CHAPTER 15

DIABETIC AUTONOMIC NEUROPATHY

Zdravko A. Kamenov* and Latchezar D. Traykov
University Hospital Alexandrovska, Medical University - Sofia, Sofia, Bulgaria
**Corresponding Author: Zdravko A. Kamenov—Email: zkamenov@hotmail.com*

Abstract: Diabetic autonomic neuropathy (DAN) affects each tissue, organ, system and the whole body, and presents with a diverse clinical picture. Originating from endocrine factors, this neurological disease may cause symptoms, whose differential diagnosis needs a good knowledge of the whole internal medicine. DAN is strongly involved in the development of diabetic foot, ulceration and amputation. The life threatening consequences of cardiac and patient-frustrating sequels of other types of DAN is more difficult to estimate.

In this chapter the different clinical aspects of DAN will be discussed, according to the involved system—cardiovascular, gastrointestinal, genitourinary, sudomotor and pupillary dysfunctions and the unawareness and unresponsiveness to hypoglycaemia. The diagnostic tests for DAN are more complicated and time consuming, compared with the somatic tools. There is a need for simple devices and methods for evaluation of autonomic functions in the everyday clinical practice. Tight glycaemic control is the cornerstone of the prevention, progression and retardation of DAN. An effective broad-spectrum pathogenetic treatment of neural deterioration remains to be established. In most cases symptomatic drugs are the treatment of choice.

INTRODUCTION

Diabetic neuropathy (DN) is related to all three regulatory systems of the body: (1) it is caused by malfunctions of the endocrine system, (2) directly affects the nervous system, and (3) includes elements of, also causes alterations to the immune system. Being both a consequence of and simultaneously a cause for further dysregulation, DN affects each tissue, organ, and systems, and the whole body presents with diverse clinical pictures.

Diabetes: An Old Disease, a New Insight, edited by Shamim I. Ahmad.

Diabetic neuropathy has been defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes".[1] DAN develops in most cases simultaneously with somatic DN and is seldom an object of investigations. It affects the whole body, but here we mostly discuss the aspects of the symptoms in the cardiovascular, gastrointestinal, genitourinary, sudomotor and pupillary dysfunctions and the unawareness and unresponsiveness to hypoglycaemia. The prevalence of autonomic impairment is up to 54% in Type 1 and 73% in Type 2 diabetic patients.[2]

The pathogenetic aspects of DN have been already discussed in Chapter 14, *Diabetic Somatic Neuropathy*, by Kamenov and Traykov, in this volume. Epidemiological data concerning the prevalence of DAN vary extremely with a range from 1.6 to 90%[3] depending on the methodological aspects (studied different body systems with different diagnostic methods and/or cut-offs) and epidemiological (different in age, type and duration of DM populations). Low et al reported autonomic impairment up to 54% in Type 1 and 73% in Type 2 diabetic patients.[2]

Clinical symptoms of DAN generally do not occur until long after the onset of diabetes. Whereas symptoms suggestive of autonomic dysfunction may common, they may frequently be due to other causes rather than to true autonomic neuropathy. Subclinical autonomic dysfunction can, however, occur within a year of diagnosis in Type 2 diabetes mellitus (T2DM) patients and within two years in Type 1 diabetes mellitus (T1DM) patients.[4,5]

Multiple factors influence autonomic function-body position, emotional state, ingested food and medicines, as well as other factors.[6] Several conditions have to be taken into consideration when performing tests for DAN. Caffeine and nicotine should be withheld for at least 3-4 hours and alcohol for 8 hours before test. Also sympathomimetic drugs may be stopped for 24-48 hours before test and anticholinergics for 48 hours. Standardization of test conditions is crucial in order to make them comparable, especially during the assessment of cardiovascular reflexes. Directly before testing, the patient should be laid down or seated for about 30 minutes in a quiet room with neutral temperature and humidity.[7,8]

The treatment of DAN is build according to the same principles, described for somatic DN—elimination of risk factors, strict glycaemic control and education. Apart from these common aspects, the therapeutic approach is specific for the particular involved system.

CLASSIFICATION

The classification which will be used here is a modification based on the Consensus of San Antonio Conference[9] and P.K. Thomas.[10,11] It should be mentioned that as a rule different forms of DN co-exist in the same patient.

Classification of Diabetic Neuropathy

Class I: Subclinical (asymptomatic)

Class II: Clinical (symptomatic)

1. Somatic (discussed in detail in Chapter 14 by Kamenov and Traykov)

2. Autonomic
   - 2.1. Cardiovascular
     - 2.1.1. resting fixed tachycardia
     - 2.1.2. orthostatic hypotension
     - 2.1.3. silent myocardial ischemia/infarction
     - 2.1.4. sudden death
     - 2.1.5. exercise intolerance
   - 2.2. Gastrointestinal
     - 2.2.1. esophageal dysmotility
     - 2.2.2. gastroparesis
     - 2.2.3. diarrhea
     - 2.2.4. constipation
     - 2.2.5. Fecal incontinence
   - 2.3. Genitourinary
     - 2.3.1. erectile dysfunction
     - 2.3.2. bladder dysfunction
     - 2.3.3. retrograde ejaculation
     - 2.3.4. female sexual dysfunction
   - 2.4. Sudomotor
     - 2.4.1. dry skin
     - 2.4.2. gustatory sweating
   - 2.5. Hypoglycaemia unawareness and unresponsiveness
   - 2.6. Pupillary disturbances
     - 2.6.1. pupillomotor function impairment
     - 2.6.2. Argyll-Robertson pupil

CARDIOVASCULAR AUTONOMIC NEUROPATHY

Cardiovascular autonomic neuropathy (CAN) is the most studied and clinically important form of DAN. The prevalence varies from 2.5 to 50%, depending on the diagnostic criteria used, patient's age and the duration of diabetes.[12,13] An analysis of fifteen studies, using different end points, reported even a higher dispersion of the epidemiological data—from 1 to 90%.[5]

CAN is significantly associated with overall mortality[14] and includes different clinical presentations:[14]

- Resting and fixed tachycardia
- Silent myocardial ischemia
- Painless myocardial infarction
- Sudden cardiac death
- Orthostatic and/or postprandial hypotension
- Diabetic left ventricular dysfunction
- Skin blood flow dysregulation
- Intolerance to physical exercise

Cardiovascular reflex tests are the gold standard in clinical autonomic test (Table 1). These tests have good sensitivity, specificity and reproducibility and are non-invasive,

Table 1. Cardiovascular tests in CAN[15,16]

Method	Parameter	Normal	Borderline	Pathologic
1. Deep breathing	Difference in heart rate (bpm)	≥15	11-14	≤10
2. Valsalva manoevr	R-R length ratio	≥1.21		≤1.20
3. Heart rate response on standing	R-R ratio 30 to 15 beat	≥1.04	1.01-1.03	≤1.00
4. Blood pressure response on standing	Systolic BP drop (mm Hg)	≤10	11-29	≥30
5. Hand grip (dynamometer)	Diastolic BP rise (mm Hg)	≥16	11-15	≤10

safe, well-standardized, and easily performed.[17] However, a Valsalva maneuver must not be performed in patients with proliferative retinopathy. The most widely used tests, assessing cardiac parasympathetic function, are based on the time-domain heart rate (HR) response to deep breathing, a Valsalva maneuver, and postural change. Of these tests, HR to deep breathing has the greatest specificity (~80%). Cardiovascular sympathetic function is assessed by measuring the BP response to orthostatic change and a Valsalva maneuver. The performance of these tests should be standardized, and the influence of confounding variables such as medications, hydration, and antecedent activity should be minimized. Age normative values should be used.[12] The combination of cardiovascular autonomic tests with sudomotor function tests may allow a more accurate diagnosis of DAN.[18]

Diagnostic criteria and staging of CAN are still being debated. The Toronto Diabetic Neuropathy Expert Group (TDNEG) suggests that the presence of one abnormal cardiovagal test identifies possible or early CAN; at least two abnormal HR tests are required for a definite or confirmed diagnosis of CAN and orthostatic hypotension (asymptomatic or symptomatic); in addition to HR test abnormalities, identify a condition of severe or advanced CAN. Progressive stages of CAN are associated with an increasingly worse prognosis.

Other diagnostic methods, suggested for clinical trials and research include:[12]

- **Frequency-domain indexes** obtained by applying spectral analysis to HR variability of shorter (5-7 min) and longer (24-h) electrocardiogram recordings provide a measure of sympathetic and parasympathetic modulation of HR. HR spectral power in the high-frequency region is a measure of parasympathetic modulation, while spectral power in the low-frequency region provides a measure of both sympathetic and parasympathetic modulation.
- **Whole-body sympathetic activity** is most accurately assessed by measurements of plasma concentrations of noradrenalin and adrenaline.
- **Assessment of cardiac vagal baroreflex sensitivity** combines information derived from both, HR and BP, in response to pharmacological or spontaneous BP perturbations. Cardiac sympathetic baroreflex sensitivity can be measured with simultaneous recordings of muscle sympathetic nerve activity.
- **Scintigraphic studies with radio labeled nonmetabolized noradrenalin analogues** allow a direct semi-quantitative (^{123}I-metaiodobenzylguanidine [MIBG] and single photon emission computed tomography) assessment of cardiac

sympathetic integrity.[14] The method is more sensitive in detecting CAN than indirect autonomic reflex testing, because MIBG uptake is reduced in patients with normal autonomic tests.[19-21] The MIBG uptake defects are localized predominantly in the LV posterior and inferior segments. In advanced CAN, completely absent MIBG uptake may be observed. Another option to examine cardiac innervation defects is the norepinephrine analogue [^{11}C]-hydroxyephedrine (HED) and positron emission tomography (PET). In diabetic patients, attenuated HED retention is related to the severity of CAN and is most pronounced in the inferior, apical, and lateral segments.[22] The myocardial retention of HED is remarkably heterogenous in severe CAN, and as the extent of distal deficits increases, HED retention became paradoxically increased in the proximal myocardial segments, which shows the highest deficits in coronary blood flow reserve.[23] Such a proximal hyper innervation relative to the distal denervation could result in potentially life-threatening myocardial electrical instability. Myocardial dysinnervation correlates with the reduction in blood flow reserve. It has been suggested that augmented cardiac sympathetict one and impaired myocardial perfusion may contribute to myocardial injury in diabetes.[24]

There is no therapy currently available for the treatment of CAN. Therefore, treatment mostly focuses upon management of a number of modifiable risk factors, which can significantly reduce the risk of developing CAN.[25] Treatment of orthostatic hypotension includes different approaches:

- **Non-drug measures**—rising from bed slowly at consecutive stages, beginning with the head at 10 cm; dorsiflection of the feet; application of insulin in a lying position; compression garments; high salt and fluid diet (for adequate salt intake the sodium-uria must be around 170 m equivalents/24 hour).
- **Avoiding hypotensive factors** like hypotension inducing medication—tranquilants, antidepressants, diuretics, alcohol, etc.; hot weather and baths; consuming large amounts of food; isometric exercises; hyperventilation; standing immovable upright for a long time; tension by defecation or micturition.
- **Pharmacological approach**—several drugs have been advocated with different success—sympathomimetics; pyridostigmine; fludrocortisone; erythropoietin; somatostatin analogs; nonsteroidal anti-inflammatory drugs; dihydroergotamine; vasopressin analogs; fluoxetine; yohimbine; caffeine; clonidine; metoclopramide.

  The main drugs are:[25]

  - midodrine—alpha-agonist, starting dose 5 mg, optimal 10 mg, initial effect between 30-60 min, duration of the effect 2-4 h;
  - pyridostigmine—acetylcholinesterase inhibitor, starting with 30 mg BID, optimal total daily dose 180 mg; and
  - fludrocortisone—mineral ocorticoid agent, starting with 0.1 mg QD or BID, maximum daily dose 0.4-0.6 mg.

Screening for CAN should be performed at the diagnosis of T2DM and 5 years after the diagnosis of T1DM, particularly in patients at greater risk of CAN due to a history of poor glycaemic control, cardiovascular risk factors, DPN, and macro- and microangiopathic diabetic complications.[12]

GASTROINTESTINAL AUTONOMIC NEUROPATHY (GIAN)

The gastrointestinal (GI) system, has tremendous importance in diabetes, being one of the main participants in the blood glucose control. It is the only exogenous supplier of glucose and, including the liver—the main glucose source of the body. Together with the muscles (main energy expenditure) and the hormonal regulation, GI system frames the basic cycle of glucose homeostasis. A complex interaction of sympathetic, parasympathetic and enteric nervous systems with a basic rhythm generated by the interstitial cells of Cajal located within the smooth muscle, determine the motor, sensory, and secretory functions of GI system.

In last two decades a huge progress has been made in the field of endocrine functions of GI system. Hormones like glucagon like peptide 1 (GLP-1), glucose-dependent intestinal polypeptide (GIP), oxyntomodulin, peptid YY, and many others, secreted by the intestinal L- and K- cells, through paracrine, endocrine and neural mechanisms have strong local and central effect on appetite, GI motility and pancreatic glucose-regulating hormones. The incretine-based therapy represents a new promising paradigm in the treatment of DM2. The exact regulatory interactions between the exogenous (food and intestinal flora) and the endogenous (exocrine, endocrine, paracrine and neural functions) intestinal elements remains to be clarified in the field of neuro-endocrine gastroenterology.

Evaluation of GI autonomic function is difficult in humans, and the diagnosis of GIAN is often one of exclusion. The prevalence of GI symptoms in diabetes is not well established, but is higher, compared to general population.[26] It should be taken into consideration that many patients with GI dysfunction (mostly motor) are asymptomatic. Around 60-75% of patients, visiting diabetes clinics, report significant GI symptoms.[27,28] While irreversible autonomic neuropathy has been regarded as the cause of disordered gut motility in diabetes, recent evidence indicates a heterogeneous picture with a range of fixed pathology and reversible functional abnormalities.[29] Acute hyperglycemia slows gastric emptying (GE), while insulin-induced hypoglycemia accelerates it. Any segment of the GI tract may be affected with the most common types of GIAN being:

- esophageal enteropathy,
- gastroparesis,
- constipation,
- diarrhea, and
- fecal incontinence.

Disordered GI symptoms may be associated with GI motility, impaired oral drug absorption, poor glycaemic control, malnutrition, abnormal postprandial regulation of blood pressure, poor QoL, and a high rate of hospitalization. The relationships with symptoms and CAN are relatively weak.[30]

Esophageal transit is delayed in ~50% of patients with long standing diabetes and may be asymptomatic, but usually is associated with nonspecific symptoms like regurgitation, heartburn, dysphagia and a propensity for pill-induced esophageal erosions and strictures. One out of four diabetics has had symptomatic gastroesophageal reflux disease, compared to one in ten controls with chronic hepatitis C.[31]

Gastroparesis is an electromechanical motility disorder, which affects ~40% of patients with longstanding diabetes. It can be acute or chronic. Symptoms are variable and more common in patients with worse chronic glycaemic control and psychological

disorders.[32] Common complains are of recurrent nausea and vomiting, dyspeptic symptoms—satiety, frequent belching and bloating. On abdominal examination, a gastric splash might be detected, but it is rare. The nausea and vomiting episodes tend to follow a variable course and might be self-limited, recurrent, or unrelenting. In severe cases, the gastroparesis syndrome might lead to malnutrition or serious complications, such as bleeding from Mallory-Weiss tears secondary to repeated bouts of retching or vomiting. Symptoms tend to be worse during periods of diabetic decompensation and in fact the prototypic patient with symptomatic diabetic gastroparesis has poorly controlled, long standing, insulin-dependent diabetes.[33] Lack of correlation between gastric emptying rates and GI symptoms has been evidenced by numerous studies.[34] Postprandial hypotension occurs frequently in diabetes, and its magnitude is related directly to GE rate. In patients with gastroparesis the prevalence of disordered small and large intestinal and anorectal motility is high.

Diarrhea may result from rapid or slow transit, which is complicated by bacterial overgrowth and/or disordered secretion. The diarrhea is watery, often severe, 15-20 defecations per day particularly at night, preceded by abdominal cramps, but commonly also painless and may be accompanied by fecal incontinence. Symptoms are intermittent and might last from a few hours to several weeks. During remissions, patients may shift and complain of constipation, resembling the bowel movement alternance characteristic of irritable bowel syndrome. Mild steatorrhea, although not common is compatible with the diabetic diarrhea syndrome, whereas weight loss is unusual. Other signs of autonomic neuropathy may be present concomitantly. When steatorrhea is found, pancreatic insufficiency should be excluded by performing a pancreatic function test or, if these are not available, by a trial with oral pancreatic enzymes.[33] The very common treatment with metformin should also be taken into consideration in a patient with diarrhea.

Constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea. Because of the high prevalence of constipation in the general population it is difficult to determine the prevalence of diabetic constipation.

Fecal incontinence is not uncommon and is related to reduced and unstable internal anal sphincter tone and impaired rectal compliance and sensation.[12] The vast majority of patients with diabetes with fecal incontinence have normal or only moderately increased daily stool volumes, but also exhibit multiple abnormalities of anorectal sensory and motor functions.[35] Fecal incontinence might be associated with severe diabetic diarrhea or constitute an apparently independent disorder. Diarrhea might, of course, produce stress on the continence mechanisms that are already impaired.

A broad spectrum of diagnostic methods is available to investigate GIAN (Table 2). It should be noted, that clinical assumption for GIAN should not preclude a thorough search for an organic process, causing the GI dysfunction.

Objective GE measurement is advocated for the diagnosis of gastroparesis. Evaluation of solid emptying is probably more sensitive than that of low-nutrient liquid or semi-solid meals. Medications that may influence GE should ideally be withdrawn, glycaemia should ideally be <10 mmol/L throughout the test and other causes of gastroparesis must be excluded. Failure to demonstrate delayed GE does not necessarily imply that symptoms are not due to "diabetic gastropathy," but it does help in guiding drug therapy. Scintigraphy is still regarded as the gold standard technique for GE measurement.[12] Standardization of the meal technique has been improved by the recommendation of a low-fat, egg white meal labeled with technetium-99 (99mTc) sulfur colloid.[36] Breath tests using nonradioactive ^{13}C-acetate or -octanoic acid as a label are appealing options, at least as a screening

Table 2. Investigations in patients with GIAN

Evaluation of Upper Gut Symptoms	Evaluation of Chronic Diarrhea	Evaluation of Colonic and Anorectal Dysfunction
Esophageal symptoms • Radiographic studies • Endoscopy • Scintigraphy (esophageal transit or clearance) • Esophageal manometry • Psychological assessment **Gastroparesis syndrome** • Upper GI X-rays (only useful if showing manifest retention) • Gastroduodenoscopy, to exclude mechanical obstruction and to show retained residue • Gastric emptying studies: radioscintigraphic (liquid and/or solid component); breath test; ultrasound • Upper gut manometry • Electrogastrography (unproven reliability)	• Stools: weight, fat, occult blood, examination for ova, parasites, and culture • Colonoscopy (rectal biopsy) • Radiographic studies: plain film of the abdomen; small bowel barium studies; abdominal • CT scan • Small bowel biopsy • Small bowel aspirate for giardia and bacteria • Breath tests for malabsorption and bacterial overgrowth • Serum vitamin B12 and folate • Pancreatic function tests (elastase 1 in stools, other) • Therapeutic trials with antibiotics, gluten-free diet, pancreatic enzyme supplements	**Constipation** • Digital examination • Stools: occult blood • Barium enema • Colonoscopy (biopsy) • Colonic segmental transit time • Anorectal manometry **Fecal incontinence** • 24-hour stool weight • Anorectal manometry - Maximum basal sphincter pressure - Maximum “squeeze” sphincter pressure - Rectoanal inhibitory reflex • Tests of continence - Solids: solid sphere - Liquids: rectally infused saline

Modified with permission from Malagelada JR. Gastrointestinal Syndromes Due to Diabetes Mellitus. In: Veves A, Malik R (eds.). Diabetic Neuropathy: Clinical Management, Second Edition, Totowa, New Jersey: Humana Press Inc. 2007; 433-451.[33]

tool. They are safe, easy to perform, inexpensive, and correlate well with scintigraphy. Ultrasonography (2D and 3D) is non-invasive and 2D ultrasound has been validated for measuring emptying of liquids and semi-solids. However, obesity and abdominal gas, together with the necessity for an experienced operator, have limited its wide spread use. Surface electrogastrography, used to detect abdominal gastric slow-wave activity, should be regarded as a research tool. A barium meal has no role in quantifying GE. In the investigation of "diabetic diarrhea" celiac disease, exocrine pancreatic insufficiency and small intestinal bacterial overgrowth must be excluded. Tests of anorectal motor and sensory function are well developed for clinical use.[12]

Treatment of GIAN

Gastroparesis Diabeticorum

Dietary measures are important and include frequent meals, but in small amounts and with fluid consistence, without much fat and poorly digestible fibers. Patients with severe feeding problems might even require surgical implantation of a feeding jejunostomy, sometimes complemented by a "venting" gastrostomy that serves to decompress the gastric cavity on demand.[37,38] The standard approach to pharmacotherapy are the prokinetics (metoclopramide, domperidone, cisapride, cinitrapride, and others). Although diet and prokinetics bring symptomatic relief in most patients, it should be remembered that improvement in GE does not equate symptom relief.[39] Erythromycin, a motilin receptor agonist, is a highly effective prokinetic agent, particularly when administered as IV boluses in acute flare-ups of gastroparesis. It induces a sweeping gastric peristaltic contraction, which empties retained content into the small bowel. Unfortunately, its mid- and long-term efficacy when given orally casts doubt. In addition, concerns have arisen about recommending sustained antibiotic administration. Newer motilin agonists devoid of antibiotic properties are under development.[33] Other therapeutic options with limited evidence are clonidine, sildenafil and endoscopic injections of botulinum toxin into pyloric muscle. Gastric pacing is a relatively new treatment modality which holds promise. Gastric stimulation devices are surgically implanted, first temporarily and, permanently if patients show positive responses. Several series have been published and report substantial improvement in nausea and vomiting in association with improved quality of life,[40,41] but this method should be reserved for nonresponders to conservative treatment.

Diabetic Diarrhea

The somatostatin analogue octreotide inhibits peptide secretion including serotonin, gastrin, and motilin and at the same time directly suppresses GI motility[42] and improves fluid and electrolyte absorption. Octreotide reduces diabetic diarrhea and its consequences.[43,44] The subcutaneous injections may be started at 50 μm cg BID and increased to 100 μg TID as needed. If effective, to improve the compliance, the patient can be switched to a long-acting octreotide preparation. Blood sugar must be controlled frequently because of the increased hypoglycemic risk, after inhibition of the release of glucagon, growth hormone, and other peptides, by octreotide. Suppression of exocrine pancreatic function also may occur. Other drugs like loperamide, codeine,

clonidine may be also useful. Antibiotics may be necessary for long time to prevent or control the bacterial overgrowth.

Diabetic Constipation

Treatment of constipation in diabetics does not differ from those without diabetes. Acarbose may be helpful.

Fecal Incontinence

Besides the optimal blood glucose control and recommendations to consume more dry food biofeedback therapy has been shown to be successful. Surgical intervention should be reserved for cases refractory to medical treatment or for those patients with rectocele or obstetrical injury.[45] The clinical outcome of surgical treatment of incontinence is far from uniform and caution is advisable before recommending it.

Genitourinary Autonomic Neuropathy (GUAN)

Diabetic Erectile Dysfunction

Diabetic erectile dysfunction (DED) is more common in diabetic men with a prevalence varying from 20 to >70% depending on differences in age, diabetes type, duration and severity, and diagnostic methods.[46] The pathogenesis of DED is complex and includes atherosclerosis, neuropathy, hypogonadism and corporeal erectile tissue alterations like endothelial dysfunction, abnormal collagen deposition and smooth muscle degeneration.[47] Not only the peripheral (sensory and autonomic), but also "central" neuropathy may contribute to the profound sexual dysfunction that characterizes this condition.[48] After sexual stimulation the erectile process is initiated through neural mechanisms on central brain level—neocortex, hippocampus, septum pelucidum, to hypothalamus (medial preoptic area—the keycenter of the autonomic nervous system in both sexes and paraventricular nucleus) and ventral tegmentum in the mid brain, further descending through dorsolateral funiculus in the spinal cord, reaching finally the corpora cavernosa. The non-adrenergic noncholinergic parasympathetic cavernosal nerve terminals release nitric oxide (NO), which activates guanil cyclase to form intracellular cyclic guanosine monophosphate (GMP), a potent second messenger for smooth muscle relaxation. Cyclic GMP activates a specific protein kinase, which phosphorylates certain proteins and ion channels, resulting in a drop of cytosolic calcium concentrations and relaxation of the intracavernosal smooth muscles. Blood fills the cavernosal spaces through the helical arteries inducing the tumescence. Further, the venous outflow from the penis is blocked by compression of the veins against the rigid tunica albuginea and the full rigidity of the penis is reached. After ejaculation, during the return to the flaccid state, cyclic GMP is hydrolyzed by phosphodiesterase Type 5 (PDE-5), intracellular Ca^{++} raises and the tonus of the smooth muscles increases, leading to detumescence. Failure of each of the described stages of erection may cause DED, which is linked more to microangiopathic complications and DN than to macroangiopathic disturbances.[49]

A special problem, aggravating the DED in diabetic men is testosterone deficiency. Earlier thought to determine only libido, nowadays to testosterone has been attributed a main role in all erectile processes from the brain, through the spinal cord pathways to the fine balance of both signal initiators (neural and endothelial NO synthases) and signal terminators phosphodiesterase 5 (PDE5) of erection. Recently, a study including 2162 men over the age of 45 (mean age 60.5 years), visiting primary care centers for different reasons showed a crude prevalence of low testosterone (<10.4 nmol/L) of 38.7%. The prevalence of hypogonadism if having hyperlipidemia was 40.4% (odds ratio for having low testosterone 1.47); arterial hypertension 42.4% (1.84), diabetes 50.0% (2.09); obesity 52.4% (2.38).[50] According to other sources, the prevalence of hypogonadism in men with DM2 varies from 20 to 60%.[51,52]

The diagnosis of DED is made by questionnaires like The International Index of Erectile Function,[53] psychological consultation and rarely by intracavernosal injections of vasodilating agents like PgE1, followed by Doppler ultrasonography. More sophisticated methods for investigations like analysis of nocturnal penile tumescence, arteriography, etc. are rarely used.

After the introduction of the first PDE5 inhibitor—sildenafil on the market in 1998 a new era in the treatment of DED began. The three currently available PDE-5 inhibitors sildenafil, vardenafil and tadalafil represent the first-line therapy of DED. The interventional studies of patients with DED indicate poorer results, compared to nondiabetic erectile dysfunction (ED),[54] ordering DED to the "difficult to treat" groups of ED. Usually the highest doses of the drugs are required. Studies comparing different PDE-5 inhibitors head-to-head in diabetes are scarce.[55] Recently, the first study comparing the first intake of vardenafil and tadalafil in men with DN and DED was published.[56] Intracavernosal injections with PgE1, phentolamine and papaverine, are second-line therapy, together with vacuum erection devices and intra-urethral application of PgE1. As third line options penile prostheses are implemented and occasionally vascular surgery after traumatic injuries in younger men.

Retrograde Ejaculation

Retrograde ejaculation (RE) may be caused by anatomic (congenital and acquired), neurologic (including DM) pharmacologic factors, or may be idiopathic. In a man with absentor low-volume ejaculate, the diagnosis is made by demonstration of sperm in an analys is of a post-ejaculatory urine sample,[57] performed by centrifuging the specimen for 10 minutes at 300 g or more. In patients with absent ejaculation, the finding of greater than 10 sperm per high power field in a post-ejaculation urine specimen confirms the presence of RE. In patients with low-volume ejaculate, the finding of more sperm in the urine, than in the antegrade ejaculate indicates a significant component of RE.[58]

The conservative treatment of RE includes adrenergic agents such as ephedrine (30-60 mg), pseudoephedrine (60-120 mg), or tricyclic antidepressant with anticholinergic effects such as desipramine (50 mg), taken one to two hours before sexual activity, or imipramine (25-75 mg three times a day).[57,59] The success rate reported by different authors varied between 20 and 67%.[60] Surgical treatment for RE is not commonly used, due to the success achieved with seminal fluid harvesting, sperm processing and assisted reproductive technology.[61,58] A few specific surgical techniques for treatment of RE have been reported.[62-64]

Female Sexual Dysfunction

Female sexual dysfunctions (FSD) is at least as common in the general population as ED is. The effects of diabetes on women's sexual functioning are poorly understood and probably multifactorial.[65] There are several reasons for this information gap:

1. Most of the epidemiological research in sexual medicine is men-oriented, especially after identifying of ED as a predictor for cardiovascular and metabolic diseases and the introduction of PDE-5 inhibitors as very effective treatment.
2. There is much less therapeutic progress in FSD.
3. FSD is rarely an issue of discussion when medical history is evaluated. Men with diagnosed diabetes are more than twice as likely (46.8%) as women with diagnosed diabetes (18.8%) to discuss sex with a physician.[66]

FSD includes four main aspects:

1. Persistent or recurrent disorders of sexual interest/desire (hypoactive sexual desire disorder—HSDD),
2. Disorders of subjective (central) and genital (peripheral) arousal,
3. Orgasm disorder,
4. Sexual pain (dyspareunia and vaginismus) and difficulty with attempted or completed intercourse.

FSD is more common in T1DM compared to T2DM.[67,68] Of the sexually active women with T1DM in the EDIC study, 35% met criteria for FSD.[69] Women with FSD reported loss of libido (57%); problems with orgasm (51%), lubrication (47%), and arousal (38%); and pain (21%). Univariate analyses revealed a positive association between FSD and age, marital status, menopausal status, microvasculopathy, and depression. However, in a multivariate analysis, only depression and marital status were significant predictors of FSD.

Problems affecting sexuality in women with diabetes are fatigue, changes in perimenstrual blood glucose control, vaginitis, decreased sexual desire, decreased vaginal lubrication and an increased time to reach orgasm. Even minor episodes of depression, which is twice more frequent than in men can result in a loss of libido. To which degree these symptoms are related to autonomic neuropathy has also been examined in a few studies, the results of which are at variance.[65,70]

The examination for a women with diabetes with sexual dysfunction should include the duration of symptoms, psychological state, concommitant, medications, presence of vaginitis, cystitis and other infections, frequency of intercourse, blood pressure, BMI, retinal status, pelvic examination, presence of discharge, and glycemic control.[71] A teamwork is recommended when diagnosing FSD. Optimal referral includes *gynecologist* to exclude organic causes; *andrologist,* when the loss of desire appears to be secondary to a male sexual problem; *endocrinologist,* when endocrine and metabolic disorders are suspected; *couple therapist*, when the desire disorder reflects relational problems; *psychiatrist,* if development traumas (child abuse, parental loss, etc.) or underlying psychiatric disorders (major depressive or generalized anxiety disorder, etc.) are suspected or already established.[72]

The treatment should be etiologic, according to the underlying condition. Recently effective therapy of HSDD with 0.3 mg/day testosterone patch has been reported in surgically[73,74] and in naturally menopausal women,[75] but further studies are necessary to properly position this hormonal treatment.[76,77]

Bladder Dysfunction

Diabetic bladder dysfunction is characterized by decreased bladder sensation, increased bladder capacity, and impaired detrusor contractility. Bladder complications can be due to an alteration of the detrusor smooth muscle, neuronal dysfunction and urothelial dysfunction. Estimates of the prevalence of bladder dysfunction are 43 to 87% in Type 1 diabetic and 25% in Type 2 diabetic patients. Diabetes duration is significantly associated with severe incontinence. The correlation between diabetic cystopathy and peripheral neuropathy ranges from 75 to 100%.[12]

Common symptoms include dysuria, frequency, urgency, nocturia and incomplete bladder emptying. Other symptoms include infrequent voiding, poor stream, hesitancy in initiating micturition, recurrent cystitis and stress and urgency urinary incontinence. Since urological conditions such as benign prostatic hypertrophy in men or gynecological disorders in women may share the same symptoms, these causes must be excluded by appropriate testing.

Diagnosis should use a validated questionnaire for lower urinary tract symptoms. The type of bladder dysfunction is most readily characterized with complete urodynamic testing. Treatment includes behavioral maneuvers and medication according to the leading symptoms and detected by urological investigations disturbances.

Sudomotor Autonomic Neuropathy

The eccrine sweat glands are innervated by the sudomotor, postganglionic, unmyelinated cholinergic sympathetic C-fibers. Sudomotor dysfunction may result in hypo- or anhidrosis. Particularly, dryness of the foot skin is a predisposing factor to fissures, infection and ulceration. Gustatory sweating (GS) consists of localized hyperhidrosis of the face during meals. The mechanism of GS is not proven, but is considered to be related to sympathetic postganglionic denervation followed by aberrant re-innervation by parasympathetic misdirected fibers.

There are several tests for evaluation of sudomotor function.[78] Significant work has been done using tests like Thermoregulatory Sweat Test (TST),[79] modified by R. Fealey,[80] Quantitative Sudomotor Axon Reflex Test (QSART),[81] Skin Potential Recording[82] of the Sympathetic skin response (SSR). Recently V.A. Low et al using TST, autonomic reflex screen (ARS) and nerve conduction studies and electromyography in patients with distal small-fiber neuropathy including diabetic etiology, concluded that sudomotor examination is a highly sensitive detection tool in SFN. Autonomic involvement is mainly distal and additionally may involve adrenergic and the long cardiovagal fibers.[83]

Although very sensitive, these tests are not applicable for everyday outpatient practice. Therefore simple and reliable methods for assessing sudomotor dysfunction are needed. *Neuropad* has been developed recently[84] as an accessible tool for determining the sudomotor function (sweating) on the soles (for review see ref. 85). It has been shown, that the responses with Neuropad correlate with different somatic and autonomic tests and nerve fiber density.[86,87] The method is reliable and simple for use[88,89] with excellent reproducibility.[90]

Increased sweating can, in some cases, be reduced by glycopyrrolate, trihexyphenidyl, or propantheline, but the side effects, such as dry mouth, urinary retention, or constipation are not rare. A new approach is the injection of botulinum toxin in the symptomatic skin.[91] There are no medications that stimulate sweating and care needs to be taken to avoid overheating with physical activity or in hot weather. Other aspect of sudomotor DAN is the heat intolerance.[5]

Hypoglycaemia Unawareness and Unresponsiveness

DAN plausibly could cause or contribute to hypoglycemia unawareness, but this relationship is complex. The counter regulatory response to hypoglycemia is triggered mainly by specialized glucose-sensing neurons within the brain,[92] localized to the ventromedial hypothalamus—in particular the ventromedial and arcuate nuclei, and brainstem.[93-95] Deficient secretion of glucagon and catecholamines is in large part responsible for the morbidity and mortality associated with iatrogenic hypoglycemia.[96] The glucagon response to hypoglycemia is attenuated after several years of DM1 and the adrenergic response becomes the critical defense mechanism against insulin induced hypoglycemia.[97] Several studies support that antecedent hypoglycemia is a primary cause of the impaired adrenergic response to insulin-induced hypoglycemia, but the mechanisms whereby this impairment occurs are not fully elucidated.[98,99]

Hypoglycemia-induced autonomic failure leads to a vicious cycle of hypoglycemia unawareness that induces a further decrease in counter regulatory hormone responses to hypoglycemia. This vicious cycle occurs commonly in individuals with diabetes who are in strict glycemic control. The defective counter regulatory hormone responses can be partially restored by the meticulous avoidance of hypoglycemia in intensively treated patients with short duration[100-103] and long duration diabetes.[104,105] In most individuals with hypoglycemic unawareness, raising the target may be necessary to prevent repeat episodes.[5] Recent large-scale studies, The Action to Control Cardiovascular Risk in Diabetes (ACCORD)[106,107] and The Veteran Administration Diabetes Trial (VADT)[108,109] confirmed a more cautious and individualized approach when setting the targets for glucose control. Hypoglycaemic events not only decrease patient's motivation to keep strict glycaemic control, but may be dangerous in patients with longstanding DM and established late complications. Thus, emphasizing tight control for individuals with autonomic dysfunction should also include increased vigilance in glycemic monitoring (frequent checks, including during the night), usage of insulin analogs and re-education of the patient with regard to hypoglycemia.

Pupillary Disturbances

These include the pupillomotor function impairment (e.g., decreased diameter of dark adapted pupil) and the Argyll-Robertson pupil.[5]

CONCLUSION

Diabetic autonomic neuropathy is very common and affects all organs and systems in the body. Its diverse clinical presentation resembles symptoms and signs of various cardiovascular, gastrointestinal and genitourinary diseases. The diagnostic tests for DAN are more complicated and time consuming, compared with the somatic tools. There is a need for simple devices and methods for evaluation of autonomic functions in the everyday clinical practice. Tight glycaemic control is the cornerstone of the prevention and progression retardation of DAN. An effective broad-spectrum pathogenetic treatment of neural deterioration remains to be established. In most cases symptomatic drugs are the treatment of choice.

REFERENCES

1. Boulton AJ, Malik RA, Arezzo JC et al. Diabetic somatic neuropathies. Diabetes Care 2004; 27(6):1458-1486.
2. Low PA, Benrud-Larson LM, Sletten DM et al. Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care 2004; 27:2942-2947.
3. Boulton AJ, Vinik AI, Arezzo JC et al. American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005; 28(4):956-962.
4. Pfeifer MA, Weinberg CR, Cook DL et al. Autonomic neural dysfunction in recently diagnosed diabetic subjects. Diabetes Care 1984; 7:447-453.
5. Vinik AI, Maser RE, Mitchell BD et al. Diabetic autonomic neuropathy. Diabetes Care 2003; 26:1553-1579.
6. Scott WA. Assessment of the autonomic nervous system. In: Moss and Adams heart disease in infants and adolescents including the fetus and young adult. Baltimore (et.) Williams and Wilkins 1995; 172-181.
7. Jaradeh SS, Prieto TE. Evaluation of the autonomic nervous system. Phys Med Rehabil Clin N Am 2003; 14:287-305.
8. Zygmunt A, Stanczyk J. Methods of evaluation of autonomic nervous system function. Arch Med Sci 2010; 6(1):11-18.
9. American Diabetes Association, American Academy of Neurology: Report and recommendations of the San Antonio Conference on Diabetic Neuropathy (Consensus Statement). Diabetes Care 1988; 11:592-597.
10. Thomas PK. Classification of the diabetic neuropathies. In: Gries FA, Cameron NE, Low PA et al, (eds.). Textbook of Diabetic Neuropathy. Stuttgart: Thieme 2003:175-177.
11. Thomas PK. Classification, differential diagnosis, and staging of diabetic peripheral neuropathy. Diabetes 1997; 46(Suppl 2):S54-S57.
12. Tesfaye S, Boulton AJ, Dyck PJ et al. Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010; 33(10):2285-2293.
13. Valensi P, Pariès J, Attali JR. 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 multicenter study. Metabolism 2003; 52:815-820.
14. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation 2007; 115:387-397.
15. Ewing DJ, Martyn CN, Young RJ et al. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985; 8(5):491-498.
16. Ewing DJ. Autonomic neuropathy. In: Pickup JC, Williams G (eds.). Chronic complications of diabetes. Blackwell Scientific Publications Oxford 1994:124-136.
17. American Academy of Neurology. Assessment: clinical autonomic testing report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 1996; 46:873-880.
18. England JD, Gronseth GS, Franklin G et al. American Academy of Neurology. Practice parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review): report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology 2009; 72:177-184.
19. Langen KJ, Ziegler D, Weise F et al. Evaluation of QT interval length, QT dispersion and myocardial m-iodobenzylguanidine uptake in insulin-dependent diabetic patients with and without autonomic neuropathy. Clin Sci Colch 1997; 93:325-333.
20. Ziegler D, Langen K, Weise F. Contribution de l'imagerie scintigraphique a l'etude de l'innervation sumpathique. In: Valensi P, Feuvray, D, Sach R-N, eds. Coeur et Diabete. Paris, France: Editions Frison-Roche 1999:443-455.
21. Ziegler D, Weise F, Langen KJ et al. Effect of glycaemic control on myocardial sympathetic innervation assessed by [123 I]metaiodobenzylguanidine scintigraphy: a 4-year prospective study in IDDM patients. Diabetologia 1998; 41:443-451.
22. Stevens M, Raffel D, Allman KC et al. Cardiac sympathetic dysinnervation in diabetes implications for enhanced cardiovascular risk. Circulation 1998; 98:961-968.
23. Stevens MJ, Dayanikli F, Raffel DM et al. Scintigraphic assessment of regionalized defects in myocardial sympathetic innervation and blood flow regulation in diabetic patients with autonomic neuropathy. J Am Coll Cardiol 1998; 31:1575-1584.
24. Pop-Busui R, Kirkwood I, Schmid H et al. Sympathetic dysfunction in type 1 diabetes: association with impaired myocardial blood flow reserve and diastolic dysfunction. J Am Coll Cardiol 2004; 44:2368-2374.
25. Stevens M. Cardiovascular Autonomic Neuropathy. In: Veves A, Malik R (eds.). Diabetic Neuropathy: Clinical Management, Second Edition, Totowa, New Jersey: Humana Press Inc. 2007:389-412.
26. Bytzer P, Talley NJ, Leemon M et al. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. Arch Intern Med 2001; 161(16):1989-1996.

27. Chandran M, Chu NV, Edelman SV. Gastrointestinal disturbances in diabetes. Curr Diab Rep 2003; 3(1):43-48.
28. Perusicova J. Gastrointestinal complications in diabetes mellitus. Vnitr Lek 2004; 50(5):338-343.
29. Rayner CK, Horowitz M. Gastrointestinal motility and glycemic control in diabetes: the chicken and the egg revisited? J Clin Invest 2006; 116:299-302.
30. Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology 2004; 127:1592-1622.
31. Nishida T, Tsuji S, Tsujii M et al. Gastroesophageal reflux disease related to diabetes: Analysis of 241 cases with type 2 diabetes mellitus. J Gastroenterol Hepatol 2004; 19(3):258-265.
32. Jones KL, Russo A, Stevens JE et al. Predictors of delayed gastric emptying in diabetes. Diabetes Care 2001; 24:1264-1269.
33. Malagelada J-R. Gastrointestinal Syndromes Due to Diabetes Mellitus. In: Veves A, Malik R (eds.). Diabetic Neuropathy: Clinical Management, Second Edition, Totowa, New Jersey: Humana Press Inc. 2007; 433-451.
34. De Block CE, De Leeuw IH, Pelckmans PA et al. Delayed gastric emptying and gastric autoimmunity in type 1 diabetes. Diabetes Care 2002; 25(5):912-917.
35. Wald A. Incontinence and anorectal dysfunction in patients with diabetes mellitus. Eur J Gastroenterol Hepatol 1995; 7(8):737-739.
36. Horowitz M, Maddox AF, Wishart JM et al. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. Eur J Nucl Med 1991; 18:229-234.
37. Stanciu GO. Gastroparesis and its management. Rev Med Chir Soc Med Nat Iasi 2001;105(3):451-456.
38. Gentilcore D, O'Donovan D, Jones KL et al. Nutrition therapy for diabetic gastroparesis. Curr Diab Rep 2003; 3(5):418-426.
39. Talley NJ. Diabetic gastropathy and prokinetics. Am J Gastroenterol 2003; 98(2):264-271.
40. Forster J, Sarosiek I, Delcore R et al. Gastric pacing is a new surgical treatment for gastroparesis. Am J Surg 2001; 182(6):676-681.
41. Abell T, Lou J, Tabbaa M et al. Gastric electrical stimulation for gastroparesis improves nutritional parameters at short, intermediate, and longterm follow-up. JPEN J Parenter Enteral Nutr 2003; 27(4):277-281.
42. Farthing M. Effective treatment of diabetic diarrhea with a somatostatin analogue. Gut 1992; 33:1578-1580.
43. Nakabayashi H, Fujii S, Milwa U et al. Marked improvement of diabetic diarrhea with the somatostatin analogue octreotide. Arch Int Med 1994; 154:1863-1867.
44. Meyer C, O'Neal DN, Connell W et al. Octeotride treatment of severe diabetic diarrhoea. Int Med J 2003; 33:617-624.
45. Cooper ZR, Rose S. Fecal incontinence: a clinical approach. Mt Sinai J Med 2000; 67(2):96-105.
46. Fedele D, Coscelli C, Santeusanio F et al. Erectile dysfunction in diabetic subjects in Italy. Gruppo Italiano Studio Deficit Erettile nei Diabetici. Diabetes Care 1998; 21(11):1973-1977.
47. Saenz de Tejada I, Goldstein I, Krane RJ. Local control of penile erection. Nerves, smooth muscle and endothelium. Urol Clin North Am 1988; 15(1):9-15.
48. Nofzinger EA. Sexual Dysfunction in Patients with Diabetes Mellitus: The Role of a "Central" Neuropathy. Semin Clin Neuropsychiatry 1997; 2(1):31-39.
49. Kamenov Z, Christov V, Yankova T. Erectile dysfunction in diabetic men—linked more to microangiopathic complications and neuropathy than to macroangiopathic disturbances. Journal of Men's Health and Gender 2007; 4(1):64-73.
50. Mulligan T, Frick MF, Zuraw QC et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract 2006; 60(7):762-769.
51. Dhindsa S, Prabhakar S, Sethi M et al. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004; 89:5462-5468.
52. Corrales JJ, Burgo RM, Garca-Berrocal B et al. Partial androgen deficiency in aging type 2 diabetic men and its relationship to glycemic control. Metabolism 2004; 53:666-672.
53. Rosen RC, Riley A, Wagner G et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile function. Urology 1997; 49:822-830.
54. Costabile RA. Optimizing treatment for diabetes mellitus induced erectile dysfunction. J Urol 2003; 170(2 Pt 2):S35-S38.
55. Snow JK. Erectile dysfunction in patients with diabetes mellitus—advances in treatment with phosphodiesterase type 5 inhibitors. Br J Diabetes Vasc Dis 2002; 2:282-287.
56. Kamenov Z. Comparison of the first intake of vardenafil and tadalafil in patients with diabetic neuropathy and diabetic erectile dysfunction. JSM 2011; 8(3):851-864.
57. Colpi G, Weidner W, Jungwirth A et al. EAU Working Party on Male Infertility. EAU guidelines on ejaculatory dysfunction. Eur Urol 2004; 46(5):555-558.
58. McMahon C, Waldinger M, Rowland D et al. Ejaculatory disorders. In: Standard practice in Sexual medicine. Eds. H. Porst, J. Buvat, Blackwell Publishing 2006; 315-319.
59. Ralph DJ, Wylie KR. Ejaculatory disorders and sexual function. BJU Int 2005; 95(9):1181-1186.

60. Kamischke A, Nieschlag E. Treatment of retrograde ejaculation and anejaculation. Hum Reprod Update 1999; 5(5):448-474.
61. Jimenez C, Grizard G, Pouly JL et al. Birth after combination of cryopreservation of sperm recovered from urine and intracytoplasmic sperm injection in a case of complete retrograde ejaculation. Fertil Steril 1997; 68(3):542-544.
62. Abrahams JI, Solish GI, Boorjian P et al. The surgical correction of retrograde ejaculation. J Urol 1975; 114(6):888-890.
63. Ramadan AE, el-Demiry MI. Surgical correction of post-operative retrograde ejaculation. Br J Urol 1985; 57(4):458-461.
64. Middleton RG, Urry RL. The Young-Dees operation for the correction of retrograde ejaculation. J Urol 1986; 136(6):1208-1209.
65. Enzlin P, Mathieu C, Vanderschueren D et al. Diabetes mellitus and female sexuality: a review of 25 years' research. Diabet Med 1998; 15:809-815.
66. Lindau S, Tang H, Gomero A et al. Sexuality among middle-aged and older adults with diagnosed and undiagnosed diabetes. A national, population-based study. Diabetes Care 2010; 33(10):2202-2210.
67. Doruk H, Akbay E, Cayan S et al. Effect of diabetes mellitus on female sexual function and risk factors. Arch Androl 2005; 51(1):1-6.
68. Wallner LP, Sarma AV, Kim C. Sexual functioning among women with and without diabetes in the Boston Area Community Health Study. J Sex Med 2010; 7(2 Pt 2):881-887.
69. Enzlin P, Rosen R, Wiegel M et al. and the DCCT/EDIC Research Group. Sexual dysfunction in women with type 1 diabetes long-term findings from the DCCT/EDIC study cohort. Diabetes Care 2009; 32(5): 780-785.
70. Ziegler D, Stief C. Genitourinary Complications. In: Veves A, Malik R, eds. Diabetic Neuropathy: Clinical Management, Second Edition, Totowa, New Jersey: Humana Press Inc. 2007; 453-472.
71. Jovanovic L. Sex and the woman with diabetes: desire versus dysfunction. IDF Bull 1998; 43:23-28.
72. Dennerstein L, Alexander J, Graciotin A. Sexual desire disorders in women. In: H. Porst, J. Buva, eds. Standard practice in Sexual medicine. Blachwell Publishing 2006; 315-319.
73. Buster JE, Kingsberg SA, Aguirre O et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. Obstet Gynecol 2005; 105:944-952.
74. Davis SR, van der Mooren MJ, van Lunsen RH et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Menopause 2006; 13:387-396.
75. Shifren JL, Davis SR, Moreau M et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 study. Menopause 2006; 13(5):770-779.
76. Wierman ME, Basson R, Davis SR et al. Androgen Therapy in Women: An Endocrine Society Clinical Practice Guideline J Clin Endocrinol and Metab 2006; 91(10):3697-3716.
77. Traish A, Guay A. Spark Rand the Testosterone Therapy in Women Study Group. Are the Endocrine Society's Clinical Practice Guidelines on Androgen Therapy in Women Misguided? A Commentary. J Sex Med 2007; 4:1223-1235.
78. Low PA. Sudomotor function. In: Textbook of Diabetic Neuropathy. Eds.: FA Gries, PA Low, NE Cameron, D Ziegler. Publ. G. Thieme Verlag 2003; 274-278.
79. Guttmann L. The management of the quinizarin sweat test (QST). Postgrad Med J 1947; 23:353-366.
80. Fealey RO. The thermoregulatory sweat test. In: Low PA (ed.) Clinical autonomic disorders: evaluation and management. Boston: Little, Brown and Company 1993:217-229.
81. Lang E, Spitzer A, Claus O et al. Stimulation of sudomotor axon reflex mechanism by carbachol in healthy subjects and patients suffering from diabetic polyneuropathy. Acta Neurol Scand 1995; 91:251-254.
82. Shahani BT, Halperin JJ, Boulu P et al. Sympathetic skin response: a method of assessing unmyelinated axon dysfunction in peripheral neuropathies. J Neurol Neurosurg Psychiatry 1984; 47:536-542.
83. Low VA, Sandroni P, Fealey RD et al. Detection of small-fiber neuropathy by sudomotor testing. Muscle Nerve 2006; 34(1):57-61.
84. Papanas N, Papatheodorou K, Christakidis D et al. Evaluation of a new indicator test for sudomotor function (neuropad) in the diagnosis of peripheral neuropathy in type 2 diabetic patients. Exp Clin Endocrinology Diabetes 2005; 113:1-4.
85. Schnell O, Mueler M, Standl E. Early detection of changes in the feet of diabetic patients with indicator test Neuropad®. Diabetes, Metabolism and the Heart 2008; 17(3):203-210.
86. Liatis S, Marinou K, Tentolouris N et al. Usefulness of a new indicator test for the diagnosis of peripheral and autonomic neuropathy in patients with diabetes mellitus. Diabet Med 2007; 24(12):1375-1380.
87. Quattrini C, Jeziorska M, Tavakoli M et al. The Neuropad test: a visual indicator test for human diabetic neuropathy. Diabetologia 2008; 51(6):1046-1050.

88. Tentolouris N, Achtsidis V, Marinou K et al. Evaluation of the self-administered indicator plaster neuropad for the diagnosis of neuropathy in diabetes. Diabetes Care 2008; 31(2):236-237.
89. Kamenov Z, Petrova J, Christov V. Diagnosis of diabetic neuropathy and risk determination using simple somatic and a new autonomic (Neuropad®) tests in the clinical practice. Exp Clin Endocrinol Diabetes 2010; 118(4):226-233.
90. Papanas N, Papatheodorou K, Papazoglou D et al. Reproducibility of the new indicator test for sudomotor function (Neuropad) in patients with type 2 diabetes mellitus: short communication. Exp Clin Endocrinol Diabetes 2005; 113(10):577-581.
91. Beerens AJ, Snow GB. Botulinum toxin A in the treatment of patients with Frey syndrome. Br J Surg 2002; 89:116-119.
92. Donovan CM, Hamilton-Wessler M, Halter JB et al. Primacy of liver glucosensors in the sympathetic response to progressive hypoglycemia. Proc Natl Acad Sci U S A 1994; 91(7):2863-2867.
93. Borg WP, During MJ, Sherwin RS et al. Ventromedial hypothalamic lesions in rats suppress counter regulatory responses to hypoglycemia. J Clin Invest 1994; 93(4):1677-1682.
94. Borg WP, Sherwin RS, During MJ et al. Local ventromedial hypothalamus glucopenia triggers counterregulatory hormone release. Diabetes 1995; 44(2):180-184.
95. Ritter S, Llewellyn-Smith I, Dinh TT. Subgroups of hindbrain catecholamine neurons are selectively activated by 2-deoxy-D-glucose induced metabolic challenge. Brain Res 1998; 805(1-2):41-54.
96. Freeman R. Hypoglucemia and the autonomic nervous system. In: Veves A., Malik R (eds.). Diabetic Neuropathy: Clinical Management, Second Edition, Totowa, New Jersey: Humana Press Inc 2007:379-388.
97. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2004; 350(22):2272-2279.
98. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003; 26(6):1902-1912.
99. Diedrich L, Sandoval D, Davis SN. Hypoglycemia associated autonomic failure. Clin Auton Res 2002; 12(5):358-365.
100. Fanelli CG, Epifano L, Rambotti AM et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 1993; 42(11):1683-1689.
101. Davis M, Mellman M, Friedman S et al. Recovery of epinephrine response but not hypoglycemic symptom threshold after intensive therapy in type 1 diabetes. Am J Med 1994; 97(6):535-542.
102. Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counter regulation, in IDDM. Diabetes 1994; 43(12):1426-1434.
103. Lingenfelser T, Buettner UW, Uhl H 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.
104. Cranston I, Lomas J, Maran A et al. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. Lancet 1994; 344(8918):283-287.
105. Fanelli C, Pampanelli S, Epifano L et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. Diabetologia 1994; 37(12):1265-1276.
106. Buse JB, Bigger JT, Byington RP et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007; 99:21i-33i.
107. Gerstein HC, Miller ME, Byington RP et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358(24):2545-2559.
108. Duckworth W, Abraira C, Moritz T et al. Intensive glucose control and complications in American veterans with type 2 diabetes. N Engl J Med 2009; 360:129-139.
109. Abraira C, Duckworth WC, Moritz T. VADT Group. Glycaemic separation and risk factor control in the Veterans Affairs Diabetes Trial: an interim report. Diabetes Obes Metab 2009; 11:150-156.