Diabetic Neuropathy and Erectile Dysfunction

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Diabetic Peripheral Neuropathy

Definition:

‘The presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes: the diagnosis cannot be made without a clinical examination’

DIABETIC NEUROPATHIES - CLINICAL CLASSIFICATION

POLYNEUROPATHIES
* Sensory - Chronic sensorimotor
  - Acute sensory
* Autonomic
* Proximal motor
* Truncal

MONONEUROPATHIES
* isolated peripheral
* Cranial
* Mononeuritis multiplex
* Truncal

Boulton and Ward, 1986
CHRONIC SENSORIMOTOR NEUROPATHY

The commonest form

* Of insidious onset
* Positive symptoms – burning pain, stabbing shooting pain, hyperaesthesiae, paraesthesiae
* Negative symptoms – numbness
* Nocturnal exacerbation
CHRONIC SENSORIMOTOR NEUROPATHY

SYMPTOMS - SENSORY

SIGNS - SENSORY AND MOTOR
Human Diabetic Neuropathy
Clinical Consequences of Diabetic Peripheral Neuropathy

NEUROPATHY

PAIN
- Burning
- Paraesthesia
- Hyperaesthesia
- Allodynia
- Nocturnal-exacerbation

INSENSITIVITY
- Foot ulceration; at least 50% preventable

Diabetic Neuropathy: “The Forgotten Complication”

Results of the 2005 ADA National Survey*

- Only one in four survey respondents who experience symptoms of diabetic neuropathy have been diagnosed with the condition.
- The majority of respondents who experience symptoms (56%) remain unaware of the term diabetic neuropathy.
- 62% believe that their symptoms are associated with their diabetes, but only 42% have been told by their physician that diabetes is the cause.
- Approximately one in seven people who said they talked to their doctor about their symptoms and pain reported that no cause was mentioned.

*May 10, 2005 /PR Newswire via COMTEX
Chronic painful diabetic neuropathy

Prevalence: 16%

12.5% had never reported their symptoms to their physician

39.3% had never received any treatment for their pain

Daousi et al., Diabetic Med 2004; 21: 976-982
Prevalence of Distal Symmetric Polyneuropathy (DSP)
The MONICA/KORA Augsburg Surveys

Michigan Neuropathy Screening Instrument (MNSI) >2

- Control: 8.9%
- IGT: 13.0%
- Diabetes: 27.6%
Do not walk barefoot

- Burn to sole of foot
- Need footwear for protection
Positive and negative symptoms have a negative impact on functioning and QoL. QoL is a uniquely individual experience – how persons perceive and react to their health status.

Painful symptoms also generate anxiety. Negative symptoms (e.g. unsteadiness) associated with depression.

Pain-related sleep disturbance has a negative impact on QoL.

ASSESSMENT OF DIABETIC NEUROPATHY

- Symptoms
- Signs
- Quantitative sensory testing
  - vibration
  - temperature
- Electrophysiology
- Morphometry - from biopsy (sural nerve or skin)
- Corneal Confocal Microscopy
Neuropathic Pain

Definition:

‘Pain arising as a direct consequence of a lesion or a disease affecting the somatosensory system’

Treede RD et al. Neurology 2008; 70: 1630
Pain In DPN

“I experience sharp electric shocks that shoot up my legs.”

“When I walk it feels as if I am stepping on broken glass.”
Management of Diabetic Neuropathy

Symptomatic relief

- Medical
  - Stable near-normoglycaemia
  - Alpha-lipoic acid
  - Tricyclics
  - Anti-epileptic drugs
  - Opioids
- Physical
  - Capsaicin
  - Clonidine
  - Acupuncture
  - Electrical
  - Surgical

Influence natural history

- Stable near-normoglycaemia
- Alpha-lipoic acid
- Gamma-linolenic acid
- Aldose reductose inhibitors
- ACE inhibitors
- Protein kinase C inhibitors
- (Neurotrophic agents)

Boulton AJM et al. Diabetes Care 2004;27:1458-86
Management of Neuropathic Pain Associated With DPN and PHN

- Pharmacotherapy
- Neurostimulatory Treatment Approaches
- Interventional Regional Anesthesia
- Physical Rehabilitation
- Psychological
- Lifestyle

Management of Diabetic Neuropathy

Symptomatic relief

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Blood Glucose Flux and Neuropathic Pain

- Acute painful neuropathy often follows periods of metabolic instability
- Painful symptoms improve with stable near-normoglycaemia
- Hyperglycaemia reduces pain thresholds
- Sudden improvement in bg control may precipitate neuropathic pain
- Acute worsening of painful symptoms post pancreas transplantation

Morley J et al. 1984
Tesfaye S. 1998
Boulton A. 1999, 2004
Ndip et al, 2009
Management of Symptomatic Diabetic Neuropathy

1. Exclude non-diabetic causes including:
   - Malignant  eg, bronchogenic carcinoma
   - Toxic  eg, alcohol
   - Iatrogenic  eg, isoniazid

2. Assess level and stability of glycaemic control

3. Explanation and support
Management of Symptomatic Diabetic Neuropathy (cont’d)

4. Aim for stable, optimal glycaemic control
   - Avoid swings of glycaemia
   - Aim for near-normoglycaemia
   - Insulin not always needed in type 2 DM
   - Symptomatic improvement may be delayed
Management of Symptomatic Diabetic Neuropathy

Other Pharmacological treatment

- Non-steroidal drugs occasionally help, eg, Sulindac
- Tricyclic drugs until recently first-line agents in many countries eg, Imipramine 25–150mg nocte
  Amitriptyline 25–150mg nocte
- Proven efficacy in controlled studies
- Early symptomatic relief usual (days)

Sindrup S. 1996
McQuay H et al. 1996
Tricyclic Drugs

- Pain relief independent of mood changes
  - **BUT**
- Frequent adverse events
  - Drowsiness
  - Anticholinergic – especially dry mouth
  - These have resulted by their replacement by other agents as first line drugs in many countries
Management of Symptomatic Diabetic Neuropathy

Newer agents with proven efficacy

- Gabapentin
- Pregabalin
- Sodium Valproate
- Tramadol
- Lamotrigine
- Topiramate
- Oxycodone
- Duloxetine
Gabapentin

- Anti-epileptic for complex-partial seizures
- Efficacy in diabetic neuropathy proven in randomised double-blind trial in 165 patients
- Gabapentin dose 300-3600mg/day
- Daily pain scores and sleep disturbance less on Gabapentin
- Efficacy equivalent to amitriptyline

Backonja M et al. 1998
Morello J et al. 1999
Pregabalin

- Analog of GABA: anti-epileptic for complex-partial seizures and analgesic
- Efficacy in diabetic neuropathy proven in randomised double-blind trial in 146 patients
- Pregabalin dose 150-600mg/day
- Daily pain scores and sleep disturbance less on Pregabalin
- Convenient bid dosage, 150 or 300 mg bd

Rosenstock et al, PAIN 2004;110:628
Mechanism of Action of Pregabalin

Hyperexcited Neuron

- Presynaptic
- α2-δ Subunit
- Ca2+ Channel
- Neurotransmitters: Glutamate, Norepinephrine, Substance P
- Postsynaptic

Modulation of Hyperexcited Neuron With Pregabalin

- Presynaptic
- Pregabalin
- α2-δ Subunit
- Ca2+ Channel
- Neurotransmitters
- Postsynaptic
Pregabalin: Manchester experience

- Used regularly since mid-2005
- Start at low dose – especially in older patients, i.e., 75 mg nocte increasing slowly as needed
- Usual dose requirement: 150 or 300mg bd.
- Side effects appear less than other agents including tricyclics and Gabapentin
- Efficacy appears to be amongst the best of all agents for neuropathic pain
- ? More useful in those with anxiety
Pregabalin

- Pooled data analysis across 7 randomized trials
- Efficacy for neuropathic pain relief confirmed for 150, 300 and 600 mg daily in divided doses
- Pain and sleep interference reductions positively correlated with doses: greatest effect with 600mg/day
- Dizziness, somnolence and peripheral oedema commonest side effects
- Pregabalin treatment across dosing range associated with significant dose-related improvement in neuropathic pain

Freeman et al, Diabetes Care 2008;31:1448
Duloxetine

- 5-HT and norepinephrine reuptake inhibitor
- Efficacy in diabetic neuropathy proven in two randomised double-blind trials
- Licensed by the EMEA and FDA for DPN
- Also anti-depressant effect
- Available in the USA and most European countries

Goldstein et al, Pain 2005;116:109
Descending serotoninergic and noradrenergic inhibitory pain pathways

Increase in Serotonin and NE Concentration by Dual Blockade of Reuptake Transporters

Duloxetine “Fits” Into Computer Models of Both Serotonin and NE Transporters

Transporter for 5-HT reuptake
(Blocked)

Transporter for NE reuptake
(Blocked)

SNRI (Duloxetine)

Serotonin Transporter

Norepinephrine Transporter
Duloxetine

- 5-HT and norepinephrine reuptake inhibitor
- RCT of Duloxetine 60 mg daily or bd vs Placebo
- Rapid onset of pain relief (<7 days) in both treatment groups
- No impact on glycaemic control
- Licensed in many countries
- Duloxetine 60 mg daily or bd efficacious in the management of diabetic neuropathic pain

Wernicke et al, Neurology 2006;24:1411
Tramadol

- Opioid-like drug, fewer opioid side effects
- Efficacy proven in randomised trial
- Predictable side effects – nausea, somnolence, constipation
- Prolonged pain relief in 6-month follow-up

Harati Y et al. 1998, 2000
Controlled-Release Oxycodone

- Limited data on opioids in diabetic neuropathy
- Two RCTs on Oxycodone CR in painful DN
- Multicenter study: 159 subjects, O-CR 10-60 mg/day vs placebo.
- Mean dose 37mg, side-effects in 96%: significant improvement in symptoms.
- Single-center study: 36 subjects: O-CR 10-80 mg/day vs active placebo (Benztropine).
- Mean dose 40mg, side-effects in >90%: significant improvement in symptoms and QoL
- CR-Oxycodone may be useful in resistant cases of painful DN

Gimbel et al, Neurology 2003;60:927
Watson et al, Pain 2003;105:71
Morphine and Gabapentin

- Effect of combining two agents assessed
- Randomized, active placebo crossover trial
- Pain relief on G/M combination superior to M or G alone: also lower doses of G and P in combination
- Predictable side effects – nausea, somnolence, constipation, dry mouth
- May be a useful combination for short-term use

Gilron I et al. NEJM 2005;352:1324
Management of Diabetic Neuropathy

**Symptomatic relief**

- Medical
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  - Tricyclics
  - Anti-epileptic drugs
  - Opioids
- Physical
  - Capsaicin
  - Clonidine
  - Acupuncture
  - Electrical
  - Surgical

**Influence natural history**

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Boulton AJM et al. *Diabetes Care* 2004;27:1458-86
ACUPUNCTURE

- Open label study of traditional acupuncture in 46 DPN patients
- 6 courses over a 12 week period
- Up to one year follow-up
- 77% showed improvement in primary or secondary symptoms
- Prolonged pain relief in majority
- Most able to reduce or stop other pain medications

Abuaisha et al DRCP 1998;39:115
Diabetic Neuropathies

A statement by the American Diabetes Association

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**ADA POSITION STATEMENT 2005**

- DPN: a diagnosis of exclusion of non-diabetic causes
- Tight glycemic control the only proven preventative treatment
- Type I DM: screen annually after 5 years of diabetes
- Type 2 DM: screen at diagnosis and annually thereafter
- Clinical history and examination both essential parts of annual screen
- QST and EP may be useful in a few cases
- A number of evidence-based therapies are available for symptomatic DPN

Boulton et al, Diabetes Care 2005;28:955-962
Treatment algorithm
for Painful distal symmetrical diabetic polyneuropathy after failure of simple analgesics

Painful DPN

Gabapentin/ Pregabalin

TCA/ Duloxitine

Evidence: Class I
Recommendation: A

Evidence: Class I
Recommendation: A

Evidence: Class I
Recommendation: C

TCA/ Duloxitine

Tramadol, opioids

Other treatment options:
Oxcabazepine, topiramate, lamotrigine
WHEN TO CONSIDER NEUROLOGY REFERRAL

- Asymmetrical signs
- Predominant motor signs
- Rapid progression of signs
- Back or neck pain
- Family history of neuropathy
- Any suggestion of CIDP

Erectile Dysfunction: Definitions

- The inability to obtain and/or maintain an erection satisfactory for sexual activity for a period of at least three months
- **MAY BE**
  - **Primary**: since the beginning of sexual life;
  - **Secondary**: after a period of normal sexual activity;
  - **Total**: complete lack of an erection;
  - **Situational**: specific, partner-related.
Factors Affecting Erectile Function/Dysfunction

Signals from brain induced by sexual stimulation
- Psychogenic ED
- Performance anxiety

Blood supply
- Atherosclerosis

NO from vascular endothelium
- Endothelial dysfunction

NO from NANC nerves
- Surgery
- Trauma
- Diabetes

NO from trabecular smooth muscle

Eardley I, Sethia K: Erectile Dysfunction, Current Investigation and Management
Possible Causes of Erectile Dysfunction (ED)

Organic
- Diabetes
- Vascular disease
- CHD
- Pelvic surgery
- Peyronie’s disease

Psychogenic
- Performance anxiety
- Relationships
- Depression
- Stress

Eardley I, Sethia K: Erectile Dysfunction, Current Investigation and Management
Figure 1

Major Causes of Erectile Dysfunction in the U.S.

- Vascular: 40%
- Diabetes Mellitus: 30%
- Impotence Following Radical Surgery: 13%
- Spinal Cord Injury and Other Traumas: 8%
- Other Endocrine Problems: 6%
- Multiple Sclerosis: 3%
Erectile Dysfunction in Type 1 DM: Update from DCCT and EDIC

- A longstanding study of ED, orgasmic dysfunction (OD) and decreased libido (DL) in DCCT and EDIC

- 713 type 1 males followed for 20 years

- IIEF completed at the end of EDIC

- ED in 34%, OD in 20% and DL in 55%; ED caused most distress.

- Most anxiety induced by failure to get an erection.

Erectile Dysfunction in Type 2 DM: linked to glycaemic control

A Chinese study of ED to assess the contribution of glycaemic control

- 792 type 2 males assessed using sexual health questionnaire
- Results of prior glycaemic control recorded
- ED in 83%, severe ED in 43%
- HbA1c (p<0.03), age and diabetes duration associated with ED
- Incentive for good glycaemic control in type 2 dm males

Lu et al, J Sex Med 2009;6:1719
ED and diabetes: history

- Primary or secondary?
- Partial or complete?
- Situational?
- Psychosexual
- Drug history
  - Thiazide diuretics
  - Digoxin
  - Spironolactone
ED and diabetes: examination

- Peripheral Neuropathy?
- Peripheral Vascular Disease?
- Other vascular disease?
- Other endocrine diseases?
- Local
ED and diabetes: therapy

- Oral agents
  - PDE5 inhibitors
  - Dopamine-agonists (Apomorphine)
  - Steroids (if hypogonadism occurs)
- Intracavernous injection (ICI) of vasoactive drugs
- Vacuum Devices
- Surgery or penile implants
- Psychosexual counselling
Intracavernosal Injection

e.g. alprostadil

Drug injected directly into the corpus cavernosum away from midline

Cross-section of the shaft of the penis

Corpus cavernosum
Success consists of going from failure to failure without loss of enthusiasm.

-- Sir WINSTON CHURCHILL
## Therapeutic Options for Erectile Dysfunction

<table>
<thead>
<tr>
<th>Oral</th>
<th>Generic</th>
<th>Brand</th>
<th>Co.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>Viagra®</td>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Cialis®</td>
<td>Lilly/ICOS</td>
<td></td>
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<tr>
<td>Vardenafil</td>
<td>Levitra®</td>
<td>Bayer</td>
<td></td>
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<tr>
<td>Apomorphine</td>
<td>Uprima®</td>
<td>Abbott</td>
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<tr>
<td>Alprostadil</td>
<td>MUSE®</td>
<td>Meda</td>
<td></td>
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<tr>
<td>Alprostadil</td>
<td>Caverject®</td>
<td>Pfizer</td>
<td></td>
</tr>
</tbody>
</table>

Sublingual

Intraurethral

intracavernosai

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MIMS December 2005
Intraurethral (IU) therapy - alprostadil

MUSE (Medicated Urethral System for Erection)

Applicator for intraurethral delivery of alprostadil. Depressing the end releases the pellet into the urethra.

Pellet of alprostadil inside the urethra
Oral therapies
first-line
Structure of PDE5 inhibitors

Sildenafil

Vardenafil

Tadalafil
Sildenafil is highly effective in Pts with type II diabetes independently from complications.

Boulton AJM, Diabetologia 2001
<table>
<thead>
<tr>
<th></th>
<th>Study n (Active vs P)</th>
<th>GEQ: (Active vs P)</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sildenafil</strong></td>
<td>110 (25-100 mg) vs 109 P</td>
<td>65 vs 11% P</td>
<td>Headache 18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flushing 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dyspepsia 2%</td>
</tr>
<tr>
<td><strong>Tadalafil</strong></td>
<td>73, 72 (10,20mg) vs 71 P</td>
<td>56 – 64% P</td>
<td>Dyspepsia 11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Headache 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flushing 4%</td>
</tr>
<tr>
<td><strong>Vardenafil</strong></td>
<td>153,149 (10, 20 mg) vs 150 P</td>
<td>57 – 72% P</td>
<td>Headache 12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flushing 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rhinitis 10%</td>
</tr>
</tbody>
</table>
PDE5 Inhibitors have revolutionized ED treatment – but for how long??

- Three year follow-up of Japanese patients prescribed Sildenafil
- 1032 patients included
- 31% only used one prescription
- 48% drop-out rate after three years
- Dropout during successful treatment associated with lower baseline IIEF score

Does educating physicians help in diagnosis of ED in DM?

- 39 primary care physicians (PCPs) received training in ED diagnosis and management: control group of 39 PCPs.
- Intervention group also provided with a list of high-risk patients.
- After 6 months, no differences between the two groups in diagnosis or referrals.
- Such education therefore had no benefit

Female Sexual Dysfunction in Type 1 DM

- Long-term findings from the DCCT/EDIC studies
  - 652 females completed questionnaire at EDIC close-out
  - 35% of women met criteria for female sexual dysfunction - FSD
  - FSD reported as loss of libido (57%), problems with orgasms (51%), lubrication (47%) and arousal (38%).
  - In multivariate analysis, only depression and marital status were significant predictors of FSD
  - FSD common in longstanding type 1 DM and should be enquired of, as should be depressive symptoms

Enzlin et al, Diabetes Care 2009;32:780
All diabetic patients should be screened for long-term complications at least annually

- Hypertension and Nephropathy
- Neuropathy
- Retinopathy
- Macrovascular Disease

Boulton, Diabetic Med 1992;9:887
The Annual Review

Neuropathy

In addition to screening for sensorimotor neuropathy, ALL male patients should be asked "Do you have any problems in obtaining or maintaining an erection?"
Sure I am of this, that you have only to endure to conquer.

-- Sir WINSTON CHURCHILL