Diagnosis, Treatment and Follow-up of Diabetic Neuropathy

Authors: Manfred Haslbeck, Dieter Luft, Bernhard Neundörfer, Hilmar Stracke, Dan Ziegler

Diagnosis, Therapy and Follow-up of Sensorimotor Diabetic Neuropathy (1st edition)

Experts and authors of the 1st edition (May 2000) appointed by the managing committee of the German Diabetes Association (DDG)

Prof. Dr. M. Haslbeck, Munich, Germany (Chair)
Prof. Dr. D. Luft, Tübingen, Germany
Prof. Dr. B. Neundörfer, Erlangen, Germany (Neurology)
Prof. Dr. H. Stracke, Giessen, Germany
Prof. Dr. D. Ziegler, Düsseldorf, Germany

Literature evaluation and supporting methods:
M. Redaèlli, Cologne, Germany
F. Parandeh-Shab, Cologne, Germany

Diagnosis, Therapy and Follow-up of Diabetic Autonomic Neuropathy (1st edition)

Experts and authors of the 1st edition (October 2002) appointed by the managing committee of the German Diabetes Association (DDG)

Prof. Dr. M. Haslbeck, Munich, Germany (Chair)
Prof. Dr. D. Luft, Tübingen, Germany
Prof. Dr. B. Neundörfer, Erlangen, Germany (Neurology)
Prof. Dr. H. Stracke, Giessen, Germany
Prof. Dr. D. Ziegler, Düsseldorf, Germany

In addition, the following scientists were appointed for drafting the 1st edition:
Prof. Dr. Ch. Wienbeck, Augsburg, Germany (Gastroenterology)
Dr. S. Corvin, Tübingen, Germany (Urology)
Literature evaluation and supporting methods:
M. Redaèlli, Cologne, Germany

The revision and updating of the 2nd edition (May 2004) was undertaken by the same group of experts. Both parts, which were initially published separately, were combined.

Table of Contents

Part 1: Sensorimotor Neuropathy

1 Definition

Diabetic neuropathy is a clinically manifest or subclinical disease of the peripheral nerves as a sequela of diabetes mellitus without other pathogenetic causes. It can affect both the somatic and the autonomous nervous system [American Diabetes Association/American Academy of Neurology, 1988, level of evidence IV]. See Table 1 for the classification of the sensorimotor diabetic neuropathies. Sensorimotor diabetic neuropathies include all neuropathic manifestations listed in Table 1 except for diabetic autonomic neuropathy.

Table 1. Classification of diabetic neuropathies (according to Thomas and Tomlinson, 1993)

Symmetric Polyneuropathies
Sensory or sensorimotor polyneuropathy
Autonomic neuropathy
Symmetric proximal neuropathy of the lower extremities
Focal and multifocal neuropathies
Cranial neuropathy
Mononeuropathy of the trunk and extremities
Asymmetric proximal neuropathy of the lower extremities
Mixed forms

2 Epidemiology

For patients with type 1 or type 2 diabetes, the prevalence of sensorimotor diabetic neuropathies is about 30 per cent [Ziegler, 1994, level V; Tesfaye et al., 1996a, level IIa; Young et al., 1993, level IIb; Dyck et al., 1993, level IIb]. Quality of life is impaired in comparison with patients without sensorimotor diabetic neuropathies [Benbow et al., 1998, level III]. Moreover, the mortality risk [Forsblom et al., 1998, level IIb; Navarro et al., 1996, level IIb] and the risk for diabetic foot syndrome [McNeely et al., 1995, level IIa] are increased. Sensorimotor diabetic neuropathy is the most important risk factor for nontraumatic amputations of the lower extremities. In comparison to patients without diabetes, the risk of amputation is 10 to 22 times higher [Most and Sinnock, 1983, level III; Bild et al., 1989, level IV; Siitonen et al., 1993, level IIb; Trautner et al., 1996a, level IV]. In Germany, the number of nontraumatic amputations in patients with diabetes mellitus is estimated to be over 20,000 per year [Standl et al., 1996, level IV; Trautner et al., 1997, level IV].
Furthermore, there is an association with diabetes duration, blood sugar control, diabetic retinopathy and other risk factors (Table 3) [Pirart et al., 1978a, level IV and 1978b, level IV].
Recently, impaired glucose tolerance (IGT) was identified with oral glucose tolerance tests as an important cause of “idiopathic” sensorimotor neuropathy in about 30 per cent of the cases [Sumner et al., 2003, level IIb; Singleton et al., 2003, level IV; Novella et al., 2002, level IIb].

3 Prevention

A sensorimotor diabetic neuropathy is a major independent risk factor for the manifestation of the diabetic foot syndrome [Abbott et al., 2002; Carrington et al., 2002] (Table 4c). Early diagnosis is the primary preventive strategy of a peripheral sensory neuropathy (American Diabetes Association, 2004, level IV).
Today, as a result of prospective studies, there is increasing evidence that individual measures of polyneuropathy such as an increase in the vibration perception threshold and a slowing of the nerve conduction velocity indicate an increased mortality risk [Forsblom et al., 1998, level IIb; Reichard et al., 1994, level IIb; Coppini et al., 2000, level IIb].

4 Pathogenesis

Table 2 shows the presently discussed pathogenetic mechanisms of diabetic neuropathies. New additions include cytokines (for example, interleukins, TNF α and TNF β with their effect on the homeostasis of the peripheral and central nervous system [Skudric and Lisak, 2003, level IIa]). In Table 3, the risk factors for sensorimotor diabetic neuropathies are listed.

Table 2. Presently discussed pathogenetic mechanisms of diabetic neuropathy [according to Neundörfer, 1996 and Ziegler, 1998]

1. Increased turnover in polyol metabolism with accumulation of sorbitol and fructose, depletion of myo-inositol, reduction of the activity of Na^+-K^+-ATPase and changes in the expression of different isoenzymes of protein kinase C (PKC)
2. Disturbances in the metabolism of the n-6 essential fatty acids and prostaglandins that lead to a change in the structure of the nerve membrane as well as microvascular and haemorrheologic changes
3. Vascular causes with consecutive ischaemia or hypoxia and formation of free oxygen radicals (oxidative stress) and so-called “hyperglycaemic pseudohypoxia”
4. Disturbances in neurotrophism with reduced expression and deficiency of neurotrophic factors (e. g., nerve growth factor (NGF), neurotrophin-3 (NT-3) and insulin-like growth factor (IGF)] and disturbances in axonal transport
5. Nonenzymatic glycation with increased levels of glycated plasma proteins and accumulation of glycation end products (AGE: advanced glycation end products) on neuronal and/or on blood vessel wall proteins
6. Immune processes with autoantibodies against the vagus nerve, sympathetic ganglia and adrenal medulla as well as inflammatory changes (cytokines)

Table 3. Risk factors, risk indicators or clinical correlates of sensorimotor diabetic neuropathies

Risk Factor	References	Level of Evidence
Hyperglycaemia	DCCT Research Group, 1993; Amthor et al., 1994; Ohkubo et al., 1995; Reichard et al., 1996; Partanen et al., 1995; Valensi et al., 1997;	II b I b I b I b II a II b
Arterial hypertension: Association for type 1 diabetes likely; for type 2 diabetes not verified	Maser et al., 1989; Forrest et al., 1997; Mehler et al., 1997; Sands et al., 1997;	II b II b I b III
Diabetic retinopathy	Fagerberg, 1959; Pirart, 1978 a+b; Cohen et al., 1998;	IV IV I b
Cardiovascular autonomic neuropathy	O'Brien and Corrall, 1988; Ziegler et al., 1993;	IV I b
Diabetic nephropathy	Fagerberg, 1959; Pirart, 1978 a+b; Maser et al., 1989; Cohen et al., 1998;	IV IV II b I b
Medial arterial calcification	Clouse et al., 1974; Edmonds et al., 1982; Everhart et al., 1988;	IV III III
Hyperlipaemia	Maser et al., 1989; Forrest et al., 1997;	II b II b
Additionally Discussed Risk Factors		
Alcohol	McCulloch et al., 1980; Adler et al., 1997; Sands et al., al.,1997;	III II b III
Nicotine	Christiansen, 1978 Gay et al., 1992; Mitchell et al., 1990; Harris et al., 1993; Forrest et al., 1997;	II b II a II b III II b

5 Diagnosis

The diagnostic criteria of a sensory or sensorimotor diabetic polyneuropathy (neuropathy symptom score, neuropathy deficit score) are listed in Tables 4a and 4b [Young et al. 1993, level IIb; strength of recommendation A].
Additional validated diagnosis scores (e.g. Michigan score with a simple list of questions) have been proposed [Feldmann et al., 1994 level IIb; strength of recommendation A].

Table 4a. Neuropathy Symptom Score (NSS)*

Symptomatology: Foot/Lower Leg	yes	no	
Burning sensation	□ 2	□ 0	
Numbness	□ 2	□ 0	
Paraesthesia	□ 2	□ 0	□ pt.
Feeling of weakness (fatigue, exhaustion)	□ 1	□ 0	
Cramps	□ 1	□ 0	
Pain	□ 1	□ 0	□ pt.
Localisation			
Feet	□ 2		
Lower leg	□ 1		
Elsewhere	□ 0		□ pt.
Exacerbation			
Present at night	□ 2		
Present during day and night	□ 1		
Only present during the day	□ 0		
Patient is awakened from sleep by the symptoms	Score from □ 1 add		□ pt.
Symptom improvement when			
Walking	□ 2		
Standing	□ 1		
Sitting or lying down	□ 0		□ pt.
	Total score:		□

NSS:
3-4 = mild symptoms
5-6 = moderate symptoms
7-10 = severe neuropathic symptoms
* In each point column, the maximum score can be given only once.

Table 4b. Neuropathy Deficit Score (NDS)

Ankle jerk		Side	right	left
Reflexes:	normal		□ 0	□ 0
	diminished		□ 1	□ 1
	absent		□ 2	□ 2
Vibratory sensibility				
(Normal values see Table 5)				
Measurement dorsal on big toe joint			right	left
	normal		□ 0	□ 0
	diminished/absent		□ 1	□ 1
Pain sensation				
Measurement on the dorsum of the foot			right	left
	normal		□ 0	□ 0
	diminished/absent		□ 1	□ 1
Temperature perception				
Measurement on the dorsum of the foot			right	left
	normal		□ ○	□ ○
	diminished/absent		□ 1	□ 1
		Total score: □		

NDS:
3-5 = mild neuropathic deficits
6-8 = moderate neuropathic deficits
9-10 = severe neuropathic deficits

Based upon clinical criteria, different manifestations can be distinguished, see Table 4c [strength of recommendation A].

Table 4c. Diagnostic criteria of different manifestations of sensorimotor diabetic neuropathies [according to Boulton et al., 1998]

Classification	Diagnostic criteria
Subclinical Neuropathy	● Abnormal, quantitative neurophysiologic tests (vibration perception, thermaesthesia; electroneurography), no symptoms or clinical findings
Chronic painful neuropathy (frequent)	● Painful symptomatology at rest (symmetric and increasing at night): Burning, shooting or stabbing pain, unpleasant prickling sensation ● Loss of sensitivity of varying quality and/or bilaterally reduced muscle propioceptive reflexes
Acute painful neuropathy (rather rare)	● Predominantly symmetric pain in the lower extremities and possibly also in the trunk area ● Hypersensitivity also possible ● May be associated with the start or intensification of an insulin therapy (“insulin neuritis”) ● Minor sensitivity disturbances in the lower extremities or normal neurologic examination
Painless neuropathy	● Absence of symptoms or numbness and/or paraesthesia ● Reduced or absent sensitivity with absent muscle propioceptive reflexes (particularly Achilles jerk)
Diabetic amyotrophy	● Progressive, usually asymmetric involvement of the proximal thigh and pelvic muscles with pain and paresis
Long-term complications of the distal symmetric polyneuropathy with different locations	● Neuropathic foot lesions (foot ulcers) ● Diabetic osteoarthropathy (Charcot foot) ● Nontraumatic amputation

When the following findings are present, differential diagnosis for other aetiologies should be considered [Neundörfer, 1996, level IV].

1. Absence of another long-term diabetic complication (retinopathy, nephropathy)
2. predominantly motor deficits
3. rapid development of symptomatology
4. clear asymmetry of the neurological deficits, mononeuropathy and cranial nerve dysfunction
5. Progression of the symptoms despite near normal metabolic control
6. Symptomatology beginning in the upper extremities
7. Evidence of other neurological symptoms not fitting to the polyneuropathic syndrome
8. Family history of neuropathy.

If necessary, a referral to a neurologist should be initiated [strength of recommendation A].

To recognise at-risk patients (screening tests), the following information should be acquired and the following tests should be carried out at the yearly medical check-up (see also Diabetes Health Passport of the German Diabetes Association) [Boulton et al., 1998, level IV; Strian and Haslbeck, 1999, level IV; strength of recommendation A].

5.1 Medical history and differential diagnosis

- Age, body weight, height, diabetes duration, previous and current diabetes treatment, symptoms (e. g., sensory irritations, pain, numbness) social surroundings, physical fitness (e. g., feeling of weakness, fatigue, exhaustion), medications (e. g., cytostatic drugs), toxins (e. g., alcohol), other aetiological factors
- Exclusion of other causes, in particular alcoholism, renal insufficiency, peripheral arterial disease (PAD), HIV infection, vitamin B12 deficiency, tumour, side effects of drugs, environmental factors
- A chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered in diabetic patients with mainly demyelinating polyneuropathy due to the possibility of an immunomodulatory therapy [Haq et al., 2003, level III; Cocito et al., 2002, level III].
- Neuropathy of unknown origin (idiopathic neuropathy)

5.2 Basic examination

Inspection

- Skin: Colour, turgor, rhagades, blisters, subcutaneous bleeding, callus formation, healed foot lesions, hypohidrosis or anhidrosis
- Signs of a bacterial and/or mycotic infection
- Foot deformities (e. g., neuropathic [Charcot] arthropathy, hammer toes, claw toes)
- Foot ulcer with exact description of localisation, extent and accompanying infection

Clinical Examination

- Check skin temperature and joint mobility; assessment of gait, check of shoes and inserts
- Palpation of the pulses (posterior tibial artery and dorsal digital arteries of the foot, both sides)
- Doppler pressure measurements and calculation of the Doppler index (ankle/brachial index) on both lower extremities

Neurological Examination

Table 5 shows simple neurological tests that can be carried out by every physician in a relatively short time. The tests should always be done bilaterally. Answers should be documented as yes/no or normal/not normal. For examinations on pain, temperature, touch and vibratory sensations, a proximal and a distal location should be compared. For quantification of pain, a numeric, horizontal analogue scale should

be employed. If the tentative diagnosis of a diabetic polyneuropathy cannot be clinically verified, quantitative sensory tests (vibrometry, quantitative thermaesthesia and/or an electroneurography) should be carried out.
In exceptional cases, when there is doubt of the diabetic aetiology of the PNP, a sural nerve biopsy has to be considered.
A skin biopsy for morphological analysis of unmyelinated nerve fibres is currently primarily used to address scientific questions.

Table 5. Simple neurological test methods for the diagnosis of sensorimotor diabetic neuropathy [according to Boulton et al., 1998; Young et al., 1993]

● Sensation of pain, for example, with a toothpick, disposable needle or Neurotip. Ask: “Is this painful?” (not “Can you feel it?”)
● Sensation of touch (superficial sensitivity), for example, with a cotton swab
● Vibratory sensibility with a 128 Hz tuning fork (according to Rydel-Seiffer). First test big toe joint; if there is no sensation, test a proximal location (medial malleolus) Lower normal limit - proximal to the big toe joint for ages under 30 years 6/8, for over 30 years 5/8 [Hilz et al., 1998] Lower normal limit on the medial malleolus for ages up to 40 years 6/8, for over 40 years 5/8 [Claus et al., 1988]
● Muscle propioceptive reflexes (ankle jerk and knee jerk reflexes)
● Temperature perception with cold tuning fork, ice water cooled test tube, Tip-Therm
● Sensation of pressure and touch 10 g-monofilament on the plantar side of the os metatarsale II in the area of the ball of the toe or distally on the dorsal side of the foot

6 Follow-up

When neuropathy is not present (see NSS and NDS in Tables 4a and 4b), a yearly neurological examination is sufficient [Boulton et al., 1998, level IV]. For this, simple diagnostic tests such sensation of pain, pallaesthesia (vibratory sensibility) or sensation of touch and pressure (monofilament) can be used [Perkins et al., 2001, level IIa]. For clinical neuropathy, an examination in at least six-month intervals is recommended. This applies already for abnormal vibration thresholds over 25 V for the prevention of further foot ulcers and avoidance of high subsequent costs and amputation [Shearer et al., 2003, level IIa]. When a symptomatic treatment is initiated, more frequent check-ups may be necessary [strength of recommendation A].

7 Therapy

The treatment options for the various manifestations of sensorimotor neuropathies by diabetes mellitus Type 1 and Type 2 are summarised in Table 6.

7.1 Background

At all stages, patients must be advised concerning to their day to day habits, foot care and diabetes therapy [Boulton et al., 1998, level IV; strength of recommendation A].

Family members and health care providers must be involved in the disease-related problems [Boulton et al., 1998, level IV; strength of recommendation A].

For all patients, diabetes control must be intensified while taking into consideration the individual therapeutic goals [strength of recommendation A]. Through this, the occurrence of a clinical neuropathy can be prevented [DCCT Research Group, 1993, level IIb; Amthor et al., 1994, level Ib; Reichard et al., 1996, level Ib] or the progression can be slowed for type 1 diabetes [DCCT Research Group, 1993, level IIb; Ohkubo et al., 1995, level Ib; Lauritzen et al., 1985, level Ib]. A relevant positive influence for type 2 diabetes has not yet been clearly verified [Ohkubo et al., 1995, level Ib; Gaede et al., 1999 and 2003, level Ib; UKPDS 33, 1998, level Ib]. As efficacy measures, the American Diabetes Association has defined two HbA1c values in its position paper: below 7.0 per cent and below 6.0 per cent when especially considering the risk for hypoglycaemia [American Diabetes Association, 2004, level IV]. According to the European recommendations [European Diabetes Policy Group, 1999, level IV], 6.5 per cent is the target value for HbA1c. Up to now, optimisation of diabetes control is the single generally accepted approach for prevention and pathogenetically based therapy [Haslbeck, 1996, level IV; 1997, level IV].

For all types of diabetes, the risk factors (see Table 3) must be diagnosed and, if necessary, be treated [strength of recommendation A].

It is always important to note that neuropathic symptoms of different severity can spontaneously improve within weeks [strength of recommendation A].

Table 6. Treatment of sensorimotor diabetic neuropathies [Boulton et al., 1998; Haslbeck, 1996; 1997]

Classification	Therapy
Applying to all types and stages of neuropathy:	● Near-normalisation of diabetes control ● Normalisation of blood pressure ● Education of patients ● Lifestyle changes
Subclinical Neuropathy	● Prophylaxis of foot ulcer and amputation (foot care, orthotic care, in particular for bony foot deformities with and without peripheral neuropathy)
Chronic painful neuropathy	● Antidepressants (amitriptyline, clomipramine, imipramine [TCA], duloxetine [SSNRI]) ● Anticonvulsants (carbamazepine[1], gabapentin[1], pregabalin) ● Antioxidants (alpha-lipoic acid, intravenous) ● Opioids (tramadol, oxycodone) ● Physiotherapy
Acute painful neuropathy	● Try analgesics ● Further medications (see chronic painful neuropathy)
Painless neuropathy (hypaesthetic or anaesthetic form)	● Foot care (diabetes education) ● Prophylaxis for foot lesions(orthotic measures) ● Physiotherapy
Diabetic amyotrophy	● Referral to a neurologist for definite diagnosis ● Physiotherapy ● Further therapy (see painful neuropathies)
Long-term complications of distal symmetric polyneuropathy	● According to medical evidence and individual medical experience, immediate referral to: diabetologist, neurologist, surgeon, specialised foot clinic, orthopaedic technician, orthopaedic shoemaker

[1] Note: begin with lower doses and gradually increase

7.2 Subclinical Neuropathy

See Table 4c (page 11) for definition
The goal of all therapeutic measures is to slow the progression and to prevent the occurrence of a clinically manifest neuropathy.

7.3 Clinical Neuropathy

7.3.1 Chronic painful neuropathy

If patients do not feel impeded in their daily life, it is not necessary to treat their symptoms [Boulton et al., 1998, level IV; strength of recommendation A].
When pain and painful paraesthesia first start to interfere with quality of life, the medications listed in Table 6 may be prescribed.
Side effects of drugs should always be taken into consideration; refer to the current ROTE LISTE (Germany), Index Nominum (Europe), British National Formulary (UK) for this purpose [strength of recommendation A].
Patients whose quality of life is negatively affected should be referred to a diabetologist or neurologist with experience in treating diabetic patients [Boulton et al., 1998, level IV; strength of recommendation A].

Causal therapy

In various studies, alpha-lipoic acid has been shown to have some positive influence on symptoms, neurological deficits and nerve conduction velocity in type 1 and type 2 diabetes [Ziegler et al., 1995, level Ib; Reljanovic et al., 1999, level Ib; Ruhnau et al., 1999, level III; Ziegler et al., 1999a, level Ib; Ziegler, 1999b, level IV; The Sidney Trial Authors, 2003, level Ib, Ziegler et al., 2004, level Ia; strength of recommendation B].
Other therapies are not adequately substantiated; for example, ACE inhibitors, aldose reductase inhibitors, γ-linolenic acid, C-peptide, acetyl-L-carnitine, nerve growth factor (NGF), PKC β-inhibitor (ruboxistaurin), brain-derived growth factor (BDNF), prostanoids, among others [Ziegler and Luft, 2003, level IV].

Symptomatic therapy

The use of the listed drugs needs a detailed knowledge regarding the efficacy, side effects and contraindications [strength of recommendation A].

The order of the drugs does not represent the therapeutic importance. Some of the information is based only upon a few studies with a small number of cases.

Analgesics: Simple, peripheral acting analgesics (paracetamol, acetyl salicylic acid) show mostly insufficient efficacy [Boulton et al., 1998, level IV; Haslbeck, 1996, level IV; strength of recommendation C].

Alpha-lipoic acid (see also the section on causal therapy): In a meta-analysis of four placebo controlled studies in a total of 1258 diabetic patients with painful neuropathy, alpha-lipoic acid produced a significant improvement in the Total Symptom Scores (pain, burning sensation, tingling, numbness) after three weeks of intravenous therapy with 600 mg/day [Ziegler et al., 2004; level Ia; strength of recommendation A].

Capsaicin: In a meta-analysis by Zhang and Li Wan Po [1994, level Ia], capsaicin cream led to significant pain reduction in diabetic neuropathy. The application has to be tightly controlled because neurotoxicity cannot be excluded [Nolano et al., 1999, level IIb; strength of recommendation C].

Carbamazepine: The antiepileptic-acting drug leads to a significant pain reduction in sensorimotor diabetic neuropathies [Rull et al., 1969, level IV; Wilton, 1974, level Ib; strength of recommendation A].

Gabapentin/Pregabalin: The antiepileptic drugs produced significant pain reduction in sensorimotor diabetic neuropathies [Backonja et al., 1998, level Ib; Morello et al., 1999, level Ib; Spruce et al., 2003, level IV; strength of recommendation A]. Pregabalin has better pharmacokinetic and pharmacodynamic effects.

Mexiletin[1]: This class Ib antiarrhythmic drug led to a marginal reduction in pain, but cannot be recommended due to its unfavourable risk/benefit ratio [Dejgard et al., 1988, level Ib; Stracke et al., 1992, level Ib; Oskarsson et al., 1997, level III; Jarvis and Coukell, 1998, level IV; strength of recommendation C].

Selective serotonin reuptake inhibitors: The selective serotonin reuptake inhibitors (SSRI) citalopram[1] and paroxetine[1] produced significant pain reduction in sensorimotor diabetic neuropathies [Sindrup et al., 1990, level Ib and 1992, level Ib; Max et al., 1992, level Ib; strength of recommendation B].

Tramadol leads to significant pain reduction [Harati et al., 1998, level Ib; strength of recommendation A].

Tricyclic antidepressants (amitriptyline, clomipramine, desipramine[1], imipramine) lead to a significant pain relief [Young et al., 1985, level IV; McQuay et al., 1995, level Ia and 1996, level Ia; strength of recommendation A].

Adminstration of neuroleptic drugs together with antidepressants does not produce an improved effect. To what extent dual serotonin/norepinephrine reuptake inhibitors such as venlafaxine or duloxetine can be employed is still open. Recently duloxetine, a SSNRI, has been approved for the treatment of painful diabetic neuropathy in Europe.

The efficacy of B vitamins is not proven. Vitamin B6 did not lead to an improvement in the neuropathic symptoms [Levin et al., 1981, level IIb]. Fat-soluble vitamin B1 in combination with vitamins B6 and B12 improved the nerve conduction velocity [Stracke et al., 1992, level Ib and 1996, level Ib]. At this time, current studies on chronic painful neuropathies are lacking [strength of recommendation C].

Opiates: For therapy-resistant cases, the administration of oxycodone may be considered [Watson et al., 2003 level Ib; strength of recommendation B and Gimbel et al 2003, level Ib; strength of recommendation A].

[1] Not approved in Germany for the indication neuropathic pain.

7.3.2 Acute painful neuropathy

Patients with acute painful neuropathy should be referred to a diabetologist or to a neurologist experienced in the treatment of diabetic patients.

Until the referral, the above recommendations on causal and symptomatic therapy as well as prophylaxis should be applied (see also Table 6).

7.3.3 Painless neuropathy

Educating the patient about the risks of the progression of neuropathy (development of diabetic neuropathic foot syndrome) is important [Boulton et al., 1998, level IV; strength of recommendation A].
The above recommendations for diabetes control have to be applied [strength of recommendation A].
Patients should be given advice regarding foot care and prophylaxis for infections and mycosis [Boulton et al., 1998, level IV; strength of recommendation A].
They should be referred to a diabetologist if the disease cannot be controlled optimally or if other diabetic complications are present [Boulton et al., 1998, level IV; strength of recommendation A].
For paralysis and sensory ataxia, specific physiotherapeutic treatment is suggested [strength of recommendation B].
Patients should be referred to a neurologist if the symptoms are atypical and/or a nondiabetic aetiology is suspected (see section on diagnosis) [strength of recommendation A].

7.3.4 Supplementary therapy

The following therapies are recommended as supplementary treatment for pain:
Balneotherapy [Neundörfer, 1998, level IV; strength of recommendation B].
Transcutaneous electrical nerve stimulation, which results in significant improvement of neuropathic complaints [Forst et al., 1996, level III; Kumar and Marshall, 1997, level Ib; strength of recommendation B].
Electrical spinal cord stimulation [Tesfaye et al., 1996b, level IIa; strength of recommendation C].
Acupuncture [Abuaisha et al., 1998, level III; strength of recommendation C].

7.4 Long-term complications of distal symmetric neuropathy

The therapeutic goal is the prevention of acute and recurrent foot ulcers and amputation [strength of recommendation A].
When a foot ulcer with or without infection is present, patients should be referred to a specialised foot clinic or hospital as soon as possible [Boulton et al., 1998, level IV].
Detailed information provided by family members and other treatment providers is essential [strength of recommendation A].
Until the patient is referred, the recommendations in the guideline on the “Diagnosis, treatment, follow-up and prevention of diabetic foot syndrome” should be considered.
Patients with diabetes mellitus and nontraumatic amputations or osteoarthropathy should be immediately referred to an approved specialist for treatment of diabetic foot to prevent further complications [Boulton et al., 1998, level IV]. Important is the diagnosis and starting therapy immediately during the initial stage of neuropathic (Charcot) arthropathy [strength of recommendation A].

8 Physical activity

Patients with diabetes mellitus and numbness should avoid the following activities: Going barefoot, use of treadmills, walking for long distances, jogging and step exercises (e. g., step aerobics). In contrast, the following activities are recommended: swimming, bicycling, rowing, exercises while sitting, arm exercises and other exercises without the use of weights [LeBrasseur and Fielding, 1998, level IV; American Diabetes Association, 2000, level IV; strength of recommendation A].
Inspecting the feet every day with a mirror is helpful for early detection of foot injuries. Special muscle and sensitivity training may increase peripheral sensitivity and muscular reflexes [Graham et al., 1990, level IV; strength of recommendation A].

9 Bibliography

1. Abuaisha BB, Costanzi JB, Boulton AJ. Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. Diabetes Res Clin Pract 1998; 39,(2): 115-21
2. Abbot CA, Carrington AL, Ashe H, Bath S, Every LC, Griffith J : The north-west diabetes foot care study : Incidence of and risk factores for new diabetic foot ulceration in a community based patient cohort Diabetic Medicine.2002, 19 : 377-384
3. Adler AI, Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Smith DG. Risk factors for diabetic peripheral sensory neuropathy. Results of the Seattle Prospective Diabetic Foot Study. Diabetes Care 1997; 20,(7): 1162-7
4. American Diabetes Association, American Academy of Neurology. Consensus statement: Report and recommendations of the San Antonio conference on diabetic neuropathy.Diabetes Care 1988; 11,(7): 592-7
5. American Diabetes Association: Standards of medical care in diabetes, Diabetes Care 27 (Suppl 1), 15 - 35
6. Amthor KF, Dahl-Jorgensen K, Berg TJ, Heier MS, Sandvik L, Aagenaes O, et al. The effect of 8 years of strict glycaemic control on peripheral nerve function in IDDM patients: the Oslo Study. Diabetologia 1994; 37,(6): 579-84
7. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial .JAMA 1998; 280,(21): 1831-6
8. Benbow SJ, Wallymahmed ME, MacFarlane IA. Diabetic peripheral neuropathy and quality of life. Qjm 1998; 91,(11): 733-7
9. Bild DE, Selby JV, Sinnock P, Browner WS, Braveman P, Showstack JA.Lower-extremity amputation in people with diabetes. Epidemiology and prevention. Diabetes Care 1989; 12, (1): 24-31
10. Boulton AJ, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. Diabet Med 1998; 15, (6): 508-14
11. Carrington AL, Shaw IE, van Schie CH, Abbott CA, Vileikyte L, Boulton AJ: Can motor nerve conduction velocity predict foot problems in diabetic subjects over a 6 year outcome period? Diabetes Care 2002, 25: 2010-2015
12.Coppini DV, Bowtell PA, Weng C, Young PJ, Sönken PH: Showing neuropathy is related to increased mortality in diabetic patients-a survival analysis using an accelerated failure time model, J Clin Epidemiol 2000;53: 519-523
13.Christiansen JS. Cigarette smoking and prevalence of microangiopathy in juvenileonset insulin-dependent diabetes mellitus. Diabetes Care 1978; 1,(3): 146-9

14.Claus D, Carvalho VP, Neundorfer B, Blaise JF. Perception of vibration. Normal findings and methodologic aspects .Nervenarzt 1988; 59,(3): 138-42
15.Clouse ME, Gramm HF, Legg M, Flood T. Diabetic osteoarthropathy. Clinical and roentgenographic observations in 90 cases. Am J Roentgenol Radium Ther NuclMed 1974; 121,(1): 22-34
16.Cocito D, Ciaramitaro P, Isrardo G, BarberoP, Migliaretti G, Piperi A: Intravenous immunoglobulin as first treatment in diabetics with concomitant distal symmetric axonal polyneuropathy CIPD Journal of Neurology 2002, 249:719-722
17.Cohen J, Jeffers B, Faldut D, Marcoux M, Schrier R. Risks for sensorimotor peripheral neuropathy and autonomic neuropathy in non-insulin-dependent diabetes mellitus (NIDDM). Muscle Nerve 1998; 21,(1): 72-80
18.DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes
mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329, (14): 977-86
19. Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy .Lancet 1988; 1,(8575-6): 9-11
20. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study [published erratum appears in Neurology 1993 Nov; 43(11):2345]. Neurology 1993; 43,(4): 817-24,
21.Edmonds ME, Morrison N, Laws JW, Watkins PJ.Medial arterial calcification and diabetic neuropathy. Br Med J (Clin Res Ed) 1982; 284,(6320): 928-30
22. European Diabetes Policy Group 1999. A desktop guide to Type 2 diabetes mellitus. European Diabetes Policy Group 1999. Diabet Med 1999; 16, (9): 716-30,
23.Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. Diabetologia 1988; 31, (1): 16-23
24.Fagerberg S. Diabetic neuropathy. A clinical and histological study on the significance of vascular affections. Göteborg, 1959:1-98
25. Forrest KY, Maser RE, Pambianco G, Becker DJ, Orchard TJ. Hypertension as a risk factor for diabetic neuropathy: a prospective study. Diabetes 1997; 46,(4): 665-70
26. Forsblom CM, Sane T, Groop PH, Totterman KJ, Kallio M, Saloranta C, et al. Risk factors for mortality in Type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. Diabetologia 1998; 41,(11): 1253-62,
27. Forst T, Pfützner A, Ayric H, Ambrosch A, Lehnert H, Küstner E. Die transkutane elektrische Nervenstimulation in der Therapie der symptomatischen somatosensorischendiabetischen Polyneuropathie. Diabetes und Stoffwechsel 1996; 5,:
203-208,
28 Feldman EI, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA: A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy, Diabetes Care, 17 (11) 1994, 1281-1289, Level of evidence IIb
29. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 1999; 353,(9153): 617-22

30. Gaede P, Vedel P, Larsen N, Jansen GVH, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes NEJM 2003; 348: 383-393
31. Gay EC, Cai Y, Gale SM, Baron A, Cruickshanks KJ, Kostraba JN, et al. Smokers with IDDM experience excess morbidity. The Colorado IDDM Registry. Diabetes Care 1992; 15, (8): 947-52
32 Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial.Neurology 2003; 60: 927-34.
33. Graham C, Lasko-McCarthey P.Exercise options for persons with diabetic complications. Diabetes Educ 1990; 16,(3): 212-20, 27. Harati Y, Gooch C, Swenson M, Edelman S, Greene D, Raskin P, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998; 50,(6): 1842-6
34.Haq RU,Pendleburg WW, Fries TJ, Tandan R: Chronic inflammatory demyelinating polyradiculo-neuropathy in diabetic patients Muscle Nerve2003, 27:465-470,
35. Harris M, Eastman R, Cowie C. Symptoms of sensory neuropathy in adults with NIDDM in the U.S. population. Diabetes Care 1993; 16,(11): 1446-52
36. Haslbeck M. Therapie der diabetischen Polyneuropathien. Frühbehandlung mit guter Diabeteseinstellung steht im Vordergrund. Therapiewoche 1996; 28,: 1554-1562
37. Haslbeck M. Medikamentöse Behandlung somatischer Neuropathien bei Diabetes mellitus. Symposiumsbericht der Arbeitsgemeinschaft „Diabetes und Nervensystem“der Deutschen Diabetes-Gesellschaft. Diabetologie Informationen 1997; 3,:210-215,
38. Hilz MJ, Axelrod FB, Hermann K, Haertl U, Duetsch M, Neundorfer B. Normative values of vibratory perception in 530 children, juveniles and adults aged 3-79 years. J Neurol Sci 1998; 159,(2): 219-25
39. Jamal GA, Carmichael H. The effect of gamma-linolenic acid on human diabetic peripheral neuropathy: a double-blind placebo-controlled trial .Diabet Med 1990; 7,(4): 319-23
40. Jarvis B, Coukell A. Mexiletine. A review of its therapeutic use in painful diabetic neuropathy. Drugs 1998; 56,(4): p691-707
41. Keen H, Payan J, Allawi J, Walker J, Jamal GA, Weir AI, et al. Treatment of diabetic neuropathy with gamma-linolenic acid. The gamma- Linolenic Acid Multicenter Trial Group. Diabetes Care 1993; 16, (1): 8-15
42. Kumar D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. Diabetes Care 1997; 20,(11): 1702-1705
43. Lauritzen T, Frost Larsen K, Larsen HW, Deckert T. Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. Diabetes 1985; 34 Suppl 3, 74-9
44. LeBrasseur NK, Fielding RA. Exercise and diabetic Neuropathy: Implications for Exercise Participation and Prescriptionfor Patients with Insulin-Dependent and Non-Insulin-Dependent Diabetes Mellitus. In: Vevees; A., editor. Clinical Management of diabetic neuropathy. Totowa: Humana Press Inc., 1998:257-271
45. Levin ER, Hanscom TA, Fisher M, Lauvstad WA, Lui A, Ryan A, et al. The influence of pyridoxine in diabetic peripheral neuropathy. Diabetes Care 1981; 4, (6): 606-9
46. Malik RA, Williamson S, Abbott C, Carrington AL, Iqbal J, Schady W, et al. Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double-blind controlled trial. Lancet 1998; 352,(9145): 1978-81,

47. Maser RE, Steenkiste AR, Dorman JS, Nielsen VK, Bass EB, Manjoo Q, et al. Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes 1989; 38,(11): 1456-61
48. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R.Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992; 326, (19): 1250-6
49. McCulloch DK, Campbell IW, Prescott RJ, Clarke BF. Effect of alcohol intake on symptomatic peripheral neuropathy in diabetic men. Diabetes Care 1980; 3, (2): 245-7
50. McNeely MJ, Boyko EJ, Ahroni JH, Stensel VL, Reiber GE, Smith DG, et al. The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration.How great are the risks? Diabetes Care 1995; 18, (2): 216-9
51. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A.Anticonvulsant drugs for management of pain: a systematic review .BMJ 1995; 311,(7012): 1047-52
52. McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA.A systematic review of antidepressants in neuropathic pain .Pain 1996; 68,(2-3): 217-27
53. Mehler PS, Jeffers BW, Estacio R, Schrier RW. Associations of hypertension and complications in non-insulin-dependent diabetes mellitus. Am J Hypertens 1997; 10,(2): 152-161
54. Mitchell BD, Hawthorne VM, Vinik AI. Cigarette smoking and neuropathy in diabetic patients. Diabetes Care 1990; 13, (4): 434-7
55. Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999; 159,(16): 1931-7
56. Most RS, Sinnock P. The epidemiology of lower extremity amputations in diabetic individuals. Diabetes Care 1983; 6, (1): 87-91
57. Navarro X, Kennedy WR, Aeppli D, Sutherland DE. Neuropathy and mortality in diabetes: influence of pancreas transplantation. Muscle Nerve 1996; 19, (8): 1009-16
58. Neundoerfer B. Diabetische Polyneuropathie sicher diagnostizieren. Abgeschwächte oder fehlende Achillessehnenreflexe sind erste Zeichen. Therapiewoche 1996; 11,576-581
59. Neundoerfer B. Therapie der Polyneuropathien. Dtsch med Wschr 1998; 123, 1553-1555
60. Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR.Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation.Pain 1999; 81,(1-2): 135-45
61. Novella SP, Inzucchi SE, Goldstein JM: The frequency of undiagnosed diabetes and impaired glucose tolerance in patients with idiopathic sensory neuropathy. Muscle Nerve 2001, 24:1229-1231
62. O' Brien I, Corrall R. Epidemiology of diabetes and its complications. New England Journal of Medicine 1988; 318, (24)
63. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995; 28, (2): 103-117
64. Oskarsson P, Ljunggren JG, Lins PE. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. The Mexiletine Study Group. Diabetes Care 1997; 20, (10): 1594-7

65. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1995; 333, (2): 89-94
66. Perkins BA, Olaleye D, Zimnan B, Bril V: Simple screening tests for peripheral neuropathy in diabetes clinic. Diabetes Care 2001; 24: 250-256
67. Pirart J. Diabetes mellitus and its degnerative complications: a prospective study of 4,400 patients observed between 1947 and 1973: Part 1. Diabetes Care 1978a; 1, (3):168-188
68. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973: Part 2. Diabetes Care 1978b; 1, (4): 252-263
69. Reichard P, Phil M. Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. Diabetes 1994; 43: 313-317
70. Reichard P, Pihl M, Rosenqvist U, Sule J. Complications in IDDM are caused by elevated blood glucose level: the Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. Diabetologia 1996; 39,(12): 1483-8
71. Reljanovic M, Reichel G, Rett K, Lobisch M, Schuette K, Moller W, et al. Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy. Free Radic Res 1999; 31,(3): 171-9
72. Ruhnau KJ, Meissner HP, Finn JR, Reljanovic M, Lobisch M, Schutte K, et al. Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy. Diabet Med 1999; 16,(12): 1040-3
73. Rull JA, Quibrera R, Gonzalez-Millan H, Lozano Castaneda O. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover
trial. Diabetologia 1969; 5,(4): 215-8,
74. Sands ML, Shetterly SM, Franklin GM, Hamman RF. Incidence of distal symmetric(sensory) neuropathy in NIDDM. The San Luis Valley Diabetes Study. Diabetes Care 1997; 20,(3): 322-9
75. Shearer A, Scullham P, Gordois A, Ogleski A, Predicted costs and outcomes from reduced vibration detection in people with diabetes in the U.S. Diabetes Care 2003, 26: 2305-2310
76. Singleton JR, Smith AG, Russel JW, Feldman EL: Microvascular complications of impaired glucose tolerance. Diabetes2003; 52:2867-2873
77. Skudric DS, Lisak RP: Role of neuropoetic cytokines in development and progression of diabetic polyneuropathy: From glucose metabolism to neurodegeneration, Experimental Diabetes Research 2003; 4: 303-312
78. Siitonen OI, Niskanen LK, Laakso M, Siitonen JT, Pyorala K. Lower-extremity amputations in diabetic and nondiabetic patients. A population-based study in eastern Finland. Diabetes Care 1993; 16, (1): 16-20
79. Sindrup SH, Gram LF, Brosen K, Eshoj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990; 42, (2): 135-44
80. Sindrup SH, Bjerre U, Dejgaard A, Brosen K, Aaes-Jorgensen T, Gram LF. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. Clin Pharmacol Ther 1992; 52,(5): 547-52
81. Spruce MC, Potter J, Copini DV: The pathogenesis and management of painful diabetic neuropathy: a review. Diabetic Medicine 2003, 20: 88-98

82. Standl E, Mendler G, Zimmermann R, Stiegler H. Zur Amputationshäufigkeit von Diabetikern in Deutschland (Ergebnisse einer Erhebung in zwei Landkreisen). Diabetes und Stoffwechsel 1996; (5): 29-32
83. Stracke H, Lindemann A, Federlin K. A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy. Exp Clin Endocrinol Diabetes 1996; 104,(4): 311-6
84. Stracke H, Meyer UE, Schumacher HE, Federlin K. Mexiletine in the treatment of diabetic neuropathy. Diabetes Care 1992; 15,(11): 1550-5
85. Strian F, Haslbeck M. Neurologische Erkrankungen. In: Mehnert H, Standl, E., Usadel,K. H. (Hrsg.). Diabetologie in Klinik und Praxis. 5. Auflage Stuttgart: Thieme Verlag, 2004, 550-576
86. Sumner CJ, Shet S, GriffinJW, Cornblath DR, Polydefkis M: The spectrum of neuropathy in diabetes and impaired glucose tolerance Neurology 2003; 60: 108-111
87. The Sidney Trial Authors, for the Sidney Trial study Group:The sensory symptoms of diabetic polyneuropathy are improved with □ lipoic-acid. Diabetes Care 2003; 26:770-776
88. Tesfaye S, Stevens LK, Stephenson JM, Fuller JH, Plater M, Ionescu-Tirgoviste C, et al.´Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia 1996a; 39,(11): 1377-84
89. Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet 1996b; 348, (9043):1698-701
90. Thomas PK, Tomlinson DR. Diabetic and Hypoglycemic Neuropathy. In: Dyck PJ, [et al.], editors. Peripheral neuropathy. Philadelphia: W. B. Saunders Company, 1993: 1219-1250
91. Trautner C, Haastert B, Giani G, Berger M. Incidence of lower limb amputations and diabetes. Diabetes Care 1996; 19,(9): 1006-1009
92. Trautner C, Standl E, Haastert B, Giani G, Berger M. Geschätzte Anzahl von Amputationen in Deutschland. Diabetes und Stoffwechsel 1997; 6,: 199-202
93. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group in Process Citation. Lancet 1998; 352, (9131): 837-53,
94. Valensi P, Giroux C, Seeboth-Ghalayini B, Attali JR. Diabetic peripheral neuropathy: effects of age, duration of diabetes, glycemic control, and vascular factors. J Diabetes Complications 1997; 11, (1): 27-34
95. Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J,: Controlled release oxycodon relieves neuropathic pain: a randomised controlled trial in painful diabetic neuropathy. Pain 2003, 105: 71-78
96. Wilton TD. Tegretol in the treatment of diabetic neuropathy. S Afr Med J 1974, 48,(20): 869-72
97. Young RJ, Clarke BF. Pain relief in diabetic neuropathy: the effectiveness of imipramine and related drugs. Diabet Med 1985; 2, (5): 363-6
96. Young M, Boulton A, Macleod A, Williams D, Sonksen P. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993; 36, (2): 150-4
99. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. A metaanalysis. Eur J Clin Pharmacol 1994; 46,(6): 517-22
100. Ziegler D, Gries FA, Mühlen H, Rathmann W, Spuler M, Lessmann F. Prevalence and clinical correlates of cardiovascular autonomic and peripheral

diabetic neuropathy in patients attending diabetes centers. The Diacan Multicenter Study Group. Diabete Metab 1993; 19, (1 Pt 2): 143-51
101.Ziegler D. Diagnosis, staging and epidemiology of diabetic peripheral neuropathy.Diabetes Nutrition and Metabolism 1994; 7, 342-348
102.Ziegler D, Hanefeld M, Ruhnau KJ, Meißner HP, Lobisch M, Schutte K, et al.Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study).Diabetologia 1995; 38, (12): 1425-33
103. Ziegler D. Pathogenese der diabetischen Neuropathie. Diabetes und Stoffwechsel 1998; 7,: 251-266
104.Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schütte K, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7- month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. Diabetes Care 1999a; 22,(8): 1296- 301
105. Ziegler D, Reljanovic M, Mehnert H, Gries FA. Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. Exp Clin Endocrinol Diabetes 1999b; 107, (7): 421-30
106. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA: Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha– lipoic acid: a-meta-analysis. Diabetic Medicine, 2004, 21:114-121
107. Ziegler D, Luft D: Clinical trials for drugs against diabetic neuropathy: can we combine scientific needs with clinical practicalities? Int Rev of Neurobiology 2002; 50: 431-463

10 Search strategy

Data base: Medline (OVID): 1998 – 2004-01
Date: 2004-02

1 *Diabetes Mellitus/
2 *Glucose Intolerance/
3 *Insulin Resistance/
4 1 or 2 or 3
5 exp Diabetic Neuropathies/
6 exp MONONEUROPATHIES/
7 exp POLYNEUROPATHIES/
8 *Blood Vessels/
9 exp NEURITIS/
10 (mononeuropath$ or polyneuropath$ or neuropath$).tw.
11 (amyotroph$ or neuralg$ or neuritis).tw.
12 (peripheral nerv$ adj (diseas$ or disorder$)).tw.
13 or/5-12
14 4 and 13
15 limit 14 to (human and yr=1998-2004)

Legend:

/	=	Following an indexed term, this sign denotes that all subheadings of the term were selected.
$	=	Shows an extension/modification of the search term.
*	=	When * precedes the MeSH term, this denotes a focused MeSH term search.
expl	=	exploded: Preceding an indexed term, this denotes an expanded MeSH term search.
pt	=	Publication type: Indicates a search for the study design.
tw	=	Text word: The term is searched for in the title and in the abstract of the study.
and/ or	=	Denotes a inclusive or exclusive combination with so-called Boolean operators.
adj	=	adjacent: Denotes the search for two terms in in one sentence.
MeSH term	=	Thesaurus of the National Library of Medicine (MeSH, medical subject headings)

Diagnosis, Therapy and Follow-up of Neuropathy in Diabetes mellitus Type 1 and Type 2

Authors: Manfred Haslbeck, Dieter Luft, Bernhard Neundörfer, Hilmar Stracke, Dan Ziegler

Part 2: Autonomic Neuropathy (DAN)

1 Definition

In addition to sensorimotor diabetic neuropathy, diabetic autonomic neuropathy (DAN) is the most frequent disease in the peripheral nervous system. Symptomatic manifestations can be differentiated from asymptomatic forms only with special function tests. Basically, DAN can affect every organ innervated by the autonomic nervous system. Table 1 shows the clinically important organ manifestations and symptoms of DAN.

Table 1. Organ and clinical manifestations of DAN [mod. according to Haslbeck, 1993, level IV; Ziegler and Gries, 1996, level IV]

Cardiovascular System Resting tachycardia, reduced heart rate variability (HRV), exercise intolerance, perioperative cardiovascular instability, extended QTc interval, orthostatic hypotension, diminished or absent awareness of myocardial ischaemias
Gastrointestinal Tract Gastro-oesophageal reflux disease, diabetic gastropathy (dyspeptic symptoms, postprandial hypoglycaemia), diabetic cholecystopathy, diabetic diarrhoea, hypomotility of the colon (constipation), anorectal dysfunction (faecal incontinence)
Urogenital Tract Diabetic cystopathy (urinary tract dysfunction), erectile dysfunction, retrograde ejaculation, sexual dysfunction in women
Neuroendocrine System Hypoglycaemia associated autonomic dysfunction (HAAF) (reduction or absence of hormonal counterregulation, diminished catecholamine secretion while standing and during exercise, impaired hypoglycaemia awareness)
Sudomotor System Dyshidrosis, anhidrosis (“dry feet”), gustatory sweating
Vasomotor Dysfunction Hyperthermic skin, neuropathic oedema, orthostatic hypotension
Trophism Neuropathic ulcer, neuropathic osteopathy and neuropathic osteoarthropathy (Charcot foot)[1]
Respiratory System Central faulty regulation of breathing with reduced breathing stimulus in contrast to hypercapnia or hypoxaemia, sleep apnoea (?), respiratory arrest (?)
Pupillomotor System Abnormal pupillary reflexes, impaired dark adaptation

[1]Diabetic foot syndrome is discussed in a separate guideline.

2 Epidemiology and Prognosis

Important factors that can favour the occurrence of DAN are diabetes duration and control as well as other metabolic parameters (e.g., lipids) (see part 1). A correlation between micro- and macroangiopathic complications and overweight in type 2 diabetic patients has been ascertained. Furthermore, there is an increase in the prevalence of CAN when sensorimotor diabetic neuropathy is present [DCCT, 1998, level Ib; Gottsäter et al., 1999, level III; Maser et al., 1989, level IIb; Lluch et al., 1998, level IIb; Töyry et al., 1996, level IIb; Valensi et al., 2003; level IIb; Singh et al., 2000, level IIa]. Recently, a clinical trial in 160 type 1 diabetic patients showed that a

reduced HRV correlated at a significant level with coronary heart disease and risk factors for metabolic syndrome [Colhoun et al., 2001, level II].
The frequency of DAN in type 1 and type 2 diabetics is, on the average, 30 per cent when diagnosed with cardiovascular autonomic function tests (AFTs) [Ziegler et al., 1993, level Ib; Lluch et al., 1998, level IIb]. In diabetic patients with CAN, there is a higher mortality that increases by five to sixfold within five to six years (Table 2).
In a five-year study, type 1 diabetic patients with an extended QTc interval, which is associated with CAN, showed a clearly heightened risk for mortality (odds ratio: 24.6 [95 per cent CI: 6.5 to 92.9]) [Veglio et al., 2000]. A prospective study over nine years (The Hoorn Study, Gerritsen et al., 2001, level IIb) has recently shown that CAN approximately doubles total and cardiovascular mortality [Gerritsen et al., 2001, level IIb].
Several new publications confirm the tight connection between CAN and elevated mortality risk. A meta-analysis of 15 prospective studies from 1966 to 2000 showed a significantly increased relative risk of 3.45 (95 per cent CI: 2.66 to 4.47) for two or more abnormalities in cardiovascular autonomic function (see Table 5) [Maser et al., 2003, level Ia]. A reduced HRV during deep breathing is apparently an independent risk factor for a lowered life expectancy in diabetics [Wheeler et al., 2002, level IIa].
Moreover, an autonomic cardiac dysfunction increases the death rate after myocardial infarction and presents an independent risk factor for an apoplexy [Vinik et al., 2003, level IV; Whang and Bigger, 2003, level IIa].

Table 2. Association between mortality and CAN [Ziegler, 1999, level IV]

References	Observation period	Mortality with CAN	Mortality without CAN
Ewing et al., 1980	5 years	21/40 (53%)	5/33 (15%)
Hasslacher et al., 1983	5 years	3/16 (19%)	3/42 (7%)
Navarro et al., 1990	3.3 (1 to 7.3) years	41/175 (23%)	2/57 (4%)
Sampson et al., 1990	10 years	18/49 (37%)	4/38 (11%)
O'Brien et al., 1991	5 years	23/84 (27%)	21/422 (5%)
Ewing et al., 1991	3 years	10/32 (31%)	3/39 (8 %)
Jermendy et al., 1991	5 years	12/30 (40%)	1/23 (4 %)
Rathmann et al., 1993	8 years	8/35 (23%)	1/35 (3%)
Luft et al., 1993	8 (6 to 10) years	7/34 (21%)	1/19 (5%)
Navarro et al., 1996	1 to 11.5 years	101/359 (28%)	6/128 (5%)
Orchard et al., 1996	2 years	8/88 (9%)	9/399 (2%)
Töyry et al., 1996	10 years	3/23 (13%)	3/99 (3%)
Veglio et al., 2000	5 years	10/76 (13%)	10/240 (4%)
Total (average)	5 years	265/1041 (25%)	69/1574(4%)

Today, there is no doubt that autonomic diabetic neuropathies are clinically important diseases that have considerable prognostic consequences on life expectancy, risk assessment for organic diseases and, not the least, on the quality of life with diabetes mellitus [strength of recommendation A].

3 Aetiology

Principally the same mechanisms as for sensorimotor diabetic neuropathy are discussed for the pathogenesis of autonomic neuropathy (compare Table 2 in Part 1 "Diagnosis, Therapy and Follow-up of Sensorimotor Diabetic Neuropathy").

4 Clinical Manifestations and Diagnosis

The complete picture of a symptomatic DAN with multiple organ involvement occurs only rarely. Clinically, mostly a heterogeneous pattern of symptoms from different organ systems is observed, which can lead to misinterpretation and is associated with a reduced quality of life. Therefore, a thorough differential diagnosis is always required. In Table 3, the procedure for the diagnosis of autonomic diabetic neuropathies is presented.

Table 3.
Procedure for the diagnosis of autonomic diabetic neuropathies [modified according to Haslbeck, 1993, level IV]

Specific medical history: Neurological symptoms: autonomic NS, sensorimotor NS Diabetes mellitus: Disease duration, form of treatment, quality of control
Important findings: Current metabolic situation (blood and urinary sugar levels, urinary acetone, HbA1c, fructosamine), diabetic long-term complications (eyes, kidneys, blood vessels)
Neurological Examination: Cardiovascular function tests,* e.g., heart rate variability, orthostatic response
Organ specific investigations, differential diagnosis
Interdisciplinary collaboration

* Basic and advanced diagnostic measurements, see page 34ff.

When there is evidence for sensorimotor diabetic neuropathy (see this guideline Part 1), potential manifestations of DAN must also be considered because there is an approximately 50 per cent coincidence of sensorimotor and autonomic neuropathies [Ziegler et al., 1992a, level IIb]. Likewise, there is a positive correlation between DAN and other diabetic long-term complications (retinopathy, nephropathy) [Valensi et al., 1997, level IIb]. In Table 16 (page 59), the most important clinical manifestations of autonomic diabetic neuropathy and the possibilities for diagnosis are summarised.

4.1 Cardiovascular System

CAN is regarded as the clinically most important form of DAN. In the cardiovascular and other organ systems, an early diagnosis before the manifestation of clinical symptoms is possible (Table 1). The importance of early diagnosis is emphasised by the fact that myocardial ischaemia progresses asymptomatically (silently) in 6.4 per cent of the younger and in 26.3 per cent of the over 65-year old diabetic patients [Inoguchi et al., 2000, level IIb; MiSAD Group, 1997, level IIb].
CAN may be diagnosed when one or more of the following symptoms and diseases are present [strength of recommendation A]:
- Orthostatic hypotension
- Unexplained dizziness and syncope
- Unexplained tachycardia
- Preoperative risk assessment
- Sensorimotor neuropathy

The earliest sign of CAN is a decrease in the heart rate variability (HRV) or the so-called respiratory sinus arrhythmia [Ewing et al., 1980, level IIb; Murray et al., 1975, level IIa; Watkins and MacKay, 1980, level IIa]. In a meta-analysis, a 2.3-fold increased risk for CAN was shown in diabetic patients with an extended QTc interval [Whitsel et al., 2000, level Ia].
Advanced stages of CAN show an increase in the resting heart rate or a resting tachycardia (mainly vagus nerve lesion) and orthostatic hypotension (mostly sympathetic lesion). Together they can lead to a complete absence of heart rate variability as a result of cardiac denervation. In cases of orthostatic hypotension, a distinct drop in systolic blood pressure accompanied by appropriate symptoms may

occur (nonsystemic dizziness, syncope), whereby there have been previous indications of a dysfunction in the cerebral autoregulation of the blood supply [Mankovsky et al., 2003, level IIa]. The fundamental clinical findings for CAN are listed in Table 4.

Table 4. Important clinical findings for CAN [modified according to Ziegler, 1999, level IV]

Reduced HRV, resting tachycardia
Disturbed circadian rhythm of the heart rate and blood pressure
Silent myocardial infarction and myocardial ischaemia
Orthostatic hypotension
Denervation hypersensitivity
Exercise intolerance
Association with left ventricular dysfunction
Perioperative instability
Abnormal regulation of hormones that affect the circulatory system
QTc interval lengthening

4.1.1 Basic and advanced diagnosis

For the diagnosis of CAN, the basic tests listed in Table 5 have proven to be of value. These tests, in principle, can be carried out with a conventional electrocardiograph, a stop watch and a blood pressure instrument [strength of recommendation A]. The measurement of an orthostatic pressure response has been also recently recommended by others as a screening test for autonomic neuropathy [ADA Position Statement, 2002, level IV].

For advanced diagnosis, computer-assisted systems are available that fulfill the requirements for the measurement of R-R intervals including spectral and vector analyses. So-called test batteries, a selection of noninvasive autonomic function tests (AFTs), are used [Ewing et al., 1985, level IIa; Ewing and Clarke, 1982, level IV; Genovely and Pfeifer, 1988, level IV; Kennedy et al., 1989, level III; Weinberg and Pfeifer, 1984, level IV; Ziegler et al., 1992b, level IIa]. The determination of the QTc interval for making a diagnosis, however, cannot substitute for these AFTs [Schnell et al., 1996a, level III, Whitsel et al., 2000, level Ia]. In principle, the diagnosis may also be made on the basis of a 24-hour HRV measurement with a Holter ECG monitor [Task Force of the ESC and NASPE, 1996, level IV].

Extended QT and QTc intervals occur frequently in diabetic patients and correlate with mortality [Veglio et al., 2000, level IV; Pourmoghaddas and Hekmantia, 2003, level III], but are not suitable for the diagnosis of CAN [Claus et al., 2002, level IIb]. Test batteries, in which the individual tests detect lesions of the parasympathetic and sympathetic nervous systems, may also serve to establish the severity of the CAN. Thus, for example, 100 per cent of the examined diabetics with symptomatic peripheral neuropathy and additional autonomic symptoms had CAN (defined as three or more abnormal test results). About fifty per cent of the diabetic patients with symptomatic peripheral neuropathy are expected to have CAN. When a peripheral neuropathy can be excluded, up to 10 per cent of the cases are estimated to have CAN [Ziegler et al., 1992a, level IIb].

Table 5. Basic and advanced diagnosis of CAN [modified according to Strian and Haslbeck, 1999, level IV; Ziegler and Gries, 1994, level IV]

Basic diagnosis	**Advanced diagnosis** (additionally, with computer-assisted devices
	Heart rate variability (HRV) at rest: • Coefficient of variation (CV) • Spectral analysis (VLF, LF and HF spectral bands)
E/I ratio during deep breathing (heart rate analysis during timed rhythmic breathing	**HRV during deep breathing** • Coefficient of variation (CV) • E/I difference • E/I ratio • Mean circular resultant (MCR)
Maximum/minimum 30:15 ratio (modified Ewing test)	**Maximum/minimum 30:15 ratio** (modified Ewing test)
Valsalva ratio ("Valsalva manoeuvre")	**Valsalva ratio** ("Valsalva manoeuvre")
Orthostatic response (systolic R-R decrease after change in position)	**Orthostatic response** (systolic R-R decrease after change in position)

For advanced diagnosis, the following points should be noted: When syncope is present, the tilt table test may be necessary. The measurement of the diastolic pressure response during isometric muscle contraction in the so-called handgrip test as part of a proposed test battery from Ewing and Clarke (1982) can no longer be recommended for the diagnosis of CAN due to insufficient reproducibility and an unconfirmed standard limit value [Ziegler et al., 1992a, level IIb and 1992b, level IIa].
In addition to the mentioned diagnostic tools for CAN, a direct quantification of the sympathetic myocardial dysinnervation with radiological methods (^{11}C-hydroxyephedrine [= ^{11}C-HED] or ^{123}I-metaiodobenzylguanidine [= ^{123}I-MIBG] radionuclide imaging) for special problems can be carried out [Claus et al., 1994, level III; Mäntysaari et al., 1992, level IIa; Schnell et al., 1995, level IIa; Schnell et al., 1996b, level IIa; Stevens et al., 1999, level IIa; Ziegler et al., 1998, level IIa; strength of recommendation B].
Even though the MIBG-SPECT correlates well with the results of the autonomic reflex tests and has a greater sensitivity, the method is used primarily for research [Claus et al., 2002, level IIb; Ziegler 2001, level IV]; however, it is the only available imaging method to show the sympathetic innervation of the heart [Giordano et al., 2000, level IIb].
Changes in arterial baroreflex activity are frequently observed in diabetes mellitus and autonomic neuropathy. Up to now this test is of uncertain clinical relevance and is performed primarily for research purposes [Bernardi, 2000, level III; Airaksinen, 2001, level IV; Ziegler et al., 2001, level IV].

4.1.1.1 Implementation and methodology

In order to obtain valid test results, the recommendations in Table 6 must be followed [strength of recommendation A].

Prerequisites

Table 6. Prerequisite conditions for autonomic function tests [mod. according to the Task Force of ESC and NASPE, 1996, level IV; Ziegler and Gries, 1994, level IV]

• Informed patient
• Relaxed atmosphere (quiet, screened off room)
• Before, ample rest period in repose (> 10 min)
• Carry out in the morning, fasting: · Exclusion of hypoglycaemia · Reduced food intake for at least 8 h and, if possible, avoidance of interfering medications considering the drug half-lives · Abstinence from alcohol and nicotine: approximately 12 h · Avoidance of strong physical or emotional stress: for approximately 24 h · Exclusion of an acute illness · Exclusion of a metabolic imbalance (constant hyperglycaemia [over 250 mg/dl], ketosis, ketoacidosis: about 1 week)

The HRV examinations can yield incorrect abnormal results when the following conditions and interfering medications are present:
1. Coronary heart disease
2. Myocardial infarction during the last 14 months
3. Cardiac insufficiency
4. Cardiomyopathy
5. Arterial hypertension
6. Alcoholism, serious liver diseases
7. Renal insufficiency
8. Medications: for example, tricyclic antidepressants, antiarrhythmic drugs, clonidine [Rothschild et al., 1988, level IIb; Kleiger et al., 1987, level IIb; Genovely and Pfeifer, 1988, level IV]. ACE inhibitors, beta-blockers, and digitalis could lead to an increase in HRV (false normal results) [Ziegler, 1994, level IV].

The individual examinations should be carried out in the following manner:

Basic diagnosis

Heart rate variability (HRV) during deep breathing
The supine patient breathes with a frequency of six inspirations per minute since healthy subjects show maximal HRV at this frequency. The length of the inspiration phase is six seconds and the expiration phase, four seconds. In the breathing cycle with the maximum HRV, the longest R-R interval is determined during expiration (R-Rmax) and the shortest interval during inspiration (R-Rmin). From this, the ratio (R-

Rmax)/(R-Rmin), the so-called E/I ratio, is calculated [Smith, 1982, level IIb; Sundkvist et al., 1979, level IIa].

Maximum/minimum 30:15 ratio
For the ECG documentation, the supine person then stands up next to the examination table. The recording is taken from the beginning of the active process of standing up. For healthy patients, the shortest R-R interval occurs around the 15th heart beat (interindividual, 5th to 25th beat) after standing up. The longest R-R interval is expected around the 30th beat (20th to 40th beat). Consequently, as a test parameter, the maximum/minimum 30:15 ratio 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. The numerically exactly defined 30:15 ratio proposed by Ewing and Clarke (1982) cannot be recommended because of the physiological variability in the reflex response just described. Therefore, the ratio would not be necessarily correct [Ziegler et al., 1992c, level IIa].

Valsalva manoeuvre
While sitting, the subject blows into a mouthpiece that is connected to a manometer. A constant pressure of 40 mm Hg over 15 seconds is to be maintained. The R-R intervals are recorded during the manoeuvre and for 15 seconds afterwards. The Valsalva ratio is calculated by dividing the longest R-R interval during the 15 seconds following the forced expiration phase by the shortest R-R interval during the manoeuvre [Ewing and Clarke 1982, level IV]. Due to the potential risk of causing retinal or vitreous haemorrhages, the Valsalva manoeuvre should not be performed on patients with proliferative retinopathy.

Orthostatic response
First, the blood pressure is taken twice within a minute while the patient is supine, then, immediately after standing up and, afterwards, every 30 seconds for three minutes. The systolic blood pressure change is defined as the difference between the last value before standing up and the lowest value after standing up.

Advanced diagnosis

Heart rate variability (HRV) at rest (standard analysis)
The HRV is measured in the supine, normally breathing subject for 5 minutes. The heart rate is calculated from 150 artefact-free consecutive R-R intervals. As an index for acquiring the vagal function, the coefficient of variation (CV) of the R-R intervals is also calculated (standard analysis).

Heart rate variability (HRV) at rest (spectroscopic analysis)
As parameters of spectroscopic analysis (measurement likewise taken for 5 minutes), integrals of three frequency bands are calculated using fast Fourier transformation: VLF (= very low frequency) band: 0.003 to 0.04 Hz; LF (= low frequency) band: 0.04 to 0.15 Hz; HF (= high frequency) band: 0.15 to 0.4 Hz. The VLF band primarily represents the sympathetic nervous system, the LF band the sympathetic and parasympathetic nervous systems and the HF band primarily the parasympathetic nervous system.

Mean circular resultant (MCR)
The mean circular resultant is calculated by using vector analysis and has the advantage of being independent of heart rate and extrasystoles [Weinberg and Pfeifer, 1984, level IV]. As an alternative, the CV can be determined.

4.1.1.2 Evaluation

According to the generally accepted recommendations from a consensus conference [American Diabetes Association, 1988; level IV], two or three abnormal results from the basic diagnostic tests (see Table 5) are sufficient for a diagnosis of CAN.
The standard limits for advanced diagnosis in two commonly used computer programmes are summarised in Tables 7a and 7b. For some of the normal values, significant sex-specific differences (e.g., in certain age groups, the HF and LF bands) have been observed [Agelink et al., 2001, level IIb].
In the opiunion of others, a CAN should be assumed if three or more of the seven parameters marked with an asterisk give abnormal results. With two abnormal findings, an incipient or borderline CAN should be suspected [Ziegler and Gries, 1994, level IV; Ziegler et al., 1992a, level IIb].
The heart rate variability tests during deep breathing, maximum/minimum 30:15 ratio, and CV (HRV at rest) measure mainly the parasympathetic function; a conclusion on the sympathetic components may be made with the orthostatic response. The Valsalva manoeuvre can be regarded as a global test of parasympathetic and sympathetic function.
It has not yet been decided whether a continuous measurement of the HRV over 24 hours is more sensitive than the battery of reflex tests for the early detection of CAN [Ziegler and Rathmann, 1994, level IV]. Due to the lack of standardisation of the parameters for the 24-hour HRV with a Holter ECG monitor, no generally accepted standard values are available. A first step in the direction of standardisation was taken by the ESC and NASPE in consensus reports [ESC and NASPE, 1996; level IV].

Table 7a. Age-dependent, lower normal limits (2.3 percentile) of cardiovascular autonomic function tests in healthy persons using ProSciCard I software [according to Ziegler et al. 1992c, level IIa]

	15 yr.	**20 yr.**	**25 yr.**	**30 yr.**	**35 yr.**	**40 yr.**	**45 yr.**	**50 yr.**	**55 yr.**	**60 yr.**	**65 yr.**
HRV (at rest) CV (%)[a]	3.72	3.43	3.15	2.90	2.66	2.45	2.25	2.07	1.91	1.75	1.61
Spectroscopic analysis VLF band (0.01 – 0.05 msec^2)	0.404	0.374	0.374	0.321	0.298	0.276	0.256	0.237	0.220	0.204	0.189
LF band (0.05 – 0.15 msec^2)	0.614	0.511	0.424	0.352	0.293	0.243	0.202	0.168	0.140	0.116	0.096
HF band (0.15 – 0.5 msec^2)	0.492	0.375	0.286	0.219	0.167	0.127	0.097	0.074	0.057	0.043	0.033
HRV (deep breathing): CV (%)[a]	5.12	4.79	4.47	4.18	3.91	3.65	3.41	3.19	2.98	2.78	2.60
E/I ratio[a,b]	1.22	1.21	1.19	1.17	1.16	1.15	1.14	1.13	1.12	1.11	1.10
Mean circular resultant (MCR)[a]	0.027	0.025	0.023	0.022	0.021	0.019	0.018	0.017	0.016	0.015	0.014
Maximum/minimum 30:15 ratio	1.17	1.15	1.14	1.12	1.11	1.10	1.09	1.08	1.07	1.07	1.06
Valsalva ratio	1.23	1.22	1.22	1.21	1.20	1.19	1.19	1.18	1.17	1.17	1.16
Orthostatic response (mm/Hg)	Up to 27 for all age groups										

[a] Parameters of the test battery for CAN diagnosis with computer software
[b] Parameters of the test battery for CAN diagnosis with a conventional ECG

Table 7b. Lower normal limits of age-dependent cardiovascular autonomic function tests (Neuro-Diag, software programme) in 309 test subjects (151 men, 158 women), ages 18 – 77 years. The values given represent the 2.5 percentile (adopted from Agelink et al., 2001, level IIb)

	15 yr.	20 yr.	25 yr.	30 yr.	35 yr.	40 yr.	45 yr.	50 yr.	55 yr.	60 yr.	65 yr.
HRV (at rest):											
CV (%)[a]											
Men	3.32	3.05	2.80	2.58	2.37	2.18	2.00	1.88	1.69	1.55	1.43
Women	2.78	2.57	2.38	2.20	2.04	1.188	1.74	1.61	1.49	1.38	1.28
Spectroscopic analysis VLF band (0.003 to 0.04 msec^2)											
Men	244	219	197	176	158	142	128	114	103	92	83
Women	296	260	228	200	176	154	135	119	104	92	81
LF band (0.04 to 0.15 msec^2)											
Men	362	300	249	207	172	142	118	98	81	68	56
Women	230	193	161	135	113	94	79	66	55	46	39
HF band (0.15 to 0.4 sec^2)											
Men	236	185	145	113	89	69	54	42	33	26	20
Women	194	154	122	97	77	62	49	39	31	25	20
HRV (deep breathing):											
CV (%)[a]											
Men	6.34	5.61	4.97	4.40	3.89	3.44	3.05	2.70	2.39	2.11	1.87
Women	5.92	5.35	4.83	4.36	3.94	3.56	3.21	2.90	2.62	2.37	2.14
E-I difference (msec^2)[a,b]											
Men	200	178	159	141	126	112	100	89	79	71	63
Women	145	133	123	113	103	95	87	80	73	67	62
E/I ratio[a,b]											
Men	1.129	1.125	1.121	1.118	1.114	1.111	1.107	1.104	1.11	1.098	1.095
Women	1.117	1.113	1.110	1.107	1.104	1.102	1.099	1.096	1.094	1.091	1.089

Mean circular resultant (MCR)											
Men	0.028	0.025	0.022	0.020	0.018	0.016	0.014	0.013	0.011	0.010	0.009
Women	0.029	0.026	0.023	0.021	0.018	0.016	0.014	0.013	0.011	0.010	0.009
Max./min. 30:15 ratio[a,b]											
Men	1.107	1.105	1.103	1.101	1.099	1.097	1.096	1.094	1.092	1.091	1.089
Women	1.104	1.102	1.101	1.099	1.098	1.096	1.095	1.093	1.092	1.090	1.089

[a] Parameters of the test battery for CAN diagnosis with computer software
[b] Parameters of the test battery for CAN diagnosis with a conventional ECG

4.2 Gastrointestinal Tract

Disturbances of the digestive tract in patients with diabetes mellitus may be a sign of a gastrointestinal diabetic autonomic neuropathy. They are caused by a dysfunction of the neuronal control of motility, secretion, absorption and perception in the gastrointestinal tract and, in fact, are probably due to functional and structural injury to efferent and afferent fibres of the sympathetic and parasympathetic nervous systems, including the ganglia of the gastrointestinal tract [Bittinger et al., 1999, level IV; Enck et al., 1994, level IIb; Wienbeck, 1996, level IV].
GI symptoms occur often in diabetics and always require a thorough differential diagnosis [Spangeus et al., 1999; strength of recommendation A]. However, there is only a relatively weak connection between symptoms and gastric emptying [Horowitz et al., 2002, level IV]. Gastric emptying in diabetic patients is not affected by a *Helicobacter pylori* infection [Jones et al., 2002, level III]. In addition to the clinical syndrome with a frequently nonspecific symptomatology, a subclinical manifestation of diabetic autonomic neuropathies occurs frequently and, particularly, in the upper gastrointestinal tract [Haslbeck, 1998, level IV]. An appropriate tentative diagnosis can be made if evidence for diabetic neuropathies and other suspicious factors are present (Table 8).

Table 8. Factors for suspecting a gastrointestinal DAN [mod. according to Haslbeck, 1990, level IV; 1998, level IV]

• Long-standing diabetes
• Unequivocal sensorimotor neuropathy
• Evidence of a cardiac autonomic neuropathy and/or other autonomic manifestations, e.g., erectile dysfunction
• Hypoglycaemia and oscillations of blood glucose with poor diabetes control after exclusion of other causes

In individual cases, a gastrointestinal manifestation of autonomic neuropathy does not permit inferences on autonomic disturbances in other organs [Jebbink et al., 1994, level IIa; Jermendy et al., 1991, level IIa; Loba et al., 1997, level IIa; Mayaudon et al., 1999, level IIb].
Hyperglycaemia per se may delay gastric emptying in a scintigraphic test or may falsify an anorectal manometric measurement. For this reason, the patient should show blood sugar levels preferably below 200 mg/dl at the time of these tests [de Boer et al., 1994, level Ib; Eliasson et al., 1995, level III]. Taking into consideration their half-lives, all drugs that affect gastric motility (e.g., prokinetic and psychotropic drugs, opioids) should be discontinued. The intake of food should be stopped at least eight hours before the test (see also Table 6).

4.2.1 Oesophageal dysfunction

Autonomic disturbances in the oesophagus usually progress without symptoms. Diabetic patients have a fivefold higher risk for reflux disease [Ricci et al., 2000, level IIa]. The lengthening of the transit time, motility disturbances (contraction amplitude, contraction duration) as well as reduced pressure in the lower oesophageal sphincter can be demonstrated scintigraphically and manometrically [Horowitz et al., 1989, level IIa; Jermendy et al., 1991, level IIa; Keshavarzian et al., 1987, level III; Loo et al., 1985, level IIa]. For clinical symptoms such as dysphagia and odynophagia, a thorough differential diagnosis must always be performed [strength of recommendation A].

4.2.2 Gallbladder dysfunction

Diabetics often have gallstones, a cholecystomegaly and a delayed gallbladder contraction [Chapman et al., 1996, level III; Haffner et al., 1990, level III; Janatuinen et al., 1993, level IIa; Fraquelli et al., 2003, level III]. The pathogenesis and clinical picture of the diabetic gallbladder dysfunction, which is also known as diabetic cholecystoparesis, diabetic neurogenic gall bladder, diabetic cholecystomegaly or diabetic cholecystopathy, are even today not adequately clarified. However, there are increasing indications for a relationship between disturbed gallbladder motility and DAN [Ruhl and Everhart, 2000, level IIb; Fraquelli et al., 2003, level III; Kajacetin et al., 2003, level III]. In any case, particularly when other manifestations of autonomic neuropathy are present, a careful sonographic examination should be done [strength of recommendation A].

4.2.3 Diabetic gastropathy (diabetic gastroparesis)

Indications of disturbed gastric emptying are observed in 20 to 30 per cent of randomly selected type 1 and type 2 diabetic patients, even though dyspeptic symptoms occur relatively frequently in both diabetics and nondiabetics [Enck et al., 1994, level IIb]. Predominant symptoms are nausea, vomiting, flatulence, feeling of fullness and early feeling of satiety. A thorough diagnostic clarification is always required [strength of recommendation A]. A normal functioning of the gastrointestinal tract is a basic prerequisite for good diabetes control. When, after a fasting period of 8 to 12 hours and after exclusion of an organic cause, remainders of food are still found in the stomach, an appropriate tentative diagnosis can be made. A negative finding, however, does not exclude a gastroparesis. Today, primarily scintigraphic function tests and mass spectrometric breath tests are used for diagnosis [Fuchs et al., 1997, level IV]. The functional scintigraphy is the current diagnostic gold standard [strength of recommendation A]. The diagnostic possibilities for a suspected diabetic gastropathy are listed in Table 9 [Stacher, 2001, level IV]. Gastric scintigraphy with double isotope technique is ideal for assessing gastric emptying of solid and liquid food components [Horowitz et al., 1989, level IIa; strength of recommendation B]. As a compromise, an isotopically labelled semiliquid test meal is often used presently.

Carbon-13 breath tests (^{13}C–octanoate breath test) are used to a certain extent [Ghoos et al., 1993, level IIa; Ziegler et al., 1996, level IIa; strength of recommendation B]. For this, labelled octanoate is taken orally, rapidly absorbed in the duodenum and, subsequently, oxidized in the liver. The $^{13}CO_2$ formed can then be measured in the expired breath. A radiation exposure does not occur because a stable isotope is used [Ghoos et al., 1993, level IIa; Ziegler et al. 1996, level IIa]. Recently, very good agreement was observed in a comparison with gastric scintigraphy [Zahn et al., 2003, level IIA].

Two easily performed tests are the gastric emptying of radio-opaque markers, whose diagnostic validity is limited, and sonography [Dorlars et al., 1994, level IIa; Vogelberg and Rathmann, 1986, level IIa]. Here, for example, the change in the postprandial antral area at the aortomesenteric plane is assessed after drinking 300 ml water over 30 minutes. However, the test has also limited diagnostic value since in diabetic gastropathy gastric emptying of solid food components is primarily impaired by the disturbed antral peristalsis [Rathmann and Ziegler, 1994, level IV; strength of recommendation B]. Moreover, there is no standardised, generally recognised diagnostic procedure.

Because DAN and hyperglycaemia are important pathogenetic factors for dysmotility of the stomach and the entire gastrointestinal tract, a blood glucose value below 200

mg/dl should be achieved before the test to avoid false-positive scintigraphs [Fraser et al., 1993, level IIb; Horowitz et al., 1989, level IIa; Mearin et al., 1986, level IIa]. Whether this prerequisite also applies to the breath test is not known. It is clear that all drugs affecting gastrointestinal motility such as, for example, prokinetics, opioids and psychotropic drugs should not be taken at least one day before the examination. Other tests such as duplex sonography for assessing the transpyloric flow pattern, manometry and NMR are used only in specialised centres [Table 9, strength of recommendation C].

4.2.4 Diabetic diarrhoea

Diabetic diarrhoea occurs over ten times more frequently in type 1 than in type 2 diabetes [Lysy et al., 1999, level III]. Characteristic are intermittent, brown, watery, voluminous stools that occur frequently at night and could be associated with a sudden impulse to defaecate and tenesmus. Episodic progressions with periods of normal intestinal function or even constipation occur.
The pathogenesis has not been unequivocally resolved, but is probably multifactorial. The diagnosis, in principle, is made by exclusion. Important differential diagnoses such as bacterial overgrowth, coeliac disease (gluten-sensitive enteropathy), exocrine pancreatic insufficiency and disorders in the area of efferent bile ducts may themselves represent a part of the syndrome of diabetic diarrhoea.
The evidence of DAN in one or more organ systems (e.g., CAN) also serves as a confirmation of the diagnosis. In addition to the medical history (sugar substitutes, laxatives, diabetes therapy with metformin, alcohol) and, if necessary, a wide spectrum of laboratory tests and endoscopy, the hydrogen breath test is an important functional examination for detecting frequent bacterial miscolonisation in the small intestine of diabetic patients. Today, due to their noninvasiveness, simplicity of performing the measurement, and high sensitivity, H_2 exhalation tests have a prominent position in small intestine diagnosis [Fuchs et al., 1997, level IV; strength of recommendation A]. When bacterial miscolonisation is present, orally ingested glucose, for example, is already metabolised by the bacteria in the jejunum and leads to a rapid rise of the H_2 concentration in the respiratory air, which can be easily measured with commercially available analytical equipment. The ^{13}C breath tests are new and even more reliable [Delbende et al., 2000, level Ib; strength of recommendation A]. Further diagnostic possibilities for investigating small intestinal motility are manometry and scintigraphy of the small intestine; however, these methods are carried out only in gastroenterological clinics and specialised centres [strength of recommendation C].

4.2.5 Diabetic constipation

Frequent constipation in diabetic patients may occur. A large number of differential diagnostic possibilities may be considered that apply to the colon itself and to other causes such as endocrine metabolic disturbances, chronic medication, intoxication and diseases of the central and peripheral nervous system. In addition to the digital rectal examination and the search for occult blood in the stool, endoscopy is an important method for excluding morphological causes. Anorectal manometry helps in the recognition and differentiation of the anorectal causes of constipation. The determination of the colon transit time is an important function that is measured with radio-opaque markers, for example, in the so-called Hinton test [Hinton et al., 1969, level IIb; strength of recommendation A]. However, taking one capsule a day for six consecutive days is more practical [Schindlbeck et al., 1990, level IV]. One hard gelatine capsule contains a constant number of 20 to 24 markers. One day after taking the last capsule, the x-ray picture of the abdomen is taken. The number of the remaining markers determines the transit time.

4.2.6 Diabetic faecal incontinence

Diabetic faecal incontinence may occur together with severe diabetic diarrhoea or as an anorectal dysfunction alone. The continence mechanisms may be studied using anorectal manometry [strength of recommendation B]. Here, the pressure characteristics of the anorectal sphincter muscle are measured under standardised conditions in a specialised diagnostic unit. Further functional examinations for the diagnosis of anorectal dysfunction and morphological changes are the defaecography and the endosonography [Bielefeldt et al., 1990, level IV; Law et al., 1991, level IIb; strength of recommendation A].

Table 9
Diagnostic procedures for suspected diabetic gastropathy [strength of recommendation A]

Exclusion of other organic diseases:
•Endoscopy
Detection of motility disturbances:
•Gastric emptying scintigraphy **•^{13}C breath tests** ^{13}C-acetate breath test for liquids, ^{13}C-octanoate breath test for solid food
Additional examinations:
• **Sonography** (for screening with liquid) • **Radio-opaque markers** • **Duplex sonography** (transpyloric flow pattern) • **Magnetic resonance imaging** • **Manometry** • **Electrogastrography** (gastric dysrhythmia)

4.3 Urogenital Tract

DAN in the urogenital tract area shows two clinically relevant manifestations: The diabetic neurogenic voiding dysfunction (diabetic cystopathy) and complex sexual functional disturbances (erectile dysfunction and sexual dysfunction in women).

4.3.1 Diabetic cystopathy

The development of a sensorimotor deficit and an increase in bladder volume often develops insidiously. The consequences are a belated desire to urinate, long time intervals between individual mictions and, particularly in the decompensated stage with large bladder capacity, large urinary volumes with extended miction time and reduced maximum flow rate. The decompensated stage is characterised by bladder wall distension with residual urine, whereupon voiding succeeds only with abdominal muscular pressure. The final stage is the overflow bladder with or without urinary incontinence. This leads to a changed urination behaviour with diminished urinary stream and pollakisuria [Kaplan et al., 1995, level IV; Starer and Libow, 1990, level IV; Hampel et al., 2003, level IV]. The susceptibility to urinary tract infections increases. When, especially male diabetics have more than one urinary tract infection per year, additional diagnostic tests should be conducted. Because neurogenic voiding dysfunction often progresses asymptomatically and because of the possible detrimental effects on the entire urinary tract, every diabetic should be regularly and specifically asked about micturition difficulties (frequency of micturition, residual urine, urinary tract infections, diminished urinary stream, necessity of abdominal muscular pressure, incontinence). A semiquantitative dipstick and sediment analysis of the urine is obligatory [Stief et al., 1996, level IV; strength of recommendation A]. The diagnostic procedure for neurogenic voiding dysfunction is shown in Table 10.

Table 10
Diagnostics of diabetic cystopathy [mod. according to Stief et al., 1996, level IV; strength of recommendation A]

• Urine analysis
• Sonography
• Uroflowmetry
• Urodynamic examination
•Miction cysto-urethrography (for suspicion of pathological changes in micturition)

For the diagnosis of diabetic voiding dysfunction, sonography (determination of the bladder volume, more than 500 ml abnormal; depiction of residual urine after miction, more than 50 ml abnormal) is recommended as the screening method. Depending on these findings, further urological-radiological or endoscopic testing may be needed [Stief et al., 1996, level IV]. For stress or urge incontinence, a neurourological examination absolutely must be performed [Kaplan et al., 1995, level IV; strength of recommendation A].

4.3.2 Complex sexual dysfunctions

Sexual dysfunctions are common for diabetes mellitus, but is often a taboo subject for the physician and patient [Price, 1993, level IV]. However, sexual dysfunction seriously lowers the quality of life of those affected [Rance et al., 2003, level III]. An

autonomic diabetic neuropathy may be present in about 50 per cent of the male diabetics and in about 30 per cent of the female diabetics with sexual disturbances [Fedele et al., 1998, level III; Enzlin et al., 2002, level IIa]. The incidence of erectile dysfunction is 50.7 cases per 1000 person-years in diabetics [Johannes et al., 2000], which is about double that of nondiabetics. In a large epidemiological study in Germany, an average frequency of 19.2 per cent was found in the general population with a clear age-dependent increase of 2.3 to 53.4 per cent. Moreover, a high comorbidity with hypertension, diabetes mellitus, operations in the pelvic area and urinary tract symptoms was observed [Braun et al., 2000, level III]. Disturbances of the neurogenic and endothelium-mediated relaxations of the cavernous body and vessels, which secondarily lead to a distinct vascular deficit, are believed to be the pathogenetic mechanisms.

Erectile dysfunction

Erectile dysfunction ranks as one of the most frequent organ manifestations of DAN. It always requires a careful differential diagnosis with multidisciplinary cooperation [Haslbeck, 1998, level IV, Guidelines of the German Society for Urology, 2001, level IV]. Table 11 shows the diagnostic procedure for erectile dysfunction. From the diagnostic level 2b onwards, a referral to an urologist is recommended.

Table 11

Diagnosis of erectile dysfunction [according to Stief et al., 1996, level IV; strength of recommendation A]

Diagnostic level 1:
a) Medical history, sexual history, standard questionnaire (IIEF, IIEF-5), clinical findings, laboratory tests
b) Total testosterone (optional: free testosterone), prolactin, FSH, LH
Diagnostic level 2: (optional)
a) Test with a PDE5 inhibitor (sildenafil, vardenafil, tadalafil)
b) Intracavernous injection (ICI) test
c) Doppler/duplex sonography
Diagnostic level 3: (only when a surgical therapy is planned)
a) cavernosometry and cavernosography

In addition to being often the organic cause of DAN, erectile dysfunction is also frequently influenced secondarily by psychogenic factors. Therefore, a systematic and careful diagnosis must always be carried out [strength of recommendation A]. Potential drug side effects (antihypertensives, antidepressants, tranquilizers) must be considered [Strian and Haslbeck, 1999, level IV]. A validated short form of a 15-part questionnaire on sexual health in men has been practice-proven [Rosen et al., 1999, level IV; strength of recommendation B]. The five questions in the short questionnaire are related to erectile function and sexual satisfaction. If fewer than 22 points are reached, erectile dysfunction should be suspected (Tables 18 and 19). After conclusion of the second diagnostic level, about 60 to 80 per cent of the patients could be admitted to a therapy. If additional invasive andrological investigations are necessary, the third diagnostic level is carried out. This level consists of the selective pharmaco-cavernosometry and pharmaco-cavernosography and serves as the preparation for reconstructive surgical measures such as the penile implant surgery [Stief et al., 1996, level IV; strength of recommendation C].

Sexual dysfunction in women
Diabetic women may likewise be affected by sexual dysfunction. Complaints include loss of libido as well as the inability to become aroused, the absence of orgasm or dyspareunia [Enzlin et al., 1998; level IV; Enzlin et al., 2002, level IIa].

4.4 Neuroendocrine System

The autonomic nervous system represents an important factor for hormonal regulation. Hypoglycaemia-associated autonomic failure (HAAF) is a clinically significant syndrome which includes a limited endocrine response during hypoglycaemia, a changed threshold for the release of counterregulatory hormones and an impaired hypoglycaemia awareness (hypoglycaemia unawareness) [Heller et al., 1987, level IIb; Lingenfelser et al., 1994, level IIb; Cryer et al., 2004, level IV]. Autonomic adrenergic warning symptoms (e.g., sweating, hunger, nervousness, heart palpitations, trembling) begin belatedly (elevated threshold, which means a lower actuating blood sugar level) or are completely absent during the development of a neuroglucopenia (typical symptoms: confusion, dizziness, impaired vision and weakness). Earlier, the classic CAN was thought to be responsible for the impairment of the autonomic adrenal counterregulation, but it was soon recognised that the overlap of the two disease manifestations was partial at the most [Ryder et al., 1990, level IIa]. Ever since it has been known that antecedent hypoglycaemic episodes can compromise the counterregulation in subsequent episodes [Heller and Cryer, 1991, level IIb], it is clear that other mechanisms must be responsible. In most cases, the impairment is probably the consequence of a centrally triggered cortisol-induced suppression of catecholamine secretion caused by recurrent episodes of hypoglycaemia [Davis et al., 1996, level Ib]. DAN itself can also directly contribute to a secretion deficit of catecholamine [Bottini et al., 1997, level IIa] and, thus, limit the treatment success of a perceptual disorder [Fanelli et al., 1997, level IIa]. Appropriate diagnostic function tests (stepped hyperinsulinaemic-hypoglycaemic clamp technique, insulin infusion tests) are complicated and can be conducted only in specialised laboratories [Consensus Statement, 1996, level IV; Haslbeck, 2000a, level IV; strength of recommendation C].
The prevalence of this dysfunction in type 1 diabetics [Gerich et al., 1991, level IV], which predisposes the patient to severe hypoglycaemic episodes, is estimated to be about 25 per cent with a large spread [Hepburn et al., 1990, level III]. Affected patients are characterised by low HbA1c [Mokan et al., 1994, level IIa; Widom and Simonson, 1990, level IIa], long diabetes duration [Hepburn et al., 1990, level III; Mokan et al., 1994, level IIa] and a large number of survived severe hypoglycaemic episodes [Hepburn et al., 1990, level III; Mokan et al., 1994, level IIa]. Occasionally (about 10 per cent), symptoms or findings for a CAN are also observed.

4.5 Trophism and Sudomotor System

Trophic disorders of the extremities as well as that of the vasomotor and sudomotor systems (clinically warm and dry foot) are among the most important pathogenetic factors of the diabetic foot syndrome. An autonomic dysfunction in the lower extremities is one of the important risk factors for the diabetic foot syndrome. A series of qualitative tests for detecting sudomotor function (see Table 12) and neurovascular function tests (e.g., laser-Doppler perfusion imaging) may be used for diagnosis [Forst and Pfützner, 2004, level IV].

Disturbances in thermoregulatory sweat secretion occur frequently in diabetes mellitus [Haslbeck, 1993, level IV]. In a consensus of the American Diabetes Association, testing the sudomotor system through temperature and chemically induced sweating for DAN was recommended as the noninvasive diagnostic method of choice together with cardiovascular function tests [ADA, 1988, level IV]. If direct HRV determination is not possible due to an absolute arrhythmia, CAN may be presumed if the tests listed in Table 12 yield abnormal findings [Spitzer et al., 1997, level III; Niakan and Harati, 1988, level IIb].

Table 12
Sudomotor tests for the indirect assessment of CAN [strength of recommendation B]

Determination of the sympathetic skin response = SSR
Testing the quantitative sudomotor axon reflexes (Quantitative sudomotor axon reflex test, QSART)
Ninhydrin test, acetylcholine sweat spot test

The SSR can be measured with most EMG instruments. The QSART is presently performed only in neurological departments with specialised laboratories because of its very complex technology. Easy-to-use portable instruments are in development. The data obtained from SSR and QSART are largely in agreement [Maselli et al., 1989, level IIa].

4.5.1 Sympathetic skin response

Details on the methodology have been described at length [Spitzer et. al., 1997, level III]. Only the absence of a response is assessed as abnormal [Spitzer et al., 1997, level III; Maselli et al., 1989, level IIa; Niakan and Harati 1988, level IIb; Tzeng et al., 1993, level IIa]. The evaluation of an abnormal SSR finding is only possible in a clinical setting. The sensitivity for the detection of CAN lies by 75 per cent, the specificity by 96 per cent [Spitzer et al., 1997, level III]. An abnormal SSR result can be caused by both a central and peripheral lesion of the sudomotor system.

4.5.2 Quantitative sudomotor axon reflex test

The QSART method analyses exclusively the function of distal postganglionic sudomotor fibres. For the quantitative sudomotor axon reflex test (QSART), the moisture development in a defined skin area after direct current iontophoresis with one per cent carbachol solution or 10 per cent acetylcholine solution is determined hygrometrically [Lang et al., 1993, level IIb; Low et al., 1983, level IIa]. The sensitivity of QSART for the detection of CAN lies by 70 per cent, the specificity by 83 per cent [Spitzer et al., 1997, level III]. These values confirm preliminary experiments with similar conclusions [Low et al., 1986, level IIa; Maselli et al., 1989, level IIa]. The data obtained from SSR and QSART are largely in agreement [Maselli et al., 1989, level IIa].

4.5.3 Ninhydrin test, acetylcholine sweat spot test

This test is relatively complicated and is performed in only a few centres at present [strength of recommendation C].

4.6 Respiratory System

The disorders of the autonomic nervous system in the respiratory tract are still not yet fully clarified in their clinical and diagnostic relevance. In addition to a hypothesis of a predisposition to arrhythmias and to sudden cardiac death through CAN, a faulty central regulation of respiration is believed to be a further cause for the increased mortality from CAN [Page and Watkins, 1978, level IV]. This is supported by a study that reports the repeated incidences of sleep apnoea in CAN patients [Rees et al., 1981, level IIa]. More recent studies likewise describe the frequent incidences of sleep apnoea in CAN [Ficker et al., 1998, level IIb]. These observations, however, were not confirmed by other authors [Catterall et al., 1984, level IIa]. A reduced ventilatory response to to progressive hypercapnia or hypoxaemia is indicative of a central dysregulation of respiration that has been demonstrated in patients with CAN [Wanke et al., 1993, level IIa].

4.7 Pupillomotor System

Pupillary impairments become evident especially as a diminished dark adaptation [Isotani et al., 1995, level IIa]. Miosis is the sequela of a major sympathetic injury [Smith and Smith, 1983, level IIa; Smith and Dewhirst, 1986, level IIa]. A suitable functional examination that, however, did not gain practical acceptance in Germany, is the pupillometry [Dyck and Thomas, 1999, level IV; strength of recommendation C]. The pupillary light reflex can be measured with an infrared pupillograph by an ophthalmologist. Pupillary contraction in diabetics with autonomic pupillary dysfunction is reduced. Redilation after light stimulation is delayed. Spontaneous fluctuations in the disk diameter are decreased in comparison with that of healthy subjects [Smith and Smith, 1999, level IV]. The impaired pupillomotor function of a diabetic patient can be a hindrance during a fundus examination.

5 Therapy of DAN

The improvement or optimisation of the metabolic control is presently the only reasonably sure causal therapy for CAN in type 1 diabetes [DCCT, 1998, level Ib; Gaede et al., 1999, level Ib; strength of recommendation A]. In type 2 diabetes, different studies have shown no clear positive effect on CAN [UKPDS, 1998, level Ib]. On the other hand, a multifactorial treatment with the goal to optimise HbA1c, blood pressure and lipids, reduced the risk for CAN by about 60 per cent over eight years (see 5.1.2) [Gaede et al., 2003, level IB]. Hardly any studies are available on the remaining manifestations of DAN. A 2-year study in type 2 diabetics showed that the optimisation of blood glucose control had no effect on erectile dysfunction [Azad et al., 1999, level Ib]. On the basis of available data, it is believed that autonomic neuropathy in comparison with sensorimotor polyneuropathy in type 1 and type 2 diabetic patients responds less well to metabolic correction. This could be due to the present lack of adequately sensitive test methods that are able to detect CAN in particular. In clinical autonomic neuropathies, because so many different organs and their functions may be afflicted, there are numerous possibilities for a specific symptomatic therapy. The most common neuropathic manifestations include diabetic gastropathy (diabetic gastroparesis syndrome), erectile dysfunction and impaired hypoglycaemia awareness [Haslbeck, 1993, level IV; 1996, level IV; Haslbeck et al., 1999, level IV]. The current standard symptomatic therapeutic possibilities for different organs and organ systems are summarised in Table 15.

5.1 Cardiovascular System

5.1.1 Metabolic control

The effect of an intensified diabetes therapy on the functional parameters of the autonomic nervous systems was one of the central themes of the DCCT study [1998]. Over an observation time of 6.5 years, autonomic function tests (R-R variation, Valsalva ratio and orthostatic response) were carried out initially and in 2-year intervals on diabetic patients receiving intensified or conventional insulin therapy. In addition, patients were asked quarterly about autonomic symptoms (orthostatic hypotension, symptoms of gastroparesis, diarrhoea and constipation, urogenital symptoms, sudomotor dysfunction or impaired hypoglycaemia awareness). During the 6.5 years, the number of persons with autonomic dysfunctions almost doubled. The decline in R-R variation was the predominant factor that was significantly reduced through intensified therapy. Significant differences in the Valsalva ratio or orthostatic response were not found. Of the autonomic symptoms, aside from the statistically borderline prevalence of some symptoms (nausea, hypoglycaemia awareness), residual urine was detected significantly more often in diabetics treated with conventional therapy. In summary, this study indicates that intensified insulin therapy can delay the development and progression of abnormal autonomic test findings [DCCT, 1998, level Ib]. It should be noted that, at this time, the only proven, effective preventive therapeutic approach for CAN in type 1 diabetes is an early optimisation of the metabolic control and patient education [strength of recommendation A].

5.1.2 Multifactorial intervention

In a prospective, controlled treatment study (average duration 7.8 years) in type 2 diabetics with microalbuminuria, multifactorial drug intervention with improved diabetes control, adequate blood pressure therapy (ACE inhibitors) and lipid-lowering treatment (mostly statins) led to an approximately 50 per cent reduction of cardiovascular and microangiopathic risks (retinopathy, nephropathy). In addition, the risk for autonomic neuropathy (DAN) could be reduced by about 60 per cent [Gaede et al., 1999, level Ib, Gaede et al., 2003, level Ib, strength of recommendation A].

5.1.3 Pathogenetic-based approaches

During the past years, diverse pharmacological management strategies have been studied that have shown only limited success: aldose reductase inhibitors, antioxidants and ACE inhibitors [strength of recommendation B]. Here, risk-benefit considerations are always necessary.

Aldose reductase inhibitors
Up until now, tolrestat is the only aldose reductase inhibitor (ARI) for which an improvement in the cardiac autonomic function tests and a reduction of the systolic blood pressure response after a position change has been demonstrated [Didangelos et al., 1998, level Ib; Giugliano et al., 1993, level Ib]. A placebo-controlled study of epalrestat (150 mg/d) in type 2 diabetics over 24 weeks showed a significant improvement of the pupillomotor function and HRV during deep breathing [Nakayama et al, 2001, level Ib]. Drugs from this group have been removed from clinical tests and the market primarily due to hepatotoxic side effects. In type 1 and type 2

diabetics with neuropathy and reduced left ventricular ejection fraction, an improvement in the test findings was achieved after a one-year therapy with zopolrestat [Johnson et al., 2004, level Ib]. Furthermore, a three-month treatment with epalrestat improved gastric motility and the HRV power spectrum in diabetic patients [Okamoto et al., 2003, level Ib].

Antioxidants
The only clinically available free radical scavenger, alpha-lipoic acid (ALA), was also studied for the therapy of CAN. This study in 73 type 2 diabetics showed that an oral dosage of 4 x 200 mg ALA/day over four months brought about an improvement of some cardiac tests [Ziegler et al., 1997, level Ib; Ziegler et al., 1999, level IV]. Taken for four months, vitamin E (600 mg/day p.o.) led to an improvement of heart rate variability in type 2 diabetics [Mantella et al., 2001, level Ib].

ACE inhibitors
After three or six months, the ACE inhibitor quinalapril brought about a significant increase in parasympathetic activity [Kontopoulos et al., 1997, level Ib].

5.1.4 Symptomatic therapy

In pronounced sinus tachycardia due to a vagal dysfunction, low dosed cardioselective beta-receptor blockers may be administered. Here, the possibility of a limited awareness for warning symptoms of hypoglycaemia must be kept in mind [Ziegler and Gries, 1994, level IV; Haslbeck, 1993, level IV]. In a placebo-controlled, randomised, crossover study, a six-week therapy of 100 mg metoprolol per day in type 1 diabetics with albuminuria, increased cardiovascular risk and treatment with an ACE inhibitor, resulted in an improvement of the vagal cardiovascular reflexes [Ebbehoj et al., 2002, level Ib]. A 12-week endurance training led to a significant improvement of vagal activity and physical fitness in diabetics with CAN [Howorka et al., 1997, level IIb].
The drug treatment of orthostatic hypotension is problematic since the goal is to achieve a blood pressure increase while standing and, simultaneously, to avoid a clear increase while lying down. Therefore, physical measures should be first attempted (Table 13) before using medications such as sympathomimetics with short half-lives, for example, midodrine or fludrocortisone [Purewal and Watkins, 1995, level IV; Stumpf and Mitrzyk, 1994, level IV].

Table 13
Physical measures for the treatment of orthostatic hypotension [mod. according to Ziegler and Gries, 1994, level I; van Lieshout et al., 1992, level IV; strength of recommendation A]

• Elastic compression tights – problematic in summer or in diabetic diarrhoea
• Physical activity – compatible with the individual situation
• Sleeping with raised upper body
• Standing up slowly after laying in bed
• Crossing the legs while standing

5.2 Gastrointestinal Tract

5.2.1 Metabolic control

Diabetic gastroenteropathy often occurs in combination with CAN in advanced stages of autonomic neuropathy. Even though clinical experience indicates the potentially favourable effect of a near normal diabetes control, it has not yet been proven in specific evidence-based studies [strength of recommendation A]. Whether the supplementary administration of a gastroprokinetic drug during conventional diabetes therapy leads to an improvement of diabetes control is disputed [Braden et al., 2002, level Ib; Ueno et al., 2002, level Ib; Lehmann et al., 2003, level Ib].

5.2.2 Oesophageal dysfunction

On a subjective level, oesophageal motility disturbances and changes in the transit time in diabetic patients progress mostly asymptomatically. Indications of a reflux disease as well as symptoms such as dysphagia and odynophagia must always be clarified by endoscopy.

5.2.3 Gallbladder dysfunction

Diabetic patients often have gallstones, cholecystomegaly and delayed gallbladder contraction. Interrelationships between autonomic neuropathy, hyperglycaemia and gallbladder dysfunction have been demonstrated. An improvement of the gallbladder function could be achieved through the correction of the metabolic situation [Burgstaller et al., 1992, level IIa; Hahm et al., 1996, level IIa]. During treatment with cisapride, a gastroprokinetic drug that is no longer on the market, a significant reduction in the gallbladder volume of about 40 per cent in comparison with the placebo was observed [Kapicioglu et al., 1998]. In verified autonomic neuropathy, a potential involvement of the gallbladder should be considered, even though the clinical importance of the diabetic gallbladder dysfunction is still not yet sufficiently clarified. In further investigations, specific knowledge on the relevance of the disease in terms of the overall medical condition and, if necessary, on the treatment must be gathered [Haslbeck, 2000a, level IV; strength of recommendation B]. Gallstones must be treated.

5.2.4 Diabetic gastropathy (diabetic gastroparesis)

A diabetic gastropathy with impaired motility and gastric emptying hinders the interactions between carbohydrate absorption, drug effect and, in particular, the effect of insulin [Haslbeck, 1990, level IV]. Moreover, an acutely elevated blood glucose concentration (higher than about 10 mmol/l) can directly interfere with gastric emptying [Fraser et al., 1990, level IIb]. Sequelae of gastrointestinal dysfunction could be acute metabolic imbalances, especially hypoglycaemia, but also a long-term hyperglycaemia with corresponding long-term risks. The causal therapy of diabetic neuropathy and other long-term diabetic complications is the near-normalisation of metabolic control. However, this is hindered by a gastrointestinal dysfunction [Haslbeck, 2000a, level IV].

General therapeutic measures

For diabetic gastropathy, generally practical and especially dietetic measures are to be taken into account. These are based on the fact that the emptying of solid foodstuffs from the stomach is almost always delayed. Food should be thoroughly chewed and the patient should remain erect for at least a half hour after each meal. The following dietary measures are recommended: small, if necessary semiliquid or liquid, meals spread over the day, reduced consumption of fats and little dietary fibre [strength of recommendation A].

Pharmacotherapy

A consequence of the impaired interaction between carbohydrate absorption and the effect of an antidiabetic therapy is the necessity of treating the intestinal dysfunction with gastroprokinetics, which after diagnostic confirmation should be consequently performed (Table 15). The following prokinetic drugs may be used [IDF, 1999, level IV; Vinik et al., 2000, level IV; strength of recommendation A]: the dopamine antagonists, metoclopramide and domperidone, as well as erythromycin as a motilide. Since July 2000, the 5-HT4 antagonist, cisapride, is no longer on the market after a worldwide increase in fatal cardiac complications, especially in paediatric patients, was observed. Metoclopramide and domperidone cause an acceleration of gastric emptying by blocking the dopamine receptor. Erythromycin works by stimulating motilin receptors. The mechanism of action of metoclopramide and cisapride also comprises a stimulation of 5-hydroxytryptamine receptors and acetylcholine release. Metoclopramide may lose its efficacy already after a few weeks [Schade et al., 1985, level IIb; McCallum et al., 1991, level IIb; Malagelada et al., 1980. level IIa]. Domperidone effects an improved gastric emptying for liquid and solid foods. After longer use, the effect of this drug likewise decreases for solid foods, while that for liquids is largely sustained [Brogden et al., 1982, level IV; Horowitz et al., 1985, level IIa]. Erythromycin apparently accelerates the transport of liquid and solid food components better than metoclopramide [Richards et al., 1993, level IIb; Erbas et al., 1993, level Ib; Desautels et al., 1995, level Ib]. The therapeutic application of erythromycin is limited due to a relatively rapid development of tolerance, the antibiotic effect and side effects such as, for example, skin reactions and diarrhoea [Tanis et al., 1993, level IV].

For the long-term therapy of diabetic gastropathy, erythromycin analogues (so-called motilides) that have only motilin agonist effects and no antibiotic effect have been tested. Positive results have been reported for these drugs [Ishii et al., 1997, level IIa; Kawamura et al., 1993, level III; Nakamura et al., 1994, level IIb]. Until the gastroprokinetic cisapride was taken off the market, it was the drug of choice for its positive effect on gastric emptying and antropyloroduodenal motility. In comparison with other prokinetics, it shows an improved effect without substantial loss of efficacy for up to two years [Fraser et al., 1993, level IIb; Horowitz and Fraser, 1994, level IV; Horowitz et al., 1987, level IIa]. Cisapride is currently not available in Germany, Great Britain and Luxembourg. Unfortunately, cisapride was withdrawn worldwide by the manufacturer in 2003. Clinical experience and newer studies have shown that a therapy with gastroprokinetic drugs leads to a rapid improvement in the dyspeptic symptoms and also to a significantly better quality of life [Farup et al., 1998, level Ib; Silvers et al., 1998, level Ib; strength of evidence A].

Of practical therapeutic importance may be that type 1 diabetics with gastroparesis need about 25 per cent less insulin postprandially than diabetics without this disorder [Ishii et al. 1997, level IIa]. In addition to an overall lower insulin dosage, it may be

necessary to eliminate the injection-meal interval or, possibly, to inject the insulin after beginning the meal. According to clinical experience, short-acting insulin analogues may be advantageous in individual cases [Haslbeck, 2000b, level IV].

Nondrug therapy
Drainage by means of a gastric tube may be effective in diabetic ketoacidotic coma due to a possible gastroparesis. In rare cases of advanced diabetic gastropathy, a long-term treatment with a gastric or duodenal tube may be considered. The implantation of a gastric pacemaker has been described when conservative therapy fails [Konturek et al., 1997, level IV]. With an implantation system now commercially available (Enterra, Medtronic) and increasing clinical experience, this therapy may be considered for severe cases [Forster et al., 2001, level III; strength of recommendation C]. Afterwards, a prolonged improvement of the symptoms in the upper gastrointestinal tract has been observed [Lin et al., 2004, level III]. A surgical treatment with gastrojejunostomy should come into question only in very rare and therapy-resistant cases [Watkins et al., 2003, level III; strength of recommendation C].

5.2.5 Diabetic diarrhoea

After an exhaustive diagnostic clarification, a number of medications may be used for diabetic diarrhoea that target one or more specific causes and/or that are symptomatically effective (Table 15). For example, gluten-sensitive enteropathy and exocrine pancreatic insufficiency may be treated with a gluten-free diet and supplementation of pancreatic enzymes. After diagnosis of the frequently occurring bacterial miscolonisation of the small intestine, an antibiotic treatment (e.g., with doxycycline, ampicillin or metronidazole) for weeks to months - with interruptions for withdrawal trials - is justified [strength of recommendation B]. However, due to development of tolerance, it is recommended that this treatment be limited to severe symptomatic episodes or to a medication regime that is alternated every one to two weeks. Synthetic opioids such as loperamide may be intermittently administered for symptomatic relief [Haslbeck, 1993, level IV; strength of recommendation B]. Due to the impaired intestinal adrenergic function in autonomic neuropathy, agonists such as the peripheral alpha-2 agonist, clonidine, are effective even at lower dosages [Schiller et al., 1985, level IIa; Fedorak et al., 1985, level IV; strength of recommendation B].
In refractory cases, a therapeutic attempt with the long-acting somatostatin analogue, octreotide (e. g., Sandostatin 3 to 6 x 100 g/day as an injection) while taking into account potential side effects such as abdominal cramps, bloating and flatulence has been recommended [Tsai et al., 1986, level IV; Vogelberg et al., 1984]. In alternating episodes of diarrhoea and constipation, hydrophilic dietary fibres such as Psyllium seeds or a mixture of pectin and kaolin may be given [strength of recommendation B].

5.2.6 Diabetic constipation

The basis of the treatment of diabetic constipation is bulk-forming measures, drinking adequate amounts of liquids, dietary fibres and regular exercise. Dietary fibres that bind water well (wheat bran, flax seed, Psyllium seeds) are best when eaten with a meal and are effective in many patients (Table 15). Osmotically active laxatives include lactulose, macrogol or saline laxatives such as sodium sulphate (Glauber's salt) and magnesium sulphate (Carlsbad salt; use caution when kidney function is impaired) [strength of recommendation B]. Motility and secretion stimulating laxatives such as bisacodyl and anthraquinone derivatives should be used only

intermittently since electrolyte loss and therapy resistance have been observed. In special cases, metoclopramide, domperidone and cisapride, which is no longer available, may be tried for diabetic constipation [Lautenbacher et al., 1986, level IV; strength of recommendation C].

5.2.7 Anorectal dysfunction (diabetic faecal incontinence)

The diabetic faecal incontinence, which belongs to the less known gastrointestinal complications of diabetes mellitus, is usually associated with nightly diarrhoea in over 50 per cent of the affected diabetics. The effects of an acute hyperglycaemia on sphincter function, rectal compliance and faecal incontinence have been described [Russo et al., 2004, level IIa]. For pharmacological management, antidiarrhoeal agents (e.g., loperamide) are recommended to improve the compliance of the rectal and anal sphincter strength [strength of recommendation B]. Biofeedback training is usually also therapeutically effective [Enck et al., 1988, level IIa; strength of recommendation B].

5.3 Urogenital Tract

5.3.1 Diabetic cystopathy

Even though not conclusively demonstrated, the primary therapeutic goal for diabetic cystopathy is also the improvement of metabolic control. A thorough differential diagnosis and, if necessary, therapy of a voiding dysfunction arising from mechanical causes, for example, from an enlargement of the prostate, are of fundamental importance (Table 15).
Anticholinergics are used for the pharmacological therapy of detrusor hyperreflexia. Reduced detrusor contractility is treated with parasympathomimetics, such as, carbachol and distigmine [strength of recommendation B].
Potential side effects should be carefully considered [Stief et al., 1996, level IV]. Urinary tract infections must be treated with antibiotics. A bladder outlet obstruction or a moderate obstruction caused by a benign prostatic hyperplasia may be treated with a selective alpha-1 receptor blocker (e.g., tamsulosin) [Eri and Tveter, 1995, level IV; strength of recommendation B]. As further therapeutic measures, the preferred sterile autocatheterism or, in exceptional cases, an indwelling catheter may be applied. Urinary incontinence in female diabetic patients can be positively affected by physiotherapy (training of the pelvic floor muscles, electrostimulation, pessary) and surgical measures [Stief et al., 1996, level IV; strength of recommendation B].

5.3.2 Erectile dysfunction

The therapeutic options for erectile dysfunction are listed in Tables 14 and 15 and will be discussed below in more detail.

Table 14
Therapeutic options for erectile dysfunction

Drug therapy (sildenafil, tadalafil, vardenafil), if necessary hormone replacement
Intracavernous self-injection (ICI) therapy
MUSE (Medicated Urethral System for Erection)
Vacuum erection devices
Penile implants

For purely or primarily psychogenic erectile dysfunction, the therapy should be arranged with a psychologist or psychiatrist [Stief et al., 1996, level IV]. Three phosphodiesterase-5 inhibitors - sildenafil, tadalafil, vardenafil – are available for the treatment of erectile dysfunction [Olsson et al., 2000, level Ib; strength of recommendation A; Saenz de Tejada et al., 2002, level Ib; Goldstein et al., 2003, level Ib]. Randomised, controlled studies in diabetic patients for 12 weeks yielded success rates from 60 to 70 per cent. The effective dose for the majority of diabetic patients was 100 mg sildenafil or 20 mg vardenafil or tadalafil [Boulton et al., 2001, level Ib; Saenz de Tejada et al., 2002, level Ib; Goldstein et al., 2003, level Ib].
Contraindications, especially for a therapy with nitrate or molsidomine-containing drugs, are serious cardiovascular diseases or hypotension, a severe hepatic insufficiency or retinitis pigmentosa. The patient must be informed of the potential side effects such as headache, flushing, impaired vision, nose congestion or heartburn [Goldstein et al., 1998, level Ib; Rendell et al., 1999, level Ib; Nadma-Nathan et al., 1998, level Ib; Price et al., 1998, level Ib; Langtry and Markham, 1999, level IV; Lipshultz and Kim, 1999, level IV; Setter et al., 1999, level IV]. The same indications and contraindications basically apply to the new phosphodiesterase-5 inhibitors, vardenafil and tadalafil [Padma-Nathan et al., 2001, level Ib]. A meta-analysis of 120 studies and cardiological examinations of patients with coronary heart disease did not show an increased risk for cardiac infarction and cardiovascular-related deaths [Mitlemann et al., 2003, level Ia).
Apomorphine, a substance with sublingual form of administration, has hardly any effect in diabetic patients [Lal et al., 1989, level IIa; von Keitz et al., 2002, level IIa; strength of recommendation C].
The intracavernous self-injection (ICI) therapy may be used in patients who cannot be treated with sildenafil or for whom sildenafil is ineffective [Stief et al., 1996, level IV; Linet and Ogrine, 1996, level Ib; strength of recommendation B]. Prostaglandin is used the most. The main risks for intravenous application are prolonged erections, which require immediate countermeasures, local infections, haematomas and cavernosal fibrosis. The transurethral application of prostaglandin E1 (Medicated Urethral System for Erection = MUSE) is not as effective as the intracavernosal therapy [Padma-Nathan et al., 1997, level Ib; Williams et al., 1998, level Ib]. Side effects of these therapeutic forms are urethral pain, urethral bleeding, arterial hypotension and prolonged erections.
Vacuum erection devices are not very complicated and have only a few local side effects. Especially for patients with cardiac risks, this noninvasive therapy can be used without systemic side effects [Bodansky, 1994, level IIb; Bosshardt et al., 1995, level IIb; Cookson and Nadig, 1993, level IIb; strength of recommendation B].
Penile implants today constitute the end of the therapeutic spectrum. However, with a correct indication and good diagnostic clarification, the heteroplastic alternative is associated with high acceptance and satisfaction [Burns-Cox et al., 1997, level III; Tefilli et al., 1998, level IIb; strength of recommendation B].

5.4 Neuroendocrine System

Impaired hypoglycaemia awareness can be normalised, if hypoglycaemic episodes are avoided over a longer period (Table 15). This applies especially to nocturnal, unnoticed hypoglycaemia [Fanelli et al., 1997, level IIa; strength of recommendation A]. With a concomitant DAN, an improvement is at least possible [Dagogo-Jack, 1994, level IIa; Fanelli et al., 1997, level IIa; Kendall, 1997, level IIa]. In addition, the awareness can be learned through a special “hypoglycaemia awareness training” [Kanc et al., 1998, level Ib; Chalon et al., 1999, level Ib; strength of recommendation B].

5.5 Trophism and Sudomotor System

For dry skin resulting from anhidrosis, the application of fat-containing or, more recently, also urea-containing topical preparations is recommended for improving the water balance of the skin (Table 15). Moisture preserving ointments should be preferably used after the daily foot bath [Brand, 1983, level IV; strength of recommendation B]. Stimulating substances such as alcohol and pungent spices should be avoided in gustatory sweating. Anticholinergics or clonidine in low doses are possible candidates for the oral medication of this disorder [Janka et al., 1979, level IV; Williams, 1983, level IV; strength of recommendation B]. Recently, good success with the local application of botulinum toxin has been reported [strength of recommendation C]. For the local treatment of trophic disturbances in the lower extremities and that of the diabetic foot, refer to the respective guideline (Table 15).

5.6 Respiratory System

At the present, there is no specific therapy to recommend. If applicable, a relevant treatment for sleep apnoea with CPAP (continuous positive airway pressure therapy), is to be considered [strength of recommendation C].

5.7 Pupillomotor System

The patient should be informed of his impaired dark adaptation and possible endangerment in road traffic at night [Haslbeck, 1993, level IV; strength of recommendation A] (Table 15).

6 Follow-up

Generally, each manifestation of an autonomic neuropathy (e.g., limited heart rate variability) should be monitored at least once a year (consensus of the Guidelines Commission). Suitable screening tests are E/I ratio during deep breathing and the orthostatic response of blood pressure (Tab. 5). For pronounced symptoms and/or for the assessment of a therapeutic success, additional short-term control tests may be necessary.

Table 15
Treatment of diabetic autonomic neuropathies [consensus of the Guidelines Commission, Haslbeck et al., 2001, level IV]

Cardiovascular System

Cardiovascular autonomic neuropathy:
In general, no specific treatment necessary (important: diagnosis and therapy of coronary heart disease and cardiac insufficiency)
Orthostatic hypotension:
• General measures: increasing salt intake, physical activity, sleeping with the head elevated (reduction of diuresis), compression stockings, being mindful of hypotension inducing medications
• Fludrocortisone (beginning with low dosage while monitoring for side effects)
• Vasopressor medications with short half-life (e.g., midodrine)

Gastrointestinal System

Gastroparesis:
• Pharmacotherapy: metoclopramide, domperidone, erythromycin
• Jejunostomy/feeding tube (only in exceptional cases)
• Gastric electrostimulation
Diarrhoea:
• Synthetic opioids (loperamide)
• Clonidine (alpha$_2$ receptor agonist)
• Antibiotics: e.g., gyrase inhibitor, amoxycillin, doxycycline
• Other substances (depending on the specific aetiology of the diarrhoea): Pancreatic enzymes, cholestyramine, Psyllium seeds, kaolin, pectin,
• Octreotide (somatostatin analogue)
Constipation:
• Bulk-forming measures: drinking ample amounts of liquids
• Dietary fibre (Psyllium seeds)
• Exercise
• Osmotically active laxatives: lactulose, macrogol,
• Motility and secretion stimulating laxatives: bisacodyl, anthraquinone, Saline laxatives: magnesium sulphate, sodium sulphate
• Attempt with prokinetics: metoclopramide, domperidone
Faecal incontinence:
• Antidiarrhoeal drugs
• Biofeedback techniques

Endocrine System

Neuroendocrine dysfunction:
• Frequent blood sugar checks and medical check-ups, avoidance of symptomatic and asymptomatic (often nocturnal) hypoglycaemia
• Therapy with regular insulin or short-acting insulin analogues

Urogenital System

Diabetic cystopathy:
• Autocatheterism
• Parasympathomimetic drugs (e.g., carbachol, distigmine)
• Diagnosis and therapy of a prostatic hyperplasia (bladder outlet obstruction):

conservative (for example, hyperthermia, alpha-1 receptor blocker) or urological surgery (resection of the prostate)
• If necessary, antibiotic therapy

Erectile dysfunction:
• Avoidance of drug side effects (caused by antihypertensives, tranquilizers, antidepressants)
• Phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil)
• Erection devices (vacuum pump)
• Intraurethral application of alprostadil (MUSE)
• Intracavernous self-injection (ICI) therapy
• Penile implant

Trophism

Neuropathic foot (neuropathic ulcer, neuropathic arthropathy and osteopathy:
• Foot care (education)
• Pressure relief (orthotic shoes designed to relieve pressure from the forefoot, orthopaedic inserts and shoes)
• Fighting infections (antibiotics, disinfection)
• Local surgical measures (debridement of necroses, calluses and granulation tissue; ray resection, distal phalanx amputation, conservative or surgical therapy of an arterial vascular disease

Neuropathic oedema:
• Saluretics

Sudomotor dysfunction (diabetic anhidrosis, gustatory sweating):
• Prophylaxis for identified cause of sweating (food components), anticholinergics, clonidine (low dosage)
• Avoidance of high heat exposure
• Fat- or urea-containing topical preparations, foot care

Pupillomotor System
• Informing the patient of impaired dark adaptation and endangerment by night blindness
• Risk for glaucoma (intra-ocular pressure test)

Table 16
Clinically important findings and relevant diagnostic methods for diabetic autonomic neuropathy [consensus of the Guidelines Commission, Haslbeck et al., 2001, level IV]

Organs and Functions	Examination Methods
Cardiovascular System • Resting tachycardia • Very low heart rate variability • Exercise intolerance • Diminished or absent awareness of myocardial ischaemias • Perioperative cardiovascular instability • Postural hypotension	• Tests for heart rate variability • Systolic blood pressure response to standing, tilt table test

• Precapillary arteriovenous shunts	
Gastrointestinal System • Dysfunction: Oesophagus, stomach, intestines, gallbladder • Anorectal dysfunction (faecal incontinence)	• Gastric emptying study (radiological, sonographic) • Gastrocolic transit time (radiological) • H_2 exhalation test • Colon transit time with radio-opaque markers • Gallbladder contraction (sonographic) • Oesophageal, gastrointestinal manometry
Urogenital System • Diabetic cystopathy • Erectile dysfunction	• Max. overnight urine volume • Sonography • Urological function tests • Standardised questionnaire (IIEF-5)
Endocrine Dysfunction • Impaired hypoglycaemia awareness and/or absence of hormonal counterregulation	• Tightly monitored blood glucose levels (in particular self-monitored) and especially at night
Pupillomotor System • Miosis • Abnormal pupillary reflexes • Impaired dark adaptation	• Infrared pupillometry (pupil dilation velocity, latent period of the pupillary reflex)
Sudomotor System • Dyshidrosis (gustatory sweating, “dry feet”)	• Sweat tests
Trophism • Hyperkeratoses, rhagades • Neurotrophic ulcer • Osteopathy • Osteoarthropathy (Charcot foot) • Oedema	• Foot inspection • Clinical neurological and angiological examination • X-ray; if necessary, CT, MRI • Pedography (for quality control of orthotic measures and determination of the plantar pressure load)
Respiratory System • Central faulty regulation of breathing with reduced breathing stimulus in contrast to hypercapnia or hypoxaemia • Sleep apnoea • Respiratory arrest	• if necessary, sleep laboratory

Table 17
International index for the evaluation of the questionnaire on erectile dysfunction [mod. according to Rosen et al., 1997, level IIa]

Questions	Response possibilities
1) How often do you have an erection during sexual activity? 2) If you have an erection through sexual stimulation, how often is your erection hard enough for a penetration?	0 = do not have sexual activity 1 = almost never/never 2 = occasionally (less than half the time) 3 = sometimes (more than half the time) 4 = often (much more than half the time) 5 = almost always/always
3) When you have sexual intercourse, how often are you able to penetrate your partner? 4) During sexual intercourse, how often are you able to maintain your erection after penetration of your partner?	0 = do not have sexual intercourse 1 = almost never/never 2 = occasionally (less than half the time) 3 = sometimes (more than half the time) 4 = often (much more than half the time) 5 = almost always/always
5) How difficult is it for you to maintain your erection for the duration of intercourse?	0 = do not have sexual intercourse 1 = extremely difficult 2 = very difficult 3 = difficult 4 = somewhat difficult 5 = not difficult
6) How often have you attempted sexual intercourse?	0 = no attempt made 1 = one to two attempts 2 = three or four attempts 3 = five or six attempts 4 = seven or eight attempts 5 = eleven or more attempts
7) When you attempted sexual intercourse, how often was it satisfactory for you?	0 = do not have sexual intercourse 1 = almost never/never 2 = occasionally (less than half the time) 3 = sometimes (more than half the time) 4 = often (much more than half the time) 5 = almost always/always
8) How often are you satisfied by intercourse?	0 = do not have sexual intercourse 1 = no satisfaction 2 = little satisfaction 3 = moderate satisfaction 4 = much satisfaction 5 = a lot of satisfaction

9) How often did you have an ejaculation during sexual stimulation or intercourse? 10) How often did you have an orgasm or a climax during sexual stimulation or during intercourse?	0 = do not have sexual stimulation or intercourse 1 = almost never/never 2 = occasionally (less than half the time) 3 = sometimes (more half the time) 4 = often (much more than half the time) 5 = almost always/always
11) How often do you feel sexual desire?	1 = almost never/never 2 = occasionally (less than half the time) 3 = sometimes (more than half the time) 4 = often (much more than half the time) 5 = almost always/always
12) How do you rate your sexual desire?	1 = very low/none of the responses are correct 2 = low 3 = moderate 4 = high 5 = very high
13) How satisfied are you with your sex life? 14) How satisfied are you with your sexual relationship to your partner?	1 = very unsatisfied 2 = moderately unsatisfied 3 = alternately satisfied and unsatisfied 4 = moderately satisfied 5 = very satisfied
15) How great is the dependability of achieving and maintaining an erection?	1 = very low 2 = low 3 = moderate 4 = high 5 = very high

All questions pertain to a period of four weeks [mod. according to Rosen et al., 1997].

The IIEF-5 (Table 18) was extracted for practical application from the original questionnaire that was developed for research purposes.

Table 18
The IIEF-5 (International Index of Erectile Function) questionnaire [mod. according to Rosen et al., 1999, level III]*

Within the past six months:					
1. How great is the dependability of achieving and maintaining an erection?	very low	low	moderate	high	very high
2. If you have an erection through sexual stimulation, how often is your erection hard enough for a penetration?	never/ almost never	occasionally (less than half the time)	sometimes (about half the time)	often (much more than half the time)	almost always
3. During sexual intercourse, how often are you able to maintain your erection after penetration of your partner?	never/ almost never	occasionally (less than half the time)	sometimes (about half the time)	often (much more than half the time)	almost always
4. How difficult is it for your to maintain your erection for the duration of intercourse?	extremely difficult	very difficult	difficult	somewhat difficult	not difficult
5. When you attempted sexual intercourse, how often was it satisfactory for you?	never/ almost never	occasionally (less than half the time)	sometimes (about half the time)	often (much more than half the time)	almost always
Points	**1**	**2**	**3**	**4**	**5**

*For each question, mark the one answer that best describes the individual situation.
For evaluating the responses to the questions in Table 18, the point ranges from Table 19 apply.

Table 19
Interpretation of the total points from IIEF-5 for diagnosis of an erectile dysfunction [Rosen et al., 1999, level III]

Total points from questions 1-5	Score	Interpretation of the erectile dysfunction (ED)
Question 1: _____ Question 2: _____ Question 3: _____ Question 4: _____ Question 5: _____ Points: _____	5 – 7 8 – 11 12 – 16 17 – 21 22 – 25	severe ED moderately severe ED mild to moderately severe ED mild ED No ED

7 Bibliography

1. Agelink MW, Malessa R, Baumann B, Majewski T, Akila F, Zeit T, et al.Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. Clin Auton Res 2001; 11(2):99-108.,
2. Airaksinen KH: Silent coronary artery disease in diabetes-a feature of autonomic neuropathy or accelerated atherosclerosis Diabetologia 2001; 44: 259-266,
3. American Diabetes Association Standardized Measures in Diabetic Neuropathy In: Association AD, editor. Clinical practice recommendations 1996, 1996:S72-S92.,
4. American Diabetes Association, American Academy of Neurology. Consensus statement: Report and recommendations of the San Antonio conference on diabetic neuropathy. Diabetes Care 1988; 11(7):592-7.,
5. American Diabetes Association. Clinical Practice Recommendations 2002. DiabetesCare 2002;25 Supplement 1:S3.,
6. Azad N, Emanuele NV, Abraira C, Henderson WG, Colwell J, Levin SR, et al. The effects of intensive glycemic control on neuropathy in the VA cooperative study on type II diabetes mellitus (VA CSDM). J Diabetes Complications 1999;13(5-6):307-13.,
7. Bernardi L: Clinical evaluation of arterial baroreflex activity in diabetes; Diabetes Nutr Metab 2000; 13: 331-340,
8. Bielefeldt K, Enck P, Wienbeck M. Diagnosis and treatment of fecal incontinence.Dig Dis 1990;8(3):179-88.,
9. Bittinger M, Barnert J, Wienbeck M. Autonomic dysfunction and the gastrointestinal tract. Clin Auton Res 1999;9(2):75-81.,
10 . Bodansky HJ. Treatment of male erectile dysfunction using the active vacuum assistdevice. Diabet Med 1994;11(4):410-2.,
11. Bosshardt RJ, Farwerk R, Sikora R, Sohn M, Jakse G. Objective measurement of the effectiveness, therapeutic success and dynamic mechanisms of the vacuum device.Br J Urol 1995;75(6):786-91.,
12. Bottini P, Boschetti E, Pampanelli S, Ciofetta M, Del Sindaco P, Scionti L, et al. Contribution of autonomic neuropathy to reduced plasma adrenaline responses to hypoglycaemia in IDDM: evidence for a nonselective defect. Diabetes 1997; 46(5):814-23.,
13. Boulton AJ, Selam JL, Sweeney M, Ziegler D. Sildenafil citrate for the treatment of erectile dysfunction in men with Type II diabetes mellitus. Diabetologia2001; 44(10):1296-301.,

14 . Braden B, Enghofer M,Schaub M, Usadel KH, Caspary WF, Lemcke B: Long-term cisapride treatment improves diabetic gastroparesis but not glycemic control , Aliment Pharmacol Ther 2002, 16 (7): 1341-1346,
15. Brand P. The diabetic foot. In: Ellenberg M, Rifkin H, editors. Diabetes mellitus, theory and practice. New York: Medical Exemination Publishing Co, 1983:829-849.
16. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. Int J Impot Res 2000; 12(6):305-11.,
17. Brogden RN, Carmine AA, Heel RC, Speight TM, Avery GS. Domperidone. A review of its pharmacological activity, pharmacokinetics and therapeutic efficacy in the symptomatic treatment of chronic dyspepsia and as an antiemetic. Drugs 1982; 24(5):360-400.,
18. Burgstaller M, Barthel S, Kasper H. Diabetic gastroparesis and gallbladder disease. Ultrasound diagnosis after multiple-component meals. Dtsch Med Wochenschr 1992; 117(49):1868-73.,
19. Burns-Cox N, Burston A, Gingell JC. Fifteen years experience of penile prosthesis insertion. Int J Impot Res 1997;9(4):211-6.,
20. Catterall JR, Calverley PM, Ewing DJ, Shapiro CM, Clarke BF, Douglas NJ. Breathing, sleep, and diabetic autonomic neuropathy. Diabetes 1984;33(11):1025-7.,
21. Chalon S, Berlin I, Sachon C, Bosquet F, Grimaldi A. Propranolol in hypoglycaemia unawareness. Diabetes Metab 1999;25(1):23-6.,
22. Chapman BA, Wilson IR, Frampton CM, Chisholm RJ, Stewart NR, Eagar GM, et al. Prevalence of gallbladder disease in diabetes mellitus. Dig Dis Sci 1996; 41(11):2222w8.,
23. Claus D, Feistel H, Brunholzl C, Platsch G, Neundorfer B, Wolf F. Investigation of parasympathetic and sympathetic cardiac innervation in diabetic neuropathy: heart rate variation versus meta-iodo-benzylguanidine measured by single photon emission computed tomography. Clin Auton Res 1994;4(3):117-23.,
24 Claus D, Mendt O, Rozeik C, Engelmann-Kaupek, Huppert PE, Wietholtz H: Prospective investigation of autonomic cardiac neuropathy in diabetes mellitus. Clin Auton Res 2002; 12: 373-378**,**
25. Colhoun HM, Francis DP, Rubens MB, Underwood SR, Fuller JH. The Association of Heart-Rate Variability with Cardiovascular Risk Factors and Coronary Artery Calcification: A study in type 1 diabetic patients and the general population. Diabetes Care 2001; 24(6):1108-14.,
26. Cookson MS, Nadig PW. Long-term results with vacuum constriction device. J Urol 1993; 149(2):290-4.,
27. Cryer PE, Davies SN, Shamoon H: Hypoglycaemia in diabetes, technical review. Diabetes Care 2003; 26: 1902-1912,
28. Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 1994; 43(12):1426-34.,
29. Davis SN, Shavers C, Costa F, Mosqueda-Garcia R. Role of cortisol in the pathogenesis of deficient counterregulation after antecedent hypoglycemia in normal humans. J Clin Invest 1996; 98(3):680-91.,
30. DCCT Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). Diabetologia 1998; 41(4):416-23.,
31. de Boer SY, Masclee AA, Lam WF, Lemkes HH, Schipper J, Frohlich M, et al. Effect of hyperglycaemia on gallbladder motility in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1994; 37(1):75-81.,

32. Delbende B, Perri F, Couturier O, Leodolter A, Mauger P, Bridgi B, et al. 13C-octanoic acid breath test for gastric emptying measurement. Eur J Gastroenterol Hepatol 2000; 12(1):85-91.,
33. Desautels SG, Hutson WR, Christian PE, Moore JG, Datz FL. Gastric emptying response to variable oral erythromycin dosing in diabetic gastroparesis. Dig Dis Sci 1995; 40(1):141-6.,
34. Deutsche Gesellschaft für Urologie. Guideline for diagnosis and therapy of libido and erectioni disorders. Guidelines of the German Society of Urology. Urologe A 2001; 40(4):331-9.,
35. Didangelos TP, Karamitsos DT, Athyros VG, Kourtoglou GI. Effect of aldose reductase inhibition on cardiovascular reflex tests in patients with definite diabetic autonomic neuropathy over a period of 2 years. J Diabetes Complications 1998;12(4):201-7.,
36. Dorlars D, Schilling D, Riemann JF. Möglichkeiten der Sonographie bei der Beurteilung von Magenmotilitätsstörungen,. Dtsch Med Wochenschr 1994;119(16):575-80.,
37. Dyck PJ, Thomas PKE. Diabetic Neuropathy, W. B. Saunders Co., Philadelphia, 1999.,
38: Ebbehoj E, Poulsen PL, Hansen KW, Knudson ST, Moolgard H, Mogensen CE:Effect on heart rate variability of metoprolol to ongoing ACE-inhibitor treatment in type 1 diabetic patients with abnormal albuminuria . Diabetologia 2002; 45: 965-975,
39. Eliasson B, Bjornsson E, Urbanavicius V, Andersson H, Fowelin J, Attvall S, et al. Hyperinsulinemia impairs gastrointestinal motility and slows carbohydrate absorption. Diabetologia 1995;38(1):79-85.,
40. Enck P, Kranzle U, Schwiese J, Dietz M, Lubke HJ, Erckenbrecht JF, et al. Biofeedbacktraining in fecal incontinence. Dtsch Med Wochenschr 1988;113(46):1789-94.,
41. Enck P, Rathmann W, Spiekermann M, Czerner D, Tschope D, Ziegler D, et al. Prevalence of gastrointestinal symptoms in diabetic patients and non-diabetic subjects. Z Gastroenterol 1994; 32(11):637-41.,
42. Enzlin P, Mathieu C, Van den Bruel A, Bosteels J, Vanderschueren D, Demyttenaere K. Sexual dysfunction in women with type 1 diabetes: a controlled study. Diabetes Care 2002; 25(4):672-7.,
43. Enzlin P, Mathieu C, Vanderschueren D, Demyttenaere K. Diabetes mellitus and female sexuality: a review of 25 years' research. Diabet Med 1998; 15(10):809-15.,
44. Erbas T, Varoglu E, Erbas B, Tastekin G, Akalin S. Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. Diabetes Care 1993; 16(11):1511-4.,
45. Eri LM, Tveter KJ. _-blockade in the treatment of symptomatic benign prostatic hyperplasia. J Urol 1995; 154(3):923-34.,
46. European Diabetes Policy Group 1999. A desktop guide to Type 2 diabetes mellitus. European Diabetes Policy Group 1999. Diabet Med 1999; 16(9):716-30.,
47. European Diabetes Policy Group. A desktop guide to Type 1 (insulin-dependent) diabetes mellitus. European Diabetes Policy Group 1998. Diabet Med 1999; 16(3):253- 66.,
48. European Society of Cardiology, North American Society of Pacing and Electrophysiology.Heart rate variability: standards of measurement, physiological interpretation and clinical use.Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996; 93(5):1043-65.,

49. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. Q J Med 1980; 49(193):95-108.,
50. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. Br Med J (Clin Res Ed) 1982;285(6346):916-8.,
51. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985;8(5):491-8.,
52. Fanelli C, Pampanelli S, Lalli C, Del Sindaco P, Ciofetta M, Lepore M, et al. Long-term intensive therapy of IDDM patients with clinically overt autonomic neuropathy: effects on hypoglycemia awareness and counterregulation. Diabetes 1997; 46(7): 1172-81.,
53. Farup CE, Leidy NK, Murray M, Williams GR, Helbers L, Quigley EM. Effect of domperidone on the health-related quality of life of patients with symptoms of diabetic gastroparesis. Diabetes Care 1998;21(10):1699-706.,
54. Fedele D, Coscelli C, Santeusanio F, Bortolotti A, Chatenoud L, Colli E, et al. Erectile dysfunction in diabetic subjects in Italy. Gruppo Italiano Studio Deficit Erettile nei Diabetici. Diabetes Care 1998;21(11):1973-7.,
55. Fedorak RN, Field M, Chang EB. Treatment of diabetic diarrhea with clonidine. Ann Intern Med 1985;102(2):197-9.,
56. Ficker JH, Dertinger SH, Siegfried W, Konig HJ, Pentz M, Sailer D, et al. Obstructive sleep apnoea and diabetes mellitus: the role of cardiovascular autonomic neuropathy. Eur Respir J 1998;11(1):14-19.,
57.Forst TH, Pfützner A: Autonome Dysfunktion an der unteren Extremität. MMW-Fortschr Med 2004; 14 33-36,
58 Forster MD,Sarosiek I, Delcore R, Lin Z, Raju GS, McCallum RW: Gastric pacing is a new surgical treatment for gastroparesis The American Journal of Surgery 2001; 182: 676-681,
59.Fraquelli M, Pagliarulo M, Collucci A, Paggi S, Conze D: Gallbladder motility in obesity, diabetes mellitus and coeliac disease. Dig Liver Dis 2003, 35 (Suppl. 3) S12-S16
60. Fraser R, Horowitz M, Maddox A, Dent J. Dual effects of cisapride on gastric emptying and antropyloroduodenal motility. Am J Physiol 1993; 264(2 Pt 1):G195-201.,
61. Fraser RJ, Horowitz M, Maddox AF, Harding PE, Chatterton BE, Dent J. Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1990;33(11):675-80.,
62. Fuchs KH, Stein HJ, Thiede AH. Gastrotestinale Funktionsstörungen. Berlin: Springer,1997.,
63. Gaede P, Vedel P, Larsen N, Jansen GVH, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes N Engl J Med 2003; 348: 383-393,
64. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 1999;353(9153):617-22.,
65. Genovely H, Pfeifer MA. RR-variation: the autonomic test of choice in diabetes. Diabetes Metab Rev 1988;4(3):255-71.,
66. Gerich JE, Mokan M, Veneman T, Korytkowski M, Mitrakou A. Hypoglycemia unawareness.Endocr Rev 1991;12(4):356-71.,
67. Gerritsen J, Dekker JM, TenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM, et al. Impaired Autonomic Function Is Associated With Increased Mortality, Especially in

Subjects With Diabetes, Hypertension, or a History of Cardiovascular Disease: The Hoorn Study. Diabetes Care 2001;24(10):1793-8.,
68. Ghoos YF, Maes BD, Geypens BJ, Mys G, Hiele MI, Rutgeerts PJ, et al. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. Gastroenterology 1993; 104(6):1640-7.,
69. Giordano A, Calcagni ML, Versillo M, Frontoni S, Spallone V: Assessment of sympathetic innervation of the heart in diabetes mellitus using 123-I- MIBG. Diabetes Nutr Metab 2000; 13: 350-355,
70. Giugliano D, Marfella R, Quatraro A, De Rosa N, Salvatore T, Cozzolino D, et al. Tolrestat for mild diabetic neuropathy. A 52-week, randomized, placebo-controlled trial.Ann Intern Med 1993; 118(1):7-11.,
71. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group [published erratum appears in N Engl J Med 1998 Jul 2; 339(1):59]. N Engl J Med 1998; 338(20):1397-404.,
72. Goldstein I, Young JM, Fischer J, Bangerter K, Segerson T, Taylor T; Vardenafil Diabetes Study Group. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 2003; 26: 777-783.
73. Gottsäter A, Ahmed M, Fernlund P, Sundkvist G. Autonomic neuropathy in Type 2 diabetic patients is associated with hyperinsulinaemia and hypertriglyceridaemia. Diabet Med 1999;16(1):49-54.,
74. Haffner SM, Diehl AK, Mitchell BD, Stern MP, Hazuda HP. Increased prevalence of clinical galbladder disease in subjects with non-insulin-dependent diabetes mellitus.Am J Epidemiol 1990; 132(2):327-35.,
75. Hahm JS, Park JY, Park KG, Ahn YH, Lee MH, Park KN. Gallbladder motility in diabetes mellitus using real time ultrasonography. Am J Gastroenterol 1996; 91(11):2391-4.,
76. Hampel C, Gillitzer R, Pahernik S, Thurdoff JW: Diabetes mellitus and bladder function. What should be considered? Urologe, 2003 8, 42: 1556-1563,
77. Haslbeck M, Krob G, Kothny T. Diabetische Polyneuropathie. Der Bay. Internist1999;19:398-408.,
78. Haslbeck M, Redaèlli M, Parandeh-Shab F, Luft D, Neundörfer B, Stracke H, et al.Diagnostik, Therapie und Verlaufskontrolle der sensomotorischen diabetischen Neuropathien. In: Scherbaum W, Lauterbach K, Renner R, editors. Evidenzbasierte Diabetes-Leitlinien DDG. Köln: DDG, 2000:42.,
79. Haslbeck M. Autonomic neuropathies in diabetes mellitus: diagnosis--therapy--risks. Z Gesamte Inn Med 1993;48(3):162-176.,
80. Haslbeck M. Funktionsprüfungen des visceralen autonomen Nervensystem. In: Dichgans J, Diener H, Felgenhauer K, Wallesch C, Buyck E, editors. Neurologie 2000. Stuttgart: G Thieme, 2000:A5: 1-12.,
81. Haslbeck M. Klinik der diabetischen Neuropathien. In: Federlin K, editor. Pathophysiologie diabetischer Folgeerkrankungen, 1998:108-121.,
82. Haslbeck M. Treatment of diabetic gastroparesis. Z Gastroenterol 1990;28 Suppl 1:39-42; discussion 47-8.,
83. Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes1991; 40(2):223-6.,
84. Heller SR, Macdonald IA, Herbert M, Tattersall RB. Influence of sympathetic nervous system on hypoglycaemic warning symptoms. Lancet 1987;2(8555):359-63.,

85. Hepburn DA, Patrick AW, Eadington DW, Ewing DJ, Frier BM. Unawareness of hypoglycaemia in insulin-treated diabetic patients: prevalence and relationship to autonomic neuropathy. Diabet Med 1990; 7(8):711-7.,
86. Hinton JM, Lennard-Jones JE, Young AC. A new method for studying gut transittimes using radioopaque markers. Gut 1969; 10(10):842-7.,
87. Horowitz M, Fraser R. Disordered gastric motor function in diabetes mellitus. Diabetologia 1994; 37(6):543-51.,
88. Horowitz M, Harding PE, Chatterton BE, Collins PJ, Shearman DJ. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. DigDis Sci 1985; 30(1):1-9.,
89. Horowitz M, Harding PE, Maddox AF, Wishart JM, Akkermans LM, Chatterton BE, et al. Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1989; 32(3):151-9.,
90. Horowitz M, Maddox A, Harding PE, Maddern GJ, Chatterton BE, Wishart J, et al.Effect of cisapride on gastric and esophageal emptying in insulin-dependent diabetesmellitus. Gastroenterology 1987; 92(6):1899-907.,
91. Horowitz M, O'Donovan D, Jones KL, Feinke C, Rayner CK, Samson M: Gastric emptying in diabetes: clinical significance and treatment Diabet.Med.2002; 19 : 177-194,
92 Howorka K, Pumprla J, Haber P: Effekts of physical training on heart rate variability in diabetic patients with various degrees of cardiovascular autonomic neuropathy Cardivascular Res 1997; 34: 206-214,
93. Inoguchi T, Yamashita T, Umeda F, Mihara H, Nakagaki O, Takada K, et al. High incidence of silent myocardial ischemia in elderly patients with non-insulin-dependent diabetes mellitus. Diabetes Res Clin Pract 2000;47(1):37-44.,
94. Ishii M, Nakamura T, Kasai F, Baba T, Takebe K. Erythromycin derivative improves gastric emptying and insulin requirement in diabetic patients with gastroparesis. Diabetes Care 1997; 20(7):1134-7.,
95. Isotani H, Fukumoto Y, Kitaoka H, Furukawa K, Ohsawa N, Utsumi T. Oval pupil in patients with diabetes mellitus: examination by measurement of the dark-adapted pupillary area and pupillary light reflex. Diabetes Res Clin Pract 1995; 29(1):43-8.,
96. Janatuinen E, Pikkarainen P, Laakso M, Pyorala K. Gastrointestinal symptoms in middleaged diabetic patients. Scand J Gastroenterol 1993; 28(5):427-32.,
97. Janka HU, Standl E, Mehnert H. Clonidine effect on diabetic gustatory sweating. AnnIntern Med 1979; 91(1):130.
98. Jebbink HJ, Bruijs PP, Bravenboer B, Akkermans LM, vanBerge-Henegouwen GP, Smout AJ. Gastric myoelectrical activity in patients with type I diabetes mellitus and autonomic neuropathy. Dig Dis Sci 1994; 39(11):2376-83.,
99. Jermendy G, Fornet B, Koltai MZ, Pogatsa G. Correlation betw een oesophageal dysmotility and cardiovascular autonomic dysfunction in diabetic patients without gastrointestinal symptoms of autonomic,neuropathy. Diabetes Res 1991; 16(4):193-7.,
100. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol 2000; 163(2):460-3.,
101. Johnson BF, Nesto RW, Pfeifer MA, Slater, WR, Vinik, AI, Chyun DA, Law G, Walkers FJTh, Young, LH Cardiac abnormalities in diabetic patients with neuropathy. Effects of aldose reductase inhibitor administration. Diabetes Care 2004, 27: 448-454,
102. Jones KL, Wiskart LM Berry M, Russo A, Dia HH, Talley NJ: Helicobacter pylori infection is not associated with delayed gastric emptying or other gastrointestinal symptoms in diabetes mellitus Dig Dis Sci 2002; 47: 704-709,

103. Kanc K, Janssen MM, Keulen ET, Jacobs MA, Popp-Snijders C, Snoek FJ, et al. Substitution of night-time continuous subcutaneous insulin infusion therapy for bedtime NPH insulin in a multiple injection regimen improves counterregulatory hormonal responses and warning symptoms of hypoglycaemia in IDDM. Diabetologia 1998; 41(3):322-9.,
104. Kapicioglu S, Senturk O, Bambul N, Ilgun K. Action of cisapride on gallbladder contraction in patients with diabetes mellitus. Hepatogastroenterology 1998; 45(23): 1410-4.,
105. Kaplan SA, Te AE, Blaivas JG. Urodynamic findings in patients with diabetic cystopathy. J Urol 1995; 153(2):342-4.,
106. Kawamura O, Sekiguchi T, Itoh Z, Omura S. Effect of erythromycin derivative EM523L on human interdigestive gastrointestinal tract. Dig Dis Sci 1993; 38(6):1026-31.,
107. Kayacetin E, Kisakol G, Kaya A, Akpinar Z: Real-time sonography for screening of gallbladder motility in diabetic patients: relation to autonomic and peripheral neuropathy. Neuroendocrinol Lett 2003; 24: 73-76,
108. Kendall DM, Rooney DP, Smets YF, Salazar Bolding L, Robertson RP. Pancreas transplantation restores epinephrine response and symptom recognition during hypoglycaemia in patients with long-standing type I diabetes and autonomic neuropathy. Diabetes 1997; 46(2):249-57.,
109. Kennedy WR, Navarro X, Sakuta M, Mandell H, Knox CK, Sutherland DE. Physiological and clinical correlates of cardiorespiratory reflexes in diabetes mellitus. Diabetes Care 1989; 12(6):399-408.,
110. Keshavarzian A, Iber FL, Nasrallah S. Radionuclide esophageal emptying and manometric studies in diabetes mellitus. Am J Gastroenterol 1987; 82(7):625-31.,
111. Kleiger RE, Millr JP, Bigger JT, Jr., Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59(4):256-62.,
112. Kontopoulos AG, Athyros VG, idangelos TP, Papageorgiou AA, Avramidis MJ, Mayroudi MC, et al. Effect of chronic quinapril administration on heart rate variability in patients with diabetic autonomic neuropathy. Diabetes Care 1997;20(3):35561.,
113. Konturek JW, Ditl K-H, Domschke W. Magenschrittmacher-Implantation: Neue Therapie der Gastroparese. Deutsches Ärzteblatt 1997;27:A-1871.,
114. Lal S, Tesfaye Y, Thavundayil JX, Thompson TR, Kiely ME, Nair NP, et al. Apomorphine: clincal studies on erectile impotence and yawning. Prog Neuropsychopharmacol Biol Psychiatry 1989; 13(3-4):329-39.,
115. Lang E, Foerster A, Pfannmuller D, Handwerker HO. Quantitative assessment of sudomotor activity by capacitance hygrometry. Clin Auton Res 1993; 3(2):107-15.,
116. Langtry HD, Markham A. Sildenafil: a review of its use in erectile dysfunction. Drugs 1999; 57(6):967-89.,
117. Law PJ, Kamm MA, Bartram CI. Anal endosonography in the investigation of faecal incontinence. Br J Surg 1991; 78(3):312-4.,
118. Lehmann R, Honnegger RA, Feinle C, Fried M, Spinas GA, Schwizer W. Glucose control is not improved by accelerating gastric emptying in patients with type 1 diabetes mellitus and gastroparesis. A pilot study with cisapride as a model drug. Exp Clin Endocrinol Diabetes 2003; 111: 255 – 261
119. Lin Z, Forster J, Sarosiek I, McCallum RW: Treatment of diabetic gastroparesis by high-frequency gastric electrical stimulation. Diabetes Care 2004; 27: 1071-1076,
120. Linet OI, Ogrinc FG. Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. The Alprostadil Study Group. N Engl J Med 1996; 334(14):873-7.,

121. Lingenfelser T, Buettner UW, Uhl H, Renn W, Tobis M, Teichmann R, et al. Recovery of hypoglycaemia-associated compromised cerebral function after a short interval of euglycaemia in insulin-dependent diabetic patients. Electroencephalogr Clin Neurophysiol 1994; 92(3):196-203.,
122. Lipshultz LI, Kim ED. Treatment of erectile dysfunction in men with diabetes. JAMA 1999; 281(5):465-6.,
123. Lluch I, Hernandez A, Real JT, Morillas C, Tenes S, Sanchez C, et al. Cardiovascular autonomic neuropathy in type 1 diabetic patients with and without peripheral neuropathy. Diabetes Res Clin Pract 1998; 42(1):35-40.,
124. Loba JM, Saryusz-Wolska M, Czupryniak L, Kukulski K. Pancreatic polypeptide secretion in diabetic patients with delayed gastric emptying and autonomic neuropathy. J Diabetes Complications 1997; 11(6):328-33.,
125. Loo FD, Dodds WJ, Soergel KH, Arndorfer RC, Helm JF, Hogan WJ. Multipeaked esophageal peristaltic pressure waves in patients with diabetic neuropathy. Gastroenterology 1985; 88(2):485-91.,
126. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ. Quantitative sudomotor axon reflex test in normal and neuropathic subjects. Ann Neurol 1983; 14(5):573-80.,
127. Low PA, Zimmerman BR, Dyck PJ. Comparison of distal sympathetic with vagal function in diabetic neuropathy. Muscle Nerve 1986; 9(7):592-6.,
128. Lysy J, Israeli E, Goldin E. The prevalence of chronic diarrhea among diabetic patients. Am J Gastroenterol 1999; 94(8):2165-70.,
129. Malagelada JR, Rees WD, Mazzotta LJ, Go VL. Gastric motor abnormalities in diabeticand postvagotomy gastroparesis: effect of metoclopramide and bethanechol R, Gastroenterology 1980; 78(2):286-93.,
130. Mankovsky BN, Piolot R, Mankovsky OL, Ziegler D: Impairment of cerebral autoregulation in diabetic patients with cardiovascular autonomic neuropathy and orthostatic hypotension. Diabetic Medicine 2003; 20: 119-120,
131. Mäntysaari M, Kuikka J, Mustonen J, Tahvanainen K, Vanninen E, Lansimies E, et al.Noninvasive detection of cardiac sympathetic nervous dysfunction in diabetic patients using [123I]metaiodobenzylguanidine. Diabetes 1992; 41(9):1069-75.,
132. Manzella D, Barbieri M, Rango E, Paolisso G. Chronic administration of pharmacologoc doses of vitamin E improves the cardiac autonomic nervous system in patients with type 2 diabetes. Am J Clin Nutr 2001; 73(6):1052-7.,
133. Maselli RA, Jaspan JB, Soliven BC, Green AJ, Spire JP, Arnason BG. Comparison of sympathetic skin response with quantitative sudomotor axon reflex test in diabetic neuropathy. Muscle Nerve 1989; 12(5):420-3.,
134. Maser RE, Braxton DM, Vinik AL, Freeman R: The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes. A meta-analysis Diabetes Care 2003; 26: 1895-1901,
135. Maser RE, Steenkiste AR, Dorman JS, Nielsen VK, Bass EB, Manjoo Q, et al. Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes 1989;38(11):1456-61.,
136. Mayaudon H, Bauduceau B, Dupuy O, Cariou B, Ceccaldi B, Farret O, et al. Assessment of gastric neuropathy using electrogastrography in asymptomatic diabetic patients. Correlation with cardiac autonomic neuropathy. Diabetes Metab1999; 25(2):138-42.,
137. McCallum RW, Valenzuela G, Polepalle S, Spyker D. Subcutaneous metoclopramide in the treatment of symptomatic gastroparesis: clinical efficacy and pharmacokinetics. J Pharmacol Exp Ther 1991; 258(1):136-42.,
138. Mearin F, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. Gastroenterology 1986;90(6):1919-25.,

139. MiSAD. Prevalence of unrecognised silent myocardial ischemia and its association with atherosclerotic risk factors in noninsulin-dependent diabetes mellitus. Milan Study on Atherosclerosis and Diabetes (MiSAD) Group. Am J Cardiol 1997; 79(2):134-9.,
140. Mittleman MA, Glasser DB, Orazem J: Clinical trials of sildenafil citrate (Viagra) demonstrate no increase in risk of myocardial infarction and cardiovascular death compared with placebo. Int J Clin Pract 2003; 57: 597-600,
141. Mokan M, Mitrakou A, Veneman T, Ryan C, Korytkowski M, Cryer P, et al. Hypoglyceamia mia unawareness in IDDM. Diabetes Care 1994; 17(12):1397-403.,
142. Murray A, Ewing DJ, Campbell IW, Neilson JM, Clarke BF. RR interval variations in young male diabetics. Br Heart J 1975; 37(8):882-5.,
143. Nakamura T, Ishii M, Arai Y, Tandoh Y, Terada A, Takebe K. Effect of intravenous administration of EM523L on gastric emptying and plasma glucose levels after a meal in patients with diabetic gastroparesis: a pilot study. Clin Ther 1994; 16(6):989-99.,
144. Nakayama M, Nakamura J, Hamada Y, Chaya S, Mizubayashi R, Yasuda Y, et al. Aldose reductase inhibition ameliorates pupillary light reflex and F-wave latency in patients with mild diabetic neuropathy. Diabetes Care 2001; 24(6):1093-8.,
145. Niakan E, Harati Y. Sympathetic skin response in diabetic peripheral neuropathy. Muscle Nerve 1988; 11(3):261-4.
146. Okamoto H, Nomura M, Nakaja Y, Uehara K, Saito K, Kimura M: Effects of epalrestat, an aldosereductase inhibitor on diabetic neuropathy and gastroparesis. Intern Med 2003; 42 (8): 655-664.
147. Olsson AM, Speakman MJ, Dinsmore WW, Giuliano F, Gingell C, Maytom M, et al. Sildenafil citrate (Viagra) is effective and well tolerated for treating erectile dysfunction of psychogenic or mixed aetiology. Int J Clin Pract 2000; 54(9):561-6.,
148. Padma-Nathan H, Hellstrom WJ, Kaiser FE, Labasky RF, Lue TF, Nolten WE, et al. Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. N Engl J Med 1997; 336(1):1-7.,
149. Padma-Nathan H Steers WD, Wicker PA. Efficacy and safety of oral sildenafil in the treatment of erectile dysfunction: a double-blind, placebo-controlled study of 329 patients. Sildenafil Study Group. Int J Clin Pract 1998; 52(6):375-9.,
150. Page MM, Watkins PJ. Cardiorespiratory arrest and diabetic autonomic neuropathy. Lancet 1978; 1(8054):14-6.,
151. Pourmoghaddas A, Hekmantia A: The relationship between QTc interval and cardiac autonomic neuropathy in diabetes mellitus Mol Cell Biochem 2003; 249:125-128,
152. Price DE, Gingell JC, Gepi-Attee S, Wareham K, Yates P, Boolell M. Sildenafil: study of a novel oral treatment for erectile dysfunction in diabetic men. Diabet Med1998; 15(10):821-5.,
153. Price DE. Managing impotence in diabetes. BMJ 1993; 307(6899):275-6.,
154. Purewal TS, Watkins PJ. Postural hypotension in diabetic autonomic neuropathy: a review. Diabet Med 1995; 12(3):192-200.,
155. Rance J, Phillips C, Davies S, O'Malley BO, Zaman Q, Price D: How much of a priority is treating erectile dysfunction? A study of patients perceptions. Diabetic Medicine 2003, 20: 205-209 ,
156. Rathmann W, Ziegler D. Aktuelle Aspekte zur Pathogenese, Diagnostik und Therapie der diabetischen Gastroparese. Diabetes und Stoffwechsel 1994;3:417-21.,
157. Rees PJ, Prior JG, Cochrane GM, Clark TJ. Sleep apnoea in diabetic patients with autonomic neuropathy. J R Soc Med 1981; 74(3):192-5.,

158. Rendell MS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. JAMA 1999; 281(5):421-6.,
159. Ricci JA, Siddique R, Stewart WF, Sandler RS, Sloan S, Farup CE. Upper gastrointestinal symptoms in a U.S. national sample of adults with diabetes. Scand J Gastroenterol 2000;35(2):152-9.,
160. Richards RD, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. Am J Gastroenterol 1993; 88(2):203-7.,
161. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999; 11(6):319-26.,
162. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49(6):822-30.,
163. Ruhl CE, Everhart JE. Association of diabetes, serum insulin, and C-peptide with gallb ladder disease. Hepatology 2000; 31(2):299-303.,
164. Russo A, Botton R, Koney M-F, Chapman IM, Fraser JL, Horowitz M, Sum W-M: Effects of acute hyperglycaemia on anorectal motor and sensory function in diabetes mellitus Diabetic Medcine 2004, 21: 176-182,
165. Ryder RE, Hardisty CA. Which battery of cardiovascular autonomic function tests? Diabetologia 1990;33(3):177-9; discussion 180-1.,
166. Ryder RE, Owens DR, Hayes TM, Ghatei MA, Bloom SR. Unawareness of hypoglycaemia and inadequate hypoglycaemic counterregulation: no causal relation with diabetic autonomic neuropathy. BMJ 1990; 301(6755):783-7.,
167. Saenz de Tejada I, Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 2002; 25: 2159-2164,
168. Schade RR, Dugas MC, Lhotsky DM, Gavaler JS, Van Thiel DH. Effect of metoclopramide on gastric liquid emptying in patients with diabetic gastroparesis. Dig Dis Sci1985; 30(1):10-5.,
169. Schiller LR, Santa Ana CA, Morawski SG, Fordtran JS. Studies of the antidiarrheal action of clonidine. Effects on motility and intestinal absorption. Gastroenterology 1985; 89(5):982-8.,
170. Schindlbeck NE, Klauser AG, Muller-Lissner SA. Measurement of colon transit time. Z Gastroenterol 1990; 28(8):399-404.,
171. Schnell O, Kirsch CM, Stemplinger J, Haslbeck M, Standl E. Scintigraphic evidence for cardiac sympathetic dysinnervation in long-term IDDM patients with and without ECG-based autonomic neuropathy. Diabetologia 1995; 38(11):1345-52.,
172. Schnell O, Muhr D, Weiss M, Dresel S, Haslbeck M, Standl E. Reduced myocardial 123I-metaiodobenzylguanidine uptake in newly diagnosed IDDM patients. Diabetes 1996b; 45(6):801-5.,
173. Schnell O, Stenner T, Standl E, Haslbeck M. The diagnostic value of the rate-corrected QT interval in long-term type-1 diabetes mellitus. Dtsch Med Wochenschr1996a; 121(25-26):819-22.,
174. Setter SM, Baker DE, Campbell RK, Johnson SB. Sildenafil (Viagra) for the treatment of erectile dysfunction in men with diabetes. Diabetes Educ 1999; 25(1):79-80, 83-4, 87 passim.,
175. Silvers D, Kipnes M, Broadstone V, Patterson D, Quigley EM, McCallum R, et al. Domperidone in the management of symptoms of diabetic gastroparesis: efficacy,

tolerability, and quality-of-life outcomes in a multicenter controlled trial. DOM-USA-5 Study Group. Clin Ther 1998; 20(3):438-53.,
176. Singh JP, Carson MG, O'Donnel CJ, Wilson PF Tsuji H, Lloyd-Jones DM: Association of hyperglycemia with reduced heart rate variability (The Framingham Heart study) Am J. Cardiol 2000; 86: 309-312,
177. Smith SA, Dewhirst RR. A simple diagnostic test for pupillary abnormality in diabetic autonomic neuropathy. Diabet Med 1986; 3(1):38-41.,
178. Smith SA, Smith SE. Pupil function: tests and disorders. Autonomic failure 1999:592.
179. Smith SA, Smith SE. Reduced pupillary light reflexes in diabetic autonomic neuropathy. Diabetologia 1983; 24(5):330-2.,
180. Smith SA. Reduced sinus arrhythmia in diabetic autonomic neuropathy: diagnostic value of an age-related normal range. Br Med J (Clin Res Ed) 1982; 285(6355):1599-601.,
181. Spamgeus A, El-Salhy M, Suhr O, Eriksson J, Lithner F. Prevalence of gastrointestinal symptoms in young and middle-aged diabetic patients. Scand J Gastroenterol 1999; 34(12):1196-202.,
182. Spitzer A, Lang E, Birklein F, Claus D Neundörfer B. Cardiac autonomic involvement and peripheral nerve function in patients with diabetic neuropathy. Functional Neurology, 1997; 12:115-22.,
183. Stacher G. Diabetes mellius and the stomach. Diabetologia 2001; 44(9):1080-93.,
184. Starer P, Libow L. Cystometric evaluation of bladder dysfunction in elderly diabetic patients. Arch Intern Med 1990;150(4):810-3.,
185. Stevens MJ, Raffel DM, Allman KC, Schwaiger M, Wieland DM. Regression and progression of cardiac sympathetic dysinnervation complicating diabetes:an assessment by C-11 hydroxyephedrine and positron emission tomography.Metabolism 1999; 48(1):92-101.,
186. Stief C, Thon W, Truss M, Staubesand J, Jonas U. Blasenfunktionsstörungen und erektile Dysfunktion bei Diabetes mellitus. Deutsches Ärzteblatt 1996;33:A2082-A2086.,
187. Strian F, Haslbeck M. Neurologische Erkrankungen. In: Mehnert H, Standl, E., Usadel,K. H.(Hrsg.). Diabetologie in Klinik und Praxis. 5. Auflage ed. Stuttgart: Thieme Verlag, 2004, 550-576
188. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. Am J Hosp Pharm 1994;51(5):648-60; quiz 697-8.,
189. Sundkvist G, Almer L, Lilja B. Respiratory influence on heart rate in diabetes mellitus.Br Med J 1979;1(6168):924-5.,
190. Tanis AA, Baggen MG, Wiggers RH, Ouwendijk RJ. Side-effects of oral erythromycin for treatment of diabetic gastroparesis. Lancet 1993; 342(8884):1431.
191. Tefilli MV, Dubocq F, Rajpurkar A, Gheiler EL, Tiguert R, Barton C, et al. Assessment of psychosexual adjustment after insertion of inflatable penile prosthesis. Urology 1998;52(6):1106-12.,
192. Töyry JP, Niskanen LK, Mantysaari MJ, Lansimies EA, Uusitupa MI. Occurrence,predictors, and clinical significance of autonomic neuropathy in NIDDM. Ten-year follow-up from the diagnosis. Diabetes 1996; 45(3):308-15.,
193. Tsai ST, Vinik AI, Brunner JF. Diabetic diarrhea and somatostatin. Ann Intern Med 1986; 104(6):894.
194. Tzeng SS, Wu ZA, Chu FL. The latencies of sympathetic skin responses. Eur Neurol 1993; 33(1):65-8.,

195. Ueno N, Inui A, Asakawa A, Takoo F, Komatsu J, Katami K, Nishimura R, KasyjaM: Mosapride, a 5HT-4 receptor agonist, improves insulin sensitivity and glycaemic control in patients with type 2 diabetes mellitus Diabetologia 2002; 45: 792-797,
196. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet1998; 352(9131):837-53.,
197. Valensi P, Huard JP, Giroux C, Attali JR. Factors involved in cardiac autonomic neuropathy in diabetic patients. J Diabetes Complications 1997; 11(3):180-7.,
198. Valensi P, Paries J, Attali JR and the French Group for Research and Study of Diabetic Neuropathy: Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications- The French Multi Center Study Metabolism 2003; 52: 815-820,
199. van Lieshout JJ, ten Harkel AD, Wieling W. Physical manoeuvres for combating orthostatic dizziness in autonomic failure. Lancet 1992; 339(8798):897-8.,
200. Veglio M, Chinaglia Perin PC: The clinical utility of QT interval assessment in diabetes Diabetes Nutr Metab 2000; 13:356-365,
201. Vinik AI, Park TS, Stansberry KB, Pittenger GL. Diabetic neuropathies. Diabetologia 2000;43(8):957-73.,
202. Vinik AL, Maser, RE, Braxton DM, Freeman R: Diabetic autonomic neuropathy Diabetes Care 2003;26: 1553-1579,
203. Vogelberg KH, Muller HJ, Hubinger A. The somatostatin infusion test for the evaluation of glucose utilization in bezafibrate medication. Arzneimittelforschung1984; 34(9):1038-41
204. Vogelberg KH, Rathmann W. Sonographic criteria for studying gastric motility in diabetics with autonomic neuropathy. Dtsch Med Wochenschr 1986; 111(44):1687-91.,
205. Von Keitz AT, Stroberg P, Bukofzer S, Mallard N, Hibberd M. A European multicentre study to evaluate the tolerability of apomorphine sublingual administered in a forced dose-escalation regimen in patients with erectile dysfunction. BJU Int2002;89(4):409-15.,
206. Wanke T, Abrahamian H, Lahrmann H, Formanek D, Merkle M, Auinger M, et al. No effect of naloxone on ventilatory response to progressive hypercapnia in IDDM patients. Diabetes 1993; 42(2):282-7.,
207. Watkins PJ, Buxton-Thomas MS, Horwardt ER Long-Term outcome after gastrectomy for intractable diabetic gastroparesis Diabetic Medicine 2003; 20: 58-63,
208. Watkins PJ, Mackay JD. Cardiac denervation in diabetic neuropathy. Ann Intern Med 1980; 92(2 Pt 2):304-7.,
209. Weinberg CR, Pfeifer MA. An improved method for measuring heart-rate variability: assessment of cardiac autonomic function. Biometrics 1984; 40(3):855-61.
210 Whang W, Bigger JT: Comparison of the prognostic value of RR-interval variability after akute myocardial infarction in patients with versus those without diabetes mellitus Am J Cardiol 2003; 92: 247-251,
211. Wheeler SG, Akroni JH, Boyko EJ: Prospective study of autonomic neuropathy as a predicter of mortality in patients with diabetes. Diabetes Res Clin Pract 2002; 58: 131-138,
212. Whitsel EA, Boyko EJ, Siscovick DS. Reassessing the role of QTc in the diagnosis of autonomic failure among patients with diabetes: a meta-analysis. Diabetes Care 2000; 23(2):241-7.,

213. Widom B, Simonson DC. Glycemic control and neuropsychologic function during hypoglycemia in patients with insulin-dependent diabetes mellitus. Ann Intern Med 1990;112(12):904-12.,
214. Wiefels K, Gries FA. Diagnosis of diabetic neuropathies. Dtsch Med Wochenschr 1988;113(26):1067-70.,
215. Wienbeck M. Gastrointestinale Motilitätsstörungen und Diabetes mellitus. Ernährungs-Umschau 1996;43:S38-9.,
216. Williams G, Abbou CC, Amar ET, Desvaux P, Flam TA, Lycklama a Nijeholt GA, et al. The effect of transurethral alprostadil on the quality of life of men with erectile dysfunction, and their partners. MUSE Study Group. Br J Urol 1998; 82(6):847-54.,
217. Williams JG. Autonomic neuropathy in diabetics: a review. J R Soc Med 1983; 76(6):502-7.,
218. Zahn A, Langhans C-D, Hoffner S, Haberkorn U, Rating D, Haas M: Measurement of gastric emptying with ^{13} C-octanoic acid breath test versus scintigraphy in diabetes Zeitschrift für Gastroenterologie 2003; 41: 383-390,
219. Ziegler D, Dannehl K, Muhlen H, Spuler M, Gries FA. Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses at various stages of diabetic neuropathy. Diabet Med 1992a;9(9):806-14.,
220. Ziegler D, Dannehl K, Volks D, Muhlen H, Spuler M, Gries FA. Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis and standard tests of heart-rate variation in newly diagnosed IDDM patients. Diabetes Care 1992b;15(7): 908-11.,
221. Ziegler D, Gries F. Klassifikation, Epidemiologie, Prognose und sozialmedizinische Bedeutung. Deutsches Ärzteblatt 1996;93(11):44-48.,
222. Ziegler D, Gries FA, Muhlen H, Rathmann W, Spuler M, Lessmann F. Prevalence and clinical correlates of cardiovascular autonomic and peripheral diabetic neuropathy in patients attending diabetes centers. The Diacan Multicenter Study Group. Diabete Metab 1993;19(1 Pt 2):143-51.,
223. Ziegler D, Gries FA. Diagnostik und Therapie der kardiovaskulären autonomen diabetischen Neuropathie. Diabetes und Stoffwechsel 1994;3:22-31.,
224. Ziegler D, Laude D, Akila F, Elghosi JL: Time and frequency domain estimation of early diabetic cardiovascular autonomic neuropathy. Clinical Autonomic Research 2001:11: 369-376,
225. Ziegler D, Laux G, Dannehl K, Spuler M, Muhlen H, Mayer P, et al. Assessment of cardiovascular autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. Diabet Med 1992c; 9(2):166-75.,
226. Ziegler D, Luft D: Clinical trials for drugs against diabetic neuropathy: can we combine scientific needs with clinical practicalities? Int Rev of Neurobiology 2002; 50: 431-463,
227. Ziegler D, Rathmann W. Neue Aspekte zur kardiovaskulären autonomen diabetischen Neuropathie. Diabetes und Stoffwechsel 1994;3:410-6.,
228. Ziegler D, Reljanovic M, Mehnert H, Gries FA. _-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. Exp Clin Endocrinol Diabetes 1999; 107(7):421-30.,
229. Ziegler D, Schadewaldt P, Pour Mirza A, Piolot R, Schommartz B, Reinhardt M, et al. Octanoic acid breath test for non-invasive assessment of gastric emptying in diabetic patients: validation and relationship to gastric symptoms and cardiovascular autonomic function. Diabetologia 1996; 39(7):823-30.,

230. Ziegler D, Schatz H, Conrad F, Gries FA, Ulrich H, Reichel G. Effects of treatment with the antioxidant _-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. A 4-month randomized controlled multicenter trial (DEKAN Study). Deutsche Kardiale Autonome Neuropathie. Diabetes Care 1997; 20(3):369-373.,
231. Ziegler D, Weise F, Langen KJ, Piolot R, Boy C, Hubinger A, et al. Effect of glycaemic control on myocardial sympathetic innervation assessed by [123I] metaiodobenzyl guanidine scintigraphy: a 4-year prospective study in IDDM patients. Diabetologia 1998; 41(4):443-51.,
232. Ziegler D. Cardiovascular autonomic neuropathy: clinical manifestations and measurement. Diabetic Reviews 1999; 7:342-357.
233. Ziegler D. Diabetic cardiovascular autonomic neuropathy: prognosis, diagnosis and treatment. Diabetes Metab Rev 1994;10(4):339-83.,
234. Ziegler D. Diagnostik und Therapie der diabetischen Neuropathie. Hamburger Ärzteblatt 1997; 3:125-30.
235. Ziegler D: Diagnosis and treatment of diabetic autonomic neuropathy Curr Diab Report 2001;1:216-217,

8 Search strategy

Data base: Medline (OVID): 1998 – 2004-01
Date: 2004-02

1 *Diabetes Mellitus/
2 *Glucose Intolerance/
3 *Insulin Resistance/
4 1 or 2 or 3
5 exp Diabetic Neuropathies/
6 exp MONONEUROPATHIES/
7 exp POLYNEUROPATHIES/
8 *Blood Vessels/
9 exp NEURITIS/
10 (mononeuropath$ or polyneuropath$ or neuropath$).tw.
11 (amyotroph$ or neuralg$ or neuritis).tw.
12 (peripheral nerv$ adj (diseas$ or disorder$)).tw.
13 or/5-12
14 4 and 13
15 limit 14 to (human and yr=1998-2004)

Legend:

/	=	Following an indexed term, this sign denotes that all subheadings of the term were selected.
$	=	Shows an extension/modification of the search term.
*	=	When * precedes the MeSH term, this denotes a focused MeSH term search.
expl	=	exploded: Preceding an indexed term, this denotes an expanded MeSH term search.
pt	=	Publication type: Indicates a search for the study design.

tw	=	Text word: The term is searched for in the title and in the abstract of the study.
and/ or	=	Denotes a inclusive or exclusive combination with so-called Boolean operators.
adj	=	adjacent: Denotes the search for two terms in in one sentence.
MeSH term	=	Thesaurus of the National Library of Medicine (MeSH, medical subject headings)