillography (constriction rate, dilatation rate, latency of pupillary light reflex)	– Advise patient of impaired adaptation to dark and danger of night blindness – Danger of glaucoma (check intraocular pressure)
Respiratory system		
– Central respiratory dysregulation with reduced respiratory drive in response to hypercapnia or hypoxia – Sleep apnoea syndrome – Respiratory arrest	Sleep laboratory, as applicable	CPAP therapy, as applicable

Table 3 The International Index of Erectile Function (IIEF-5) Questionnaire [4, 5].

Over the past 6 months: for each question, mark the single answer that best describes your situation.						
1. How do you rate your **confidence** that you could get and keep an erection?						
		very low	low	moderate	high	very high
2. When you had erections with sexual stimulation, **how often** were your erections hard enough to enable penetration?						
	No sexual activity	almost never/never	occasionally (much less than half the time)	sometimes (about half the time)	most times (much more than half the time)	almost always/ always
3. During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?						
	Did not attempt intercourse	almost never/never	occasionally (much less than half the time)	sometimes (about half the time)	most times (much more than half the time)	almost always/ always
4. During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?						
	Did not attempt intercourse	extremely difficult	very difficult	difficult	somewhat difficult	not difficult
5. When you attempted sexual intercourse, **how often** was it satisfactory for you?						
	Did not attempt intercourse	almost never/never	occasionally (much less than half the time)	sometimes (about half the time)	most times (much more than half the time)	almost always/ always
points	0	1	2	3	4	5

Table 4 Interpretation of the points scored in the IIEF-5 questionnaire for diagnosis of erectile dysfunction.

Points for questions 1 – 5	Total points	Interpretation of erectile dysfunction (ED)
question 1: _____	5 – 7	severe ED
question 2: _____	8 – 11	moderate ED
question 3: _____	12 – 16	mild to moderate ED
question 4: _____	17 – 21	mild ED
question 5: _____	22 – 25	no ED
total: _____		

Sources of Tables and Figures

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