Practical tips in diagnosis and treatment of autonomic neuropathies in diabetes

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28 Sep 2017
Conflict of interest disclosure

None

Committee of Scientific Affairs
1 DAN

Diabetic Autonomic Neuropathy
Diabetic Autonomic Neuropathy
Prevalence of Diabetic autonomic neuropathy (DAN)

- In community based study\(^1\)
  as defined by one or more abnormal HRV test results
  - 16.7%

- At least 3 of 6 autonomic function test\(^2\)
  - 16.8% for T1DM
  - 22.1% for T2DM
**Sx & Sn of DAN**

<table>
<thead>
<tr>
<th>CAN</th>
<th>Gastrointestinal</th>
<th>Urogenital</th>
</tr>
</thead>
</table>
| Resting tachycardia | **Gastroparesis**  
• Nausea  
• Bloating  
• Loss of appetite  
• Early satiety  
• Postprandial vomiting  
• Brittle diabetes | **Bladder dysfunction**  
• Frequency  
• Urgency  
• Nocturia  
• Hesitancy  
• Weak stream  
• Dribbling  
• Urinary incontinence  
• Urinary retention |

| Abnormal blood pressure regulation  
• Non-dipping  
• Reverse dipping | **Esophageal dysfunction**  
• Heartburn  
• Dysphagia for solids | **Male sexual dysfunction**  
• Erectile dysfunction  
• Decreased libido  
• Abnormal ejaculation |

| Orthostatic hypotension/tachycardia/bradycardia  
• Lightheadedness  
• Weakness  
• Faintness  
• Dizziness  
• Visual impairment  
• Syncope | **Diabetic diarrhea**  
• Profuse and watery diarrhea  
• Fecal incontinence  
• Alternates with constipation | **Female sexual dysfunction**  
• Decreased sexual desire  
• Increased pain during intercourse  
• Decreased sexual arousal  
• Inadequate lubrication |

(All with standing)  
**Constipation**

2

CAN

Cardiac Autonomic Neuropathy
## Prevalence of CAN

<table>
<thead>
<tr>
<th>Author</th>
<th>Date of publication</th>
<th>Diabetes type</th>
<th>Subjects (n)</th>
<th>Test(§) used</th>
<th>% Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharpey-Schafer and Taylor (26)</td>
<td>1960</td>
<td>Mixed with autonomic symptoms</td>
<td>337</td>
<td>Valsalva maneuver</td>
<td>21</td>
</tr>
<tr>
<td>Ewing et al. (27)</td>
<td>1974</td>
<td>Mixed with autonomic symptoms</td>
<td>124</td>
<td>Handgrip test</td>
<td>18</td>
</tr>
<tr>
<td>Morley et al. (28)</td>
<td>1977</td>
<td>Adult diabetic patients</td>
<td>70</td>
<td>Heart rate variation</td>
<td>24</td>
</tr>
<tr>
<td>Hilsted and Jensen (29)</td>
<td>1979</td>
<td>Insulin-treated</td>
<td>126</td>
<td>Heart rate variation</td>
<td>40</td>
</tr>
<tr>
<td>Mackay et al. (30)</td>
<td>1980</td>
<td>Mixed with autonomic symptoms</td>
<td>287</td>
<td>Heart rate variation</td>
<td>30</td>
</tr>
<tr>
<td>Ewing et al. (31)</td>
<td>1980</td>
<td>Mixed with autonomic symptoms</td>
<td>73</td>
<td>Valsalva maneuver</td>
<td>47</td>
</tr>
<tr>
<td>Ewing et al. (32)</td>
<td>1980</td>
<td>Mixed with autonomic symptoms</td>
<td>61</td>
<td>Handgrip</td>
<td>35</td>
</tr>
<tr>
<td>Hulper and Wills (33)</td>
<td>1980</td>
<td>Insulin-dependent</td>
<td>92</td>
<td>Handgrip</td>
<td>17</td>
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<tr>
<td>Dyrberg et al. (34)</td>
<td>1981</td>
<td>Insulin-dependent</td>
<td>75</td>
<td>Heart rate variation</td>
<td>27</td>
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<tr>
<td>Xuani et al. (35)</td>
<td>1981</td>
<td>Newly diagnosed non-insulin-dependent</td>
<td>506</td>
<td>Valsalva maneuver</td>
<td>17</td>
</tr>
<tr>
<td>O'Brien et al. (36)</td>
<td>1991</td>
<td>Insulin-dependent</td>
<td>506</td>
<td>At least two of the following: heart rate variation in response to 1) rest 2) single deep breath 3) Valsalva maneuver or 4) standing</td>
<td>17</td>
</tr>
<tr>
<td>Ziegler et al. (24)</td>
<td>1992</td>
<td>Newly diagnosed insulin-dependent</td>
<td>130</td>
<td>At least three of the following: CV of heart rate variation, low-and mid-frequency bands of spectral analysis, MCR, Valsalva maneuver, or lying-to-standing</td>
<td>7.7</td>
</tr>
<tr>
<td>Ziegler et al. (24)</td>
<td>1992</td>
<td>Insulin-dependent</td>
<td>647</td>
<td>Greater than two of the following: coefficient of variation of heart rate variation, low- and mid-frequency bands of spectral analysis, MCR, Valsalva maneuver, or lying-to-standing</td>
<td>25.3</td>
</tr>
<tr>
<td>Kennedy et al. (25)</td>
<td>1995</td>
<td>Insulin-dependent</td>
<td>290</td>
<td>Heart rate variation</td>
<td>90</td>
</tr>
<tr>
<td>DCCT Research Group (37)</td>
<td>1998</td>
<td>Insulin-dependent, primary cohort 1–3 years’ duration; secondary cohort 1–15 years’ duration</td>
<td>1,441</td>
<td>Heart rate variation</td>
<td>2.6–2.3</td>
</tr>
</tbody>
</table>

BP, blood pressure; MCR, mean circular resultant.
# Mortality of CAN

## A meta-analysis of 9 studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Follow-up (years)</th>
<th>Mortality CAN+ n (%)</th>
<th>Mortality CAN- n (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewing, 1980</td>
<td>5</td>
<td>21/40 (53)</td>
<td>5/33 (15)</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Hasslacher and Bassler, 1983</td>
<td>5</td>
<td>3/16 (19)</td>
<td>3/42 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Navarro, 1990$^{28}$</td>
<td>3.3</td>
<td>41/175 (23)</td>
<td>2/57 (4)</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Sampson, 1990</td>
<td>10</td>
<td>18/49 (37)</td>
<td>4/38 (11)</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>O’Bien, 1991$^{29}$</td>
<td>5</td>
<td>23/84 (27)</td>
<td>21/422 (5)</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Ewing, 1991</td>
<td>3</td>
<td>10/32 (31)</td>
<td>3/39 (8)</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Jermendy, 1991</td>
<td>5</td>
<td>12/30 (40)</td>
<td>1/23 (4)</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Rathmann, 1993$^{27}$</td>
<td>8</td>
<td>8/35 (23)</td>
<td>1/35 (3)</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Luft, 1993</td>
<td>8</td>
<td>7/34 (21)</td>
<td>1/19 (5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5.8</strong></td>
<td><strong>143/495 (29)</strong></td>
<td><strong>41/708 (6)</strong></td>
<td></td>
</tr>
</tbody>
</table>
Natural progression of CAN

Subclinical CAN
- Impaired R-R variability
- Abnormal LV torsion decreased

Early stages of clinical CAN
- Resting tachycardia
- Reduced exercise tolerance

Advanced or severe CAN
- Orthostatic hypotension
- Sympathetic denervation observed at the base of the heart
Abnormalities in LV systolic, diastolic Fx

Echocardiographic studies

Em, Early diastolic relaxation velocity
LVDD, left ventricular diastolic dysfunction

Diabet Med 2011;28:311-8
• **Resting Tachycardia**
  - late findings with vagal impairment
  - Resting HR of 90-100 bpm
  - Occasional increments up to 130 bpm
  - fixed HR unresponsive to moderate exercise, stress, sleep
    : almost complete cardiac denervation

• **Exercise Intolerance**
  - Patients who are likely to have CANa
    : should be tested for cardiac stress test before exercise program

• **Intraoperative Cardiovascular Liability**
  - Two- to threefold increase of perioperative CV morbidity and mortality

• **Orthostatic Hypotension**
  - a fall in BP (>20 mmHg for systolic or >10 mmHg for diastolic) in response to
    postural change, from supine to standing
  - due to damage to the efferent sympathetic vasomotor fibers, particularly in the
    splanchnic vasculature.
  - Diminished cardiac acceleration and cardiac output

• **Silent MI/Cardiac Denervation Syndrome**
  - Features of MI in patients with CAN
    : silence, cough, nausea and vomiting, dyspnea, tiredness and ECG changes
Significance of CAN
Screening for CAN in the patients with DM should be considered good clinical practice, due to the following:

(1) It enables the accurate and clinical relevant diagnosis of various CAN forms
(2) It assists in the appropriate detection and subsequently the tailored treatment of CAN multiple clinical manifestations
(3) It provides a clinical tool for the risk stratification for diabetic complications as well as the cardiovascular morbidity and mortality
(4) It can be used for the modulation of targets of diabetes treatment
Assessment of Autonomic Neuropathy
# Differential Diagnosis of DAN

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Cardiovascular disorders</td>
</tr>
<tr>
<td>Resting tachycardia, exercise intolerance</td>
<td>Idiopathic orthostatic hypotension, multiple system atrophy with Parkinsonism, orthostatic tachycardia, hyperadrenergic hypotension</td>
</tr>
<tr>
<td>Orthostatic tachycardia and bradycardia syndromes</td>
<td>Syh-Drager syndrome</td>
</tr>
<tr>
<td>Cardiac denervation, painless myocardial infarction</td>
<td>Panhypopituitarism</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Intraoperative and perioperative cardiovascular instability</td>
<td>Hypovolemia</td>
</tr>
<tr>
<td></td>
<td>Congestive heart disease</td>
</tr>
<tr>
<td></td>
<td>Carcinoid syndrome</td>
</tr>
</tbody>
</table>
## Tests of ANS function

<table>
<thead>
<tr>
<th>Parasympathetic</th>
<th>Sympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Beat to beat variation with deep breathing (E/I ratio)</td>
<td>• Resting heart rate</td>
</tr>
<tr>
<td>• Resting heart rate</td>
<td>• Orthostatic BP</td>
</tr>
<tr>
<td>• 30:15 heart rate ratio with standing</td>
<td>• Hand grip BP</td>
</tr>
<tr>
<td>• Valsalva ratio</td>
<td>• HRV; low frequency power</td>
</tr>
<tr>
<td>• HRV; high frequency power (HFP: 0.15-0.40 Hz)</td>
<td>(LFP: &lt;0.14 Hz)</td>
</tr>
</tbody>
</table>
## ANS Function 5 test

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>Normal</th>
<th>Borderline</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep breathing</td>
<td>Difference in HR (bpm)</td>
<td>≥15</td>
<td>11-14</td>
<td>≤10</td>
</tr>
<tr>
<td>Valsalva manoevr</td>
<td>R-R length ratio</td>
<td>≥1.21</td>
<td></td>
<td>≤1.20</td>
</tr>
<tr>
<td>Heart rate response on standing</td>
<td>R-R ratio 30 to 15 beat</td>
<td>≥1.04</td>
<td>1.01-1.03</td>
<td>≤1.00</td>
</tr>
<tr>
<td>Blood pressure response on standing</td>
<td>Systolic BP drop (mmHg)</td>
<td>≤10</td>
<td>11-29</td>
<td>≥30</td>
</tr>
<tr>
<td>Hand grip (dynamometer)</td>
<td>Diastolic BP rise (mmHg)</td>
<td>≥16</td>
<td>11-15</td>
<td>≤10</td>
</tr>
</tbody>
</table>
HRV PSD (Power Spectral Density)

**Time Domain**

HR, SDNN (Standard Deviation Normal to Normal), RMSSD

**Frequency Domain**

Low frequency wave, High frequency wave
HRV Tachogram

SDNN (Standard Deviation Normal to Normal),
RMS-SD (the square root of the mean squared differences of successive NN intervals)
**Frequency Domain Analysis**

**Very low-frequency (VLF) band (0.003-0.04 Hz)**
Thermoregulatory activity: sympathetic

**Low-frequency (LF) band (0.04-0.15 Hz)**
Baroreceptor activity: parasympathetic & sympathetic

**High-frequency (HF) band (0.15-0.4 Hz)**
Respiratory activity: parasympathetic

**LF norm = LF/LF + HF** → Sympathetic
**HF norm = HF/Lf + HF** → Parasympathetic
**LF/HF ratio → balance between Sym. & Parasymp.**
**HRV Orthostatic Test**

**Normal response**

- LF/HF ratio, normalized LF (Sympathetic) \(\rightarrow\) increase
- HF, normalized HF (Parasympathetic) \(\rightarrow\) decrease
DICAN

Autonomic Function 5 Test

HSV Orthostatic Test

**CAN risk index** = HR + SDNN + RMSSD + LF/HF ratio + TP
Assessment of DAN

Measures of autonomic nervous system in diabetes

SDNN SDANN pNN50 triangular index RMSSD

Time domain analysis

Power spectral analysis

LF
HF
LF:HF ratio

Thermoregulatory sweat testing
Quantitative sudomotor axon reflex test

Sudomotor function

Beat to beat measures

CVT CSB

World J Diabetes 2016;7:321-332
Sudorimetry
The Sudomotor Axon Reflex

[Diagram showing the sudomotor axon reflex with labels for epidermis, dermis, eccrine sweat glands, postganglionic sympathetic sudomotor neuron, and acetylcholine.]
Neuropad

![Image of Neuropad application on feet with a bar graph showing time until complete colour change for healthy volunteers, patients without peripheral neuropathy, and patients with peripheral neuropathy.]

- Healthy volunteers (n=20) *: 4.6 minutes
- Patients without peripheral neuropathy (n=33) **: 7.7 minutes
- Patients with peripheral neuropathy (n=71) ***: 23.8 minutes

**p = 0.0002**
# Newer sudomotor function technology

## Thermoregulatory sweat testing

- Camera
- Infrared heaters
- Thermometer
- Temperature probes

## Quantitative sudomotor axon reflex test

- Flow meter
- Data acquisition
- Hygrometer
- Heat exchanger
- QSART capsule
- Iontophoresis box

## Silicon Impressions

- **A**
  - ![Silicon Impression A](image)
- **B**
  - ![Silicon Impression B](image)
- **C**
  - ![Silicon Impression C](image)

## Quantitative direct and indirect axon reflex testing (QDIRT)

- **A**
  - ![QDIRT A](image)
- **B**
  - ![QDIRT B](image)
- **C**
  - ![QDIRT C](image)
FIG. 1. Feet and hands electrochemical skin conductance (ESC) in healthy control (HC) subjects and diabetes mellitus (DM) patients with and without diabetic neuropathy. Data are mean±SEM values. *P<0.0001 versus HC and DM without neuropathy (by analysis of variance with post hoc analysis).

Traditional tests for DN | Mean ESC | Spearman’s rho | P value
--- | --- | --- | ---
Clinical neuropathy scores | | | |
NIS-LL motor score | Feet | −0.4773 | <0.0001 |
| Hands | −0.3144 | 0.0064 |
NIS-LL sensory score | Feet | −0.2951 | 0.0107 |
| Hands | −0.2612 | 0.0246 |
NIS-LL total score | Feet | −0.3969 | 0.0005 |
| Hands | −0.3256 | 0.0046 |
QST (big toe) | | | |
Pressure | Feet | −0.4048 | 0.0064 |
CS threshold | Feet | −0.3041 | 0.0336 |
WS threshold | Feet | −0.2841 | 0.0500 |
CP threshold | Feet | −0.3028 | 0.0345 |
Autonomic function measures | | | |
E/I ratio | Feet | 0.2744 | 0.0175 |
| Hands | 0.3708 | 0.0012 |
DB LFA | Feet | 0.2635 | 0.0299 |
| Hands | 0.3921 | 0.0009 |
DB RFA | Feet | 0.3620 | 0.0018 |
| Hands | 0.4726 | <0.0001 |
DB TSP | Feet | 0.2859 | 0.0149 |
| Hands | 0.3694 | 0.0014 |
DB sdNN | Feet | 0.2424 | 0.0402 |
| Hands | 0.3374 | 0.0038 |
Val LFA | Hands | 0.2778 | 0.0181 |
Val RFA | Feets | 0.2480 | 0.0357 |
| Hands | 0.2985 | 0.0109 |
Pain scores | | | |
Average pain score | Feet | −0.3663 | 0.0170 |
# Feet ESC Diagnostic Accuracy vs Established Clinical Tools

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic Variable</th>
<th>Comparison</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casellini et al. (2013)</td>
<td>DPN</td>
<td>NIS-LL</td>
<td>78.34</td>
<td>92.38</td>
<td>74.6</td>
<td>93.72</td>
</tr>
<tr>
<td>Selvarajah et al. (2015)</td>
<td>DPN</td>
<td>AAN guidelines for DPN</td>
<td>87.5</td>
<td>76.2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Selvarajah et al. (2015)</td>
<td>CAN—diabetes</td>
<td>5 Cardiac autonomic reflex tests</td>
<td>65</td>
<td>85</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Smith et al. (2014)</td>
<td>Distal symmetric polyneuropathy</td>
<td>UENS</td>
<td>77</td>
<td>67</td>
<td>59</td>
<td>83</td>
</tr>
<tr>
<td>Yajnik et al. (2012)</td>
<td>DPN</td>
<td>VPT</td>
<td>73</td>
<td>62</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Eranki et al. (2013)</td>
<td>DPN</td>
<td>VPT ≥ 15 V</td>
<td>82</td>
<td>55</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Yajnik et al. (2013)</td>
<td>CAN—diabetes</td>
<td>3 Cardiac autonomic reflex tests</td>
<td>92</td>
<td>49</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ozaki et al. (2011)</td>
<td>Diabetic kidney disease</td>
<td>eGFR, ACR</td>
<td>94</td>
<td>78</td>
<td>81</td>
<td>93</td>
</tr>
</tbody>
</table>

*ACR, albumin creatinine ratio; CAN, cardiac autonomic neuropathy; CARTs, cardiac autonomic reflex tests; DPN, diabetic peripheral neuropathy; eGFR, estimated glomerular filtration rate; NIS-LL, neuropathy impairment score—lower limbs; PPV, positive predictive value; NPV, negative predictive value; UENS, Utah Early Neuropathy Score; VPT, vibration perception threshold.*
Sudomotor function as a tool to measure progression and regression of disease

<table>
<thead>
<tr>
<th></th>
<th>Without Follow-Up of Training Level (n = 72)</th>
<th>Low Weekly Activity (n = 62)</th>
<th>High Weekly Activity (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Change in weight (kg)</td>
<td>-0.9</td>
<td>3.4</td>
<td>-1.6</td>
</tr>
<tr>
<td>Change in waist (cm)</td>
<td>-2.1</td>
<td>4.7</td>
<td>-2.4</td>
</tr>
<tr>
<td>Change in estimated VO₂max (METs)</td>
<td>+0.5</td>
<td>0.9</td>
<td>+0.8</td>
</tr>
<tr>
<td>Change in hand ESC (µS)</td>
<td>+5.0</td>
<td>8.4</td>
<td>+3.0</td>
</tr>
<tr>
<td>Change in foot ESC (µS)</td>
<td>+5.6</td>
<td>8.9</td>
<td>+4.9</td>
</tr>
<tr>
<td>Change in ESC risk score (%)</td>
<td>-5.1</td>
<td>5.3</td>
<td>-4.7</td>
</tr>
</tbody>
</table>

*a*Less than 150 min of moderate activity and 75 min of high activity.

*b*More than 150 min of moderate activity or 75 min of high activity; moderate activity 3–7 METs, high activity > 7 METs.
Restoration of Autonomic Balance
Lifestyle changes to restore balance

• Therapeutic lifestyle changes in DPP study
  - 25% reduction in risk autonomic dysfunction

• Endurance training
  - improves HRV in patients with minimal abnormalities.
  - improved vagal activity and exercise capacity in early CAN, but not severe CAN

• Chronic exercise
  - enhanced cutaneous blood flow
  - restoration of baroreceptor sensitivity

• To prescribe exercise intensity
  : use perceived exertion not heart rate of 220 minus age

→ The need of early aggressive intervention at the stage of physiological deficits in nerve function
Medications to restore sympathovagal balance

SE, β-blocker

n = 57

SW, vasopressor

n = 185

PE, anti-cholinergic

n = 50

Medications to restore sympathovagal balance

- Multiple risk factor reduction in Steno 2 study\(^1\)  
  - lower the HR for autonomic neuropathy by 63%.
- α-lipoic acid\(^2\)  
  - improve heart rate variability
- Aldose reductase inhibitors, C-peptide, RAS inhibitors, cardioselective – blocker without intrinsic sympathoimmetic activity (e.g. metoprolol), digoxin and verapamil\(^3\)  
  - increase in HRV
- Advanced glycation end product inhibitors (AGEIs), statins, carnitine, peroxisome proliferator activated receptors (PPARs), protein kinase C-β inhibitors and anti-inflammatory agents  
  - no results
- Pharmacological tools targeting peroxynitrite formation or promoting its decomposition  

1. Diabetologia 1998;41:443-451  
2. Diabetes Care 1997;20:369-373  
Pharmaceutical approaches to the treatment or prevention of DAN

Adipose tissue

IL-6, leptin, TNF-α
Angiotensinogen

Superoxide

SOD
Lipoic acid
carnitine

PPARs

Polyols
AGEs
Hexosamine flux
ACEs
Angiotensinogen

Angiotensin I
Angiotensin II

PKC
NFκB

iNOS
eNOS

Nitric oxide

Decomposition catalysts

C peptide

ARIs
AGE breakers

Statins
fibrates
ACEs
ARBs

Peroxynitrite

Adhesion molecules
Cytokines

DNA damage

NAD⁺
GADPH

PARP

PJ 34

Nitrotyrosine

Autonomic dysfunction

Diabet Med 2011;28:643–651
GIAN

GastroIntestinal Autonomic Neuropathy
Potential mechanisms involving the ENS in impaired gastrointestinal motility in DM

- Autonomic neuropathy
- Enteric neurons:
  - Reduced number
  - Increased apoptosis
  - Oxidative stress
- Impaired neurotransmission
- Imbalance between stimulations and inhibition
- Decreased growth factors
- ICC:
  - Reduced number
  - Reduced SCF
  - Reduced growth factor
- Enteric microbiota:
  - Change due to DM
  - Change in motility, secretion, permeability
- Smooth muscle:
  - Decreased contractility
  - Impaired intracellular signaling
  - Impaired phosphorylation of MLC

Neurogastroenterol Motil 2014;26:611–624
Effects of diabetes on motility in various parts of gastrointestinal tract

- Reduced Esophageal Motility
- Reduced LES Tone: GERD
- Reduced Fundal Relaxation: Early Satiety, Dyspnea
- Delayed Gastric Emptying: Gastroparesis, Nausea, Vomiting
- Increased Colonic Transit Time: Constipation
- Decreased or Increased Intestinal Transit Time: Diarrhea
- Change In Microbiota: Diarrhea

Neurogastroenterol Motil 2014;26:611–624
Investigations in patients with GI AN

### Evaluation of Upper Gut Symptoms

**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)
Evaluation of Chronic Diarrhea

- 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 I in stools, other)
- Therapeutic trials with antibiotics, gluten-free diet, pancreatic enzyme supplements
## Investigations in patients with GI AN

### Evaluation of Chronic and Anorectal Dysfunction

<table>
<thead>
<tr>
<th>Constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Digital examination</td>
</tr>
<tr>
<td>• Stools: occult blood</td>
</tr>
<tr>
<td>• Barium enema</td>
</tr>
<tr>
<td>• Colonoscopy (biopsy)</td>
</tr>
<tr>
<td>• Colonic segmental transit time</td>
</tr>
<tr>
<td>• Anorectal manometry</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fecal incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 24-hour stool weight</td>
</tr>
<tr>
<td>• Anorectal manometry</td>
</tr>
<tr>
<td>- Maximum basal sphincter pressure</td>
</tr>
<tr>
<td>- Maximum “squeeze’ sphincter pressure</td>
</tr>
<tr>
<td>- Rectoanal inhibitory reflex</td>
</tr>
<tr>
<td>• Test of continence</td>
</tr>
<tr>
<td>- Solids: solid sphere</td>
</tr>
<tr>
<td>- Liquids: rectally infused saline</td>
</tr>
</tbody>
</table>
• Dietary measures
• Frequent meals, but small amounts with fluid consistence, without much fat and poorly digestible fibers
• The standard approaches to pharmacotherapy - the prokinetics (metoclopramide, domperidone, cisapride, cinitrapride, and others).
• Erythromycin, a motilin receptor agonist, is a highly effective prokinetic agent, particularly when administered as IV boluses in acute flare-ups of gastroparesis. Unfortunately, its mid- and long-term efficacy when given orally casts doubt.
• Other therapeutic options - clonidine, sildenafil and endoscopic injections of botulinum toxin into pyloric muscle.
• Gastric pacing
• Gastric stimulation devices
Treatment of Diabetic Diarrhea

- **Octreotide, somatostatin analogue**
  - inhibits peptide secretion including serotonin, gastrin, and motilin
  - directly suppresses GI motility
  - improves fluid and electrolyte absorption
  - The subcutaneous injections may be started at 50 mm cg BID and increased to 100 mg TID as needed

- **Other drugs like loperamide, codeine, clonidine**
  - may be also useful.

- **Antibiotics** may be necessary for long time to prevent or control the bacterial overgrowth.
GenitoUrinary Autonomic Neuropathy
Diabetic erectile dysfunction

Erectile dysfunction

AMI

TIA

Peripheral arteriopathy

Penile artery 1-2 mm

Coronary artery 3-4 mm

Internal carotid artery 5-7 mm

Femoral artery 6-8 mm

Lumen obstruction%

50% obstruction: Threshold for the onset of symptoms

Eur Urol 2003;44:352-4
Pathogenesis of DED
The International Index of Erectile Function

<table>
<thead>
<tr>
<th>Erectile Function Domain</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often were you able to get an erection during sexual activity?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When you had erections after stimulation, how often were your erections hard enough</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When you attempted sexual intercourse, how often were you able to penetrate (enter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>During sexual intercourse, how often were you able to maintain erection after you</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During sexual intercourse, how difficult is it to maintain your erection to completion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>How do you rate your confidence that you could get and keep an erection?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Total score</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 = No sexual activity
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

11 = moderate EF score
Currently available PDE-5 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil</td>
<td>25, 50 *, 100</td>
<td>4.6</td>
</tr>
<tr>
<td>tadalafil</td>
<td>2.5, 5, 10, 20</td>
<td>17–21</td>
</tr>
<tr>
<td>vardenafil</td>
<td>2.5, 5, 10 *, 20</td>
<td>4–5</td>
</tr>
<tr>
<td>avanafil</td>
<td>50, 100, 200</td>
<td>5–10</td>
</tr>
<tr>
<td>udenafil #</td>
<td>100, 200</td>
<td>11–13</td>
</tr>
<tr>
<td>mirodenafil #</td>
<td>50, 100</td>
<td>2.5</td>
</tr>
</tbody>
</table>
Female Sexual Dysfunction (FSD)

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.

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.
Diabetic bladder dysfunction

- Characterized by
  - decreased bladder sensation
  - increased bladder capacity
  - impaired detrusor contractility
- An alteration of the detrusor smooth muscle, neuronal dysfunction and urothelial dysfunction
- Estimate prevalence; 43 to 87% in T1DM, 25% in T2DM
- The correlation between diabetic cystopathy and peripheral neuropathy ranges from 75 to 100%.
- Dysuria, frequency, urgency, nocturia and incomplete bladder emptying, infrequent voiding, poor stream, hesitancy in initiating micturition, recurrent cystitis and stress and urgency urinary incontinence
Diabetic bladder dysfunction

- Urological conditions such as benign prostatic hypertrophy in men or gynecological disorders in women
  - may share the same symptoms
  - be excluded by appropriate testing

- Validated questionnaire for lower urinary tract symptoms

- The type of bladder dysfunction
  - is most readily characterized with complete urodynamic testing.

- Treatment includes
  - behavioral maneuvers
  - medication according to the leading symptoms and detected by urological investigations disturbances.
Treatment of Diabetic bladder

- Diabetic bladder
  - Overactive bladder
    - Weight reduction
    - Diet change
    - Pelvic muscle exercise
    - Anticholinergic drugs
  - Hypotonic bladder
    - Crede's and Valsalva's maneuvers
    - Timing and double voiding
    - Interimtent catheterization
    - Cholinomimetic drugs
    - Alpha-methyl dopa, phenoxybenzamine
    - Surgical intervention
Autonomic imbalance in diabetes: prophet of doom or scope for hope?¹

- Diabetes can cause dysfunction of any or every part of ANS, leading to a wide range disorders

- DAN is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and QOL in people with diabetes.

- The best-studied diagnostic methods are related to the evaluation of cardiovascular reflexes.

- The combination of cardiovascular autonomic tests with sudomotor function tests may allow a more accurate diagnosis of DAN

- Restoration of autonomic balance is possible and has been shown with therapeutic lifestyle changes, increased physical activity and several potential medications.

1. By A.I Vinik