Diabetic Neuropathy in Korea

: Proceedings of a consensus development for the evaluation and management

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Diabetic Neuropathy in Korea

Korean Diabetic Neuropathy Study Group

Clinical Characteristics of diabetic Neuropathy in Korea

Guidelines for Management of Diabetic Neuropathy in Korea
Frederick William Pavy (1829-1911)

“heavy legs, numb feet, lighting pain and deep-seated pain in feet, hyperaesthesia, muscle tenderness, and impairment of patellar tendon reflexes”

Pavy also made a point that occurrence of neuropathic symptoms may precede that of clinical diabetes.

Indian physician Susruta (5th century AD), “Their premonitory symptoms are-feeling of burning in the palms and soles, body becoming unctuous and slimy and feel heavy, urine is sweat, bad in smell, and white in color, and profound thirst…Complications include diarrhea, constipation, and fainting”

Abd Allarh Ibn Sinna (Avicenna, 980-1037 AD), He observed gangrene and the ‘collapse of sexual function’ as complications of diabetes.

藤原道長 (Fujiwara No Michigawa, 966-1028 AD), considered to be the first person to suffer from diabetes (‘water-drinking illness’, mizu nomi yagi) and autonomic neuropathy.

A Venes and RA Malik, Diabetic Neuropathy, Clinical Management, 2nd ed.
Diabetic Neuropathy in Korea
Foot diseases and diabetes

Foot amputation (N= 3,829, 2003)  
- Non-diabetic: 44.8%  
- Diabetic: 55.2%

Foot ulcer (N= 8,495), 2003  
- Non-diabetic: 38.4%  
- Diabetic: 61.6%

Analysis of the medical records sampled from the health insurance data regarding claims with foot amputation (Z894-899), ulcer of lower limb (L97), gangrene (R02), insulin-dependent diabetes (E10), non-insulin dependent diabetes (E11), malnutrition related diabetes (E12), other specified diabetes (E13) or unspecified diabetes (E14) as principal or secondary diagnosis between Dec 1994 and Dec 2002.
Foot disease in patients with diabetes

Foot amputation rate (2003)

- Non-diabetic: 4.7
- Diabetic: 47.8

Foot ulcer rate (2003)

- Non-diabetic: 11.7
- Diabetic: 91.0

Per population of 100,000

Analysis of the medical records sampled from the health insurance data regarding claims with foot amputation (Z894-899), ulcer of lower limb (L97), gangrene (R02), insulin-dependent diabetes (E10), non-insulin dependent diabetes (E11), malnutrition related diabetes (E12), other specified diabetes (E13) or unspecified diabetes (E14) as principal or secondary diagnosis between Dec 1994 and Dec 2002.

KDA Diabetes in Korea, 2007
Total medical cost in patients with diabetic foot disease

Foot amputation (2003)

<table>
<thead>
<tr>
<th></th>
<th>DM (-) outpatient</th>
<th>DM (+) outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (-) hospitalization</td>
<td>579</td>
<td>1,309</td>
</tr>
<tr>
<td>DM (+) hospitalization</td>
<td>6,097</td>
<td>11,931</td>
</tr>
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</table>

Foot ulcer (2003)

<table>
<thead>
<tr>
<th></th>
<th>DM (-) outpatient</th>
<th>DM (+) outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (-) hospitalization</td>
<td>550</td>
<td>1,757</td>
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<tr>
<td>DM (+) hospitalization</td>
<td>4,538</td>
<td>7,907</td>
</tr>
</tbody>
</table>

KDA *Diabetes in Korea, 2007*
Korean Diabetic Neuropathy Study Group
Subcommittee of KDA: Diabetic neuropathy study group

Director: Prof. Kyung Soo Ko, MD

Advisory
- Prof. Bong -Yun Cha, MD
- Prof. Tae Sun Park, MD

Secretary: Hyuk -Sang Kwon MD

Program: Ji Hyun Lee MD
Research: Jong Hwa Kim MD
Publication: Jong Chul Won MD
Textbook of Diabetic Neuropathy (Korean)

Prof. Bong Yun Cha MD

And 57 doctors and professors

Korean Diabetic Neuropathy Study Group. 2006 (309 pages volume)
Guideline for management of diabetic neuropathy (2007), updated

Prof. Bong-Yun Cha MD

And 12 members of
Korean Diabetic Neuropathy Study Group

Korean Diabetic Neuropathy Study Group. 2007
(65 pages volume)
Clinical study

- Diabetic distal symmetric peripheral neuropathy (DSPN) patients survey (2005), completed
  - PI: Prof. Bong-Yun Cha MD
  - Clinical characteristic of diabetic DSPN in Korea (31 hospitals)

- Burden of illness in painful diabetic peripheral neuropathy (2009), initiated
  - PI: Prof. Kyung Soo Ko MD
  - Patients reported outcomes (pain severity, patients functioning, sleep disturbance, impact on the quality of life) (40 hospitals)
Clinical Characteristics of Diabetic Neuropathy in Korea
The survey aims to
1. Conduct a basic epidemiological study on diabetic neuropathy of Koreans,
2. Understand clinical characteristics of diabetic peripheral neuropathy of Koreans, and
3. Comprehend diagnosis criteria and treatment principals

DSPN: distal symmetric polyneuropathy
## Diabetic DSPN Patient Survey (2)

| Survey methods          | Face-to-face interview by experienced nurses  
<table>
<thead>
<tr>
<th></th>
<th>Questionnaire and chart review to understand neuropathy symptoms due to diabetics, and basic neurological examination including deep tendon reflex test, tuning folk test and monofilament test for objective results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Areas surveyed</td>
<td>Nationwide (31 Hospitals)</td>
</tr>
<tr>
<td>Subjects</td>
<td>Diabetic patients who made out-patient visits to general hospitals</td>
</tr>
</tbody>
</table>
| Samples                 | N = 875 in total (male and female, 398 and 477, respectively)  
|                         | * Neuropathy (+) : 472  

DSPN: distal symmetric polyneuropathy
Diabetic neuropathy: Distal symmetric peripheral neuropathy

Presence of DSPN

- DSPN (-): 53.9%
- DSPN (+): 46.1%

Duration of diabetes

- < 5 yr: DSPN (+) 40%, DSPN (-) 60%
- 5 - 10 yr: DSPN (+) 40%, DSPN (-) 60%
- 10 - 20 yr: DSPN (+) 40%, DSPN (-) 60%
- > 20 yr: DSPN (+) 40%, DSPN (-) 60%

N = 875, (%)
Glycemic status of patients

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSPN (-)</td>
<td>7.3</td>
</tr>
<tr>
<td>DSPN (+)</td>
<td>7.7</td>
</tr>
</tbody>
</table>

N = 875, (%)
Subjective symptoms: MNSI

1. Are you legs and/or feet numb?
2. Do you ever have any burning pain in your legs and/or feet?
3. Are your feet too sensitive to touch?
4. Do you get muscle cramps in your legs and/or feet?
5. Do you ever have any prickling feelings in your legs or feet?
6. Does it hurt when the bed covers touch your skin?
7. When you get into the tub or shower, are you able to tell the hot water from the cold water?
8. Have you ever had an open sore on your foot?
9. Has your doctor ever told you that you have diabetic neuropathy?
10. Do you feel weak all over most of the time?
11. Are your symptoms worse at night?
12. Do your legs hurt when you walk?
13. Are you able to sense your feet when you walk?
14. Is the skin on your feet so dry that it cracks open?
15. Have you ever had an amputation?

N = 472, (%)
DSPN: Duration and location

Intermittent: 71.2%
Continuous: 28.8%

Where pain is felt (multiple): Foot 77%, Hands 39%, Legs 34%
Where the most severe pain is felt (single): Foot 65%, Hands 20%, Legs 15%

N = 472, (%)
DSPN: Impact on the quality of life

- Personal Relationship
- Leisure
- Occupational activity
- Daily activity
- Walking
- Sleep
- Mood

N = 472, (%)
DSPN: Treatment

N = 472, (%)

- Unknown, 1%
- Yes, 47%
- No, 52%

Other treatments include:
- Opioid analgesics
- γ-linoleic acid
- Anticonvulsant
- Antidepressant
- Alpha lipoic acid

N = 222, (%)
DSPN: Awareness

Yes, 16%

Yes, 9%

Yes, 48%

No, 84%

No, 91%

No, 52%

Awareness

Physician-informed

Education about foot care

N = 875, (%)
Guidelines for Management of Diabetic Neuropathy in Korea
Guideline development process

Select guideline topics

Form expert author panel

Develop clinical questions

Review the literature

Disseminate & Update statement

Approval

Extensive peer review

Write the guideline

www.nice.org.uk
www.guideline.gov
www.aam.com
Select guideline topics

- Members' needs
- Prevalence of condition
- Health impact of condition for the individual and others
- Socioeconomic impact
- Extent of practice variation
- Quality of available evidence
- External constraints on practice
- Urgency for evaluation of new practice technology

www.nice.org.uk
www.guideline.gov
www.aam.com
Symposium: Diagnosis and treatment of painful diabetic neuropathy


Object: review the current practice for management of painful diabetic neuropathy and clinical question development
Diagnostic accuracy for the presence of distal symmetric polyneuropathy

1. Franse LV et al., Diabet Med 2000
2. Feldman EL et al., Diabetes Care 1994
4. Monticelli ML et al., Neuroepidemiology 1993
5. Franklin GM et al., Am J Epidemiol 1990
7. Valk GD et al., Diabet Med 1992
8. Dyck PJ et al., Neurology 1992
9. Maser RE et al., Diabetes Care 1992
Diagnosis of diabetic DSPN

1. DM and neuropathic symptoms
2. Clinical examination scores
   - Decreased vibration sense
   - 10-g monofilament test
   - Decreased or absent ankle reflex

Exclusion of other neuropathy phenotype

Diabetic DSPN
American Association of Clinical Endocrinologists (AACE) medical guidelines for clinical practice for the management of diabetes mellitus. Microvascular complications

All patients with T2DM should be assessed for neuropathy at the time of diagnosis (grade A); annual examinations should be performed thereafter in all patients. Screening may include:

- History and examination eliciting signs of autonomic dysfunction
- Testing for heart rate variability, if indicated, which may include expiration-to-inspiration ratio and response to the Valsalva maneuver and standing.

Inspect the patient's feet at every visit (grade B).

Perform an annual comprehensive foot examination (grade B).
Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy (grade C).

Tricyclic antidepressants; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities (grade C).
Annual examination with pin-prick test, temperature/vibration sense, and 10-g monofilament

Most patients with painful diabetic neuropathy need to be treated with alpha lipoic acid, γ-linoleic acid, TCA, anticonvulsant, SSRI etc.
The simultaneous presence of diabetes and peripheral neuropathy\(^1\) strongly suggest diabetic neuropathy.

Mild cases may be improved simply by glycemic control. NSAID, AR inhibitor (epalrestat) and antiarrhythmics (mexiletine), anticonvulsants (carbamazepine), and antidepressants may be effective, but chronic cases may be difficult to treat.

1. Numbness in both lower limbs, dolor, hypothesia or paraesthesia, and absence of the Achilles tendon reflex.

JDS. *Treatment Guide for Diabetes*. 2007
Clinical trials for "Diabetic Neuropathy"

Map of 290 studies found by search of: diabetes and neuropathy

Clinical trials in Korea

Found 4 studies with search of diabetes and neuropathy (Nov 2, 2009)

Completed A Study To Evaluate Pregabalin In Patients With Painful Diabetic Peripheral Neuropathy (DPN) Placebo, pregabalin

Recruiting An Efficacy and Safety Study of Carisbamate in the Treatment of Nerve Pain in Diabetics Placebo, Carisbamate 1,200 mg/d, Carisbamate 800 mg/d, Pregabalin 300 mg/d

Completed Pregabalin Peripheral Neuropathic Pain Study Placebo, pregabalin

Completed Study Evaluating the Safety and Efficacy of a Once-daily Dose of Tigecycline vs Ertapenem in Diabetic Foot Infections With a Substudy in Patients With Diabetic Foot Infections Complicated by Osteomyelitis. Tigecycline, Ertapenem
# Clinical trials in Japan

Found 6 studies with search of diabetes and neuropathy (Nov 2, 2009)

<table>
<thead>
<tr>
<th>Status</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruiting</td>
<td>A Long-Term Study To Evaluate Safety And Efficacy Of Pregabalin For Pain Associated With Diabetic Peripheral Neuropathy</td>
</tr>
<tr>
<td>Completed</td>
<td>Randomized, Double-Blind, Multicenter, Placebo-Controlled Study Of Pregabalin For Pain Associated With Diabetic Peripheral Neuropathy</td>
</tr>
<tr>
<td>Completed</td>
<td>A Study for the Treatment of Painful Diabetic Neuropathy</td>
</tr>
<tr>
<td>Recruiting</td>
<td>A Long-Term Study for the Treatment of Painful Diabetic Neuropathy</td>
</tr>
<tr>
<td>Terminated</td>
<td>ASP 8825 - Study in Patients With Painful Diabetic Polyneuropathy</td>
</tr>
<tr>
<td>Active, not recruiting</td>
<td>OlmeSartan and Calcium Antagonists Randomized (OSCAR) Study</td>
</tr>
</tbody>
</table>

- Pregabalin
- Duloxetine hydrochloride, placebo
- Duloxetine hydrochloride
- ASP8825, placebo
- Olmesartan medoxomil, Calcium channel blockers (amlodipine, azelnidipine)
Treatment of diabetic DSPN

Glycemic control

• Risk factors
  Hypertension, dyslipidemia, smoking, alcohol consumption

Alpha-lipoic acid, γ-linoleic acid, aldose reductase inhibitors, vasodilator, PKC β inhibitor, AGE inhibitor

Stepwise symptom management
Choose drugs according to the patient’s dominant symptoms

Diabetic DSPN

Pathophysiology based treatment

Symptomatic treatment
Undetermined treatment

- Additional Therapies
  - Topicals:
    - Capsaicin, lidocaine 5% patch
  - Acupuncture
  - NMDA receptor antagonists
  - Antiarrhythmics

- Physical Therapy

- Steroid injections

- Surgical decompression

- Nerve ablation

- Medications
Questions about diabetic neuropathy will be answered

Clinical question development

1) Role of electro-physiologic study in the diagnosis of DSPN.

2) Role of non-pharmacological treatment in patients with medically intractable neuropathic pain.
개원의를 위한
대한당뇨병학회
신경병증 소연구회 연수강좌

Diabetic Neuropathy Diagnosis
Korean Diabetes Association
Korean Diabetic Neuropathy Study Group

Diabetic Neuropathy Treatment
Korean Diabetes Association
Korean Diabetic Neuropathy Study Group
Training course for primary physician: Management of diabetic neuropathy

- Sep 17, 24
- Oct 15
- Nov 10, 17
- Nov 24
これからは 楽にして下さい。

これからは 自由になってく
ださい。。。

糖尿病性神経症 これ以上
耐えないので 医者と 相談し
たください
Summary and future direction

- Foot diseases in diabetic patients in Korea were 10-folds more common compared with those on non-diabetics.
- Comprehensive examination composed of composite symptom score and simple neurologic examinations should be performed annually.
- When treating patients with diabetic DSPN, consider treatment with pathophysiology-based approach and, in some cases, symptomatic treatment is required.
- Roles or indications of electrophysiologic study and non-pharmacologic treatment will be determined.
- The strategies for dissemination of current management guideline is urgent.
# Acknowledgement

<table>
<thead>
<tr>
<th>University/Institution</th>
<th>Member Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inje University</td>
<td>Kyung Soo Ko MD</td>
</tr>
<tr>
<td>Catholic University, Daegu</td>
<td>Ji-Hyun Lee MD</td>
</tr>
<tr>
<td>Catholic University, Seoul</td>
<td>Bong-Yun Cha MD</td>
</tr>
<tr>
<td>Sejong Hospital, Bucheon</td>
<td>Jong-Wha Kim MD</td>
</tr>
<tr>
<td>Chonbuk University, Jeonju</td>
<td>Hyuk Sang Kwon MD</td>
</tr>
<tr>
<td>All members of Korean Diabetic Neuropathy Study Group</td>
<td>Tae-sun Park MD</td>
</tr>
<tr>
<td>Pfizer, Korea</td>
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</tbody>
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Thank you for your attention!