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Call to Action : Changing the Paradigm of Peripheral Neuropathy

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Disclosures

The views expressed in this presentation are my own and do not reflect the official position or policy of the Dubai Academic Health Corporation.

Diabetes is a global pandemic

Diabetes is a **widespread disease on the rise.** The number of diabetic patients has been rising steadily for decades und continues to rise in future.



The economic burden of diabetes is immense

Did you know that diabetes has a substantial economic impact on countries and national health systems?





10% of the global health expenditure is spend on diabetes (2019: USD 760 billion), and numbers are estimated to rise over the next years.

Diabetes can have severe complications

If left untreated, diabetes can cause damage to many of the body's organs and have a strong impact on the health and quality of life of the patient.



Risk factors for diabetesrelated complications include smoking, overweight and obesity, physical inactivity, high blood pressure and high cholesterol.

Early diagnosis, lifestyle changes, consistent treatment and patient compliance are key to avoid disabling and lifethreatening complications.

Diabetes: #1 cause of peripheral nerve damage

Etiology of peripheral neuropathy/ polyneuropathy*







Prevalence of Lower-Extremity Disease in the U.S. Adult Population \geq 40 Years of Age With and Without Diabetes

1999–2000 National Health and Nutrition Examination Survey

N=2873, 419 with DM 14.8% with PN Prevalence increases with age



Gregg EW, et al. Diabetes Care. 2004;27:1591–1597.

The Journal of International Medical Research 2011: 39: 366 – 377

Prevalence of Painful Diabetic Peripheral Neuropathy among Patients with Diabetes Mellitus in the Middle East Region

S JAMBART¹, Z AMMACHE², F HADDAD³, A YOUNES⁴, A HASSOUN⁵, K ABDALLA⁶, C ABOU SELWAN⁷, N SUNNA⁷, D WAJSBROT⁷ AND E YOUSEIF⁷



FIGURE 2: Proportions of patients with Douleur Neuropathique-4 (DN4) total scores of 0, 1 - 3, and ≥ 4 by country, within a sample of 3989 patients with type 1 and type 2 diabetes in the Middle East region (DPN, painful diabetic peripheral neuropathy)

- 53,7 % diabetic patients met criteria for painful DPN (DN4 score >4)
- Highest incidence: Egypt (61,3%) followed by Jordan (57,5%), Lebanon 53,9%) and Gulf States (37,1%)
- Notably higher than that observed in studies conducted in Europe and the USA, which reported prevalence rates of 15 – 25%.



BMJ Open Diabetes Research & Care

Prevalence of peripheral neuropathy in pre-diabetes: a systematic review

Varo Kirthi ⁽¹⁾, ^{1,2} Anugraha Perumbalath, ³ Emily Brown, ³ Sarah Nevitt, ⁴ Ioannis N Petropoulos, ⁵ Jamie Burgess, ³ Rebecca Roylance, ⁶ Daniel J Cuthbertson, ³ Timothy L Jackson, ^{1,2} Rayaz A Malik ⁽¹⁾, ^{5,7} Uazman Alam^{3,8,9}

- Prevalence 2-77%
- Majority of study reported > 10%
- Higher prevalence among study evaluating small nerve fibre
- Pre-diabetes is a risk factor for chronic axonal polyneuropathy

BMJ Open Diab Res Care 2021;9:e002040.



The burden of peripheral neuropathy is high

PN is a chronic disease that affects patients in different dimensions

PN often **starts** with **barely noticeable symptoms** (e.g. mild numbness or tingling in fingers and toes), but symptoms can **change, get worse, or become more painful** in the course of the disease. In **advanced stages**, patients will experience **neuropathic pain** which will affect their lives significantly.



Peripheral neuropathy can have a significant impact on :

- patient's social life
- working life
- happiness
- overall well-being
- economic situation

Peripheral neuropathy can lead to **comorbidities**:

- depression
- sleep disorders
- anxiety
- influence quality of life (QoL)

Nold CS, Nozaki K. JAAPA. 2020;33: 9-15. O'Connor AB. Pharmacoecon. 2009;27: 95–112. As peripheral neuropathies are heterogeneous in their clinical presentation, diagnosis is not always straightforward.

The diagnosis of peripheral neuropathy is a challenge. Many patients remain undiagnosed and untreated.

People with peripheral neuropathy (PN) often remain undiagnosed for different reasons. Thus, the disease is considered a "silent disease".

Without timely diagnosis and appropriate treatment, patients can develop neuropathic pain, which is very difficult to treat and significantly affects their quality of life.



Who is at risk of developing PN?

Patients can develop PN due to many different diseases and risk factors!

Many patients have multiple underlying causes leading to nerve damage



Diabetes



Medication (e.g. chemotherapy)



Obesity



Alcoholism



External injury, trauma (e.g. by surgery), ischemia, inflammation



Nutritional deficiencies (e.g. B vitamin deficiency)



Smoking

Other unexplained causes

Callaghan BC, et al. JAMA. 2015;314: 2172–2181. Head KA. Altern Med Rev. 2006;11: 294–329. Landmann G. Psychiatr Neurol. 2012;5: 13–16. Gad H. et al. J Peripher Nerv Syst. 2024;1–10.



Up to 80% of patients remain undiagnosed

All over the world, a large proportion of diabetics suffer from PN but remain undiagnosed

Recent studies from different countries confirm **need to increase awareness** and educate on diagnosis:¹⁻⁵

- Proportion of **undiagnosed patients** is similar across different countries
- Similar results in different regions and countries with higher or lower economic status

Sample size	% undiagnosed DPN	Country of study conduct	Reference
N=425	99,8%	Malaysia	Lee 2022
n = 242	98,82%	Saudi Arabia	Algeffari 2018
N=1095	80%	Qatar	Ponirakis 2019
N=1850	61.5% Painful and 81.1% painless DSPN	Germany	Ziegler 2018
N=1100	91%	Germany	Bongaerts 2013
N=816	79% PNS patients undiagnosed DPN	USA	Wang 2011

PN = peripheral neuropathy

Algeffari MA. J Family Community Med. 2018;25: 43-47; Ponirakis G, et al. J Diabetes Investig. 2019;10: 1558-1564. Ziegler D, et al. Diabetes Res Clin Pract. 2018;139: 147-154; Lee PY, et al. Malays Fam Physician. 2022;17: 36-43. Wang W, et al. Diabetes Educ. 2011;37: 536-548; Bongaerts B et al; Diabetes Care Vol 36, 1141-1146; 2013



Both patients and physicians face barriers

Diagnosis of peripheral neuropathy is a challenge for both patients and physicians



Due to different challenges experienced by both – patients and physicians - **up to 80% remain undiagnosed**

Patients suffer from symptoms for around 5 years before being diagnosed

Even patients with painful peripheral neuropathy often remain undiagnosed and untreated



Gad H. et al. J Peripher Nerv Syst. 2024;1–10.



Patient barriers on the way to diagnosis

Overcoming these barriers is important for the patient to **get diagnosed as early as possible** and **receive treatment.** But here the struggle starts...



Raising awareness among the community is a critical step to get unaware patients diagnosed

Physician barriers to diagnose PN EFMS physicians, especially in primary care settings struggle to diagnose PN for several reasons ...

Limited time for each patient

Crowded clinics, too many patients, lack of medical staff

Patients do not report symptoms proactively and **physicians** have no time to ask



Diagnosis of PN is not routine clinical practice in primary care

Diagnosis of PN is **perceived complex**, requiring devices physicians don't have

Lack of consistent and simple guidance

Not aware that diagnosing PN is **possible** with simple tools



Focus on other complications perceived more severe such as CVD, retinopathy etc.

Gad H. et al. J Peripher Nerv Syst. 2024;1–10.

Simple guidance and tools for primary care settings to diagnose PN is few minutes will change the paradigm and improve patient care





Changing the paradigm of PN diagnosis

Earlier PN diagnosis will improve patients' lives!

Even today, **up to 80%** of PN patients are **undiagnosed**. Shifting the focus **from the physician** as the only one carrying the burden of diagnosis **to the patient/community** will facilitate **earlier**, **faster and easier diagnosis**.







New screening and diagnosis tool empowers the patient and helps the physician to diagnose in few minutes

Increase disease awareness among the community and provide a tool to screen for PN risk to **drive early diagnosis**

Patient can screen and **assess the risk** for peripheral neuropathy with 5 simple questions and share the outcomes with the physician

Unaware person = patient





Provide a **simple tool to physicians** to diagnose PN based on the pre-assessment of the patient

Physician can finalize the diagnosis with 2 simple tests within minutes, after reviewing the first part completed by the patient





New questionnaire developed by experts

A multinational expert panel with expert from 11 countries developed a new questionnaire

Step 1:

- Designed to increase community awareness and empower the patient
- Facilitates earlier diagnosis as the patient will be alerted to screen the risk before seeing a physician
- Patient screens the risk and obtains a score reflecting the risk for PN



Step 2:

- Patient shares the outcomes of step 1 with the physician
- The score and the responses to the questions allow to assess the risk quickly
- Two simple sensory tests
- Physicians invest significantly less time to make the diagnosis





Advantages of the new questionnaire:

- Involving the patient in the screening process will not only reduce the time a physician requires to reach a diagnosis but would also empower the patient.
- Both physicians and patients agree that simple numeric scales
 are most useful
- Physicians in primary care prefer a short, simple, and accurate tool to screen for PN in their daily practice
- Other HCPs such as nurses, pharmacists, podiatrists etc can be involved to screen early







This simple **5- step guide**, based on an expert panel recommendation by Malik et al. 2020¹, helps physicians diagnose PN within minutes despite limitations in primary care. In case the diagnosis is still unclear after this, referral to a specialist can be considered.





Step 1: Classify symptoms into acute, subacute or chronic A simple classification of the onset of symptoms provides an initial differential diagnosis.

Classify symptoms based on the onset into

- acute (days),
- subacute (weeks to months) or
- chronic (> 6 months).

While an acute onset could be due to an infectious disease or toxin exposure, a subacute onset may be caused by inflammatory, immune-mediated or metabolic (diabetes, nutritional deficiencies) causes, medication or chemotherapy. When the symptoms are chronic, consider a diabetic or hereditary neuropathy.







Step 1: Classify symptoms into acute, subacute or chronic

Acute	Subacute	Chronic	Relapsing/ remitting
Guillain-Barré syndrome	Nutritional deficiency	Hereditary neuropathy	Guillain-Barré syndrome
Acute intermittent porphyria	Prolonged toxin exposure	Diabetic neuropathy	Porphyria
Diphtheria	Metabolic (diabetic neuropathy, uremic neuropathy)	CIDP	CIDP
Toxicity due to thallium, mercury, arsenic, lead	Immune-mediated (e.g. CIDP, vasculitis, sarcoidosis)	Hereditary e.g. Charcot-Marie-Tooth, familial amyloidosis, HIV neuropathy	HIV/ AIDS
Critical illness neuropathy	Neoplastic (e.g. hematological/ lympho-proliferative malignancies)	CIPN	
	Paraneoplastic (e.g. anti-Hu)		

CIDP, chronic inflammatory demyelinating polyneuropathy; CIPN, chemotherapy-induced peripheral neuropathy; HIV, human immunodeficiency virus





Step 2: Take a careful medical history

Taking a thorough medical history helps to find out the cause of the disease which can be very various: metabolic, systemic, infectious, inflammatory, nutritional, or mediated by toxins or medication.

Ask the patient about underlying diseases, medication, general disease history, contact with toxins, and other factors.

Keep in mind that you may not find a cause in every case, as 24–27% of patients with PN have idiopathic neuropathy with an unclear etiology.

Malik RA, et al.J Diabetes Investig 2020 Vol. 2 No. 5

Business Use







Step 2: Take a careful medical history

Metabolic disease	Hypothyroidism Chronic liver disease Chronic kidney disease Diabetes Prediabetes
Systemic disease	Systemic/ non-systemic vasculitis (ANCA, cryoglobulinemia) Paraproteinemia
Infectious	Amyloidosis HIV Leprosy Hepatitis B/C
Inflammatory	(CIDP)
Nutritional	Deficiency of B vitamins (B12, B1, B6) Malabsorption syndromes Bariatric surgery
Toxins	Organophosphorus agents, alcohol, arsenic, mercury, isoniazid
Medication	Colchicine, dapsone, amiodarone, nitrofurantoin, metronidazole, ethambutol, chemotherapy (vincristine, cisplatin, taxol, bortezomib)

ANCA, anti-neutrophil cytoplasmic antibodies; CIDP, chronic inflammatory demyelinatingneuropathy; HIV, human immunodeficiency virus





Step 3: Assess symptoms and signs of peripheral neuropathy

Some patients might have difficulties in describing their symptoms properly. Ask the patient proactively and focus on the main characteristics of PN: numbness, pins and needles and tingling sensation, lancinating, stabbing or electric shock like pain.

Use picturesque everyday examples such as 'feeling of ants' or 'electric shocks' to help the patient.

It may also be difficult for the patient to express their symptom localization in words. Let the patient circle the symptom localization in a simple sketch, which also helps to assess symmetry.





Step 3: Assess symptoms and signs of peripheral neuropathy

Simple questions to ask about symptoms*:

- Do you have a feeling as if **ants are crawling** along your feet?
- Does it **feel like electric shocks** out of nothing?
- Does the bedsheet on your feet feel painful sometimes?
- Where do you experience the pain/sensation?
- Does it occur on **both sides** (symmetrical)?
 Is it worse at night?
- * listed questions not exhaustive

Simple sketch to circle symptom localization







Step 4: Perform a neurological examination

Easy to perform sensory tests take no longer than a few minutes and guide the diagnosis.

Perform vibration perception testing with a 128 Hz tuning fork and a pin-prick test and examine temperature sensation and reflexes.

If professional tools are not on hand, use simple everyday objects, for example a painter's brush, a feather, a toothpick, or a cotton swab.





Texture perception

Cotton wool



Touch sensitivity

Cocktail stick



Pressure and pain

Paperclip



Two-point discrimination test







Step 5: Order laboratory tests

Different laboratory tests can help to refine the diagnosis, although no definite blood marker is available to clearly diagnose PN.

None of the tests is mandatory but will help to investigate the possible underlying cause, such as diabetes.

Order appropriate laboratory tests to support or refute a diagnosis, if needed. Serum glucose, HbA1c and vitamin B12 levels can often be done in a primary care setting.

For more complex tests like anti-HIV antibodies, refer the patient to a specialist practice or send the blood sample to an external laboratory.







Step 5: Order laboratory tests

Common/ simple	Serum glucose, HbA1c, oral glucose tolerance test, vitamin B12	
	Erythrocyte sedimentation rate (ESR), serum and urine electrophoresis	
	Liver and renal function test Thyroid function test	
May require	Anti-HIV antibodies	
referral depending	Tumor (paraneoplastic) markers	
resources	Vasculitis profile (ANA, ANCA, Ro/La, cryoglobulin)	





Tests at General Practice and by specialists

Some patients need to be referred to a neurologist.

Blood tests can be performed by both, but they will only deliver **supportive information**. There is currently **no known blood marker** for peripheral neuropathy, therefore it **can not be diagnosed by blood testing**. GP

Blood tests

can detect vitamin deficiencies, diabetes, abnormal immune function, and other signs for conditions that can cause PN.



Tests that the specialist will perform are different and require a **specific equipment and knowledge**.



Some tests (if required) normally have to be done by a **specialist** – either because they depend on very **special equipment** or because interpretation of the results requires **highly specialized knowledge**.

Imaging tests:¹

Computer tomography or magnet resonance imaging scans can look for herniated disks, tumors or other abnormalities.

Nerve function tests:⁴

Electromyography records electrical activity in muscles to detect nerve damage. A probe sends electrical signals to a nerve, and an electrode placed along the nerve's pathway records the nerve's response to the signals (nerve conduction studies).

Other nerve function tests:⁴

These might include an autonomic reflex screen that records how the autonomic nerve fibers work, a sweat test, and sensory tests that record how the patient feels touch, vibration, cooling and heat.

Nerve biopsy:^{5,6}

This involves removing a small portion of a nerve, usually a sensory nerve, to look for abnormalities.

Skin biopsy:⁶

The doctor removes a small portion of skin to look for a reduction in nerve endings.



1. Peyron R, et al. Neurophysiol Clin. 2000;30: 263-288. | 2 Garcia-Larrea L, et al. Pain. 199;83: 259–273. | 3. Garcia-Larrea L, et al. Eur J Pain. 2006;10: 677–688. 4. Cruccu G, et al. Eur J Neurol. 2010;17: 1010–1018. | 5. Baron R, et al. Lancet Neurol. 2010;9(8): 807–819. | 6. Lauria G, et al. Eur J Neurol. 2005;12: 747–758.

EFMS

Summary and conclusion

- PN is a chronic disease that affects patients on different levels: physically, emotionally, socially, and economically.
- The diagnosis of PN is a challenge. Around 80% of affected persons all over the world are undiagnosed.
- Patients suffer from PN for around 5 years before being diagnosed.
- Without timely diagnosis and appropriate treatment, patients can develop neuropathic pain, which will significantly affect their quality of life.
- Shifting the focus from the physician to the patient who can also screen for PN and see a physician earlier facilitates a faster and easier diagnosis.
- Using the new questionnaire developed by experts can change the paradigm of PN diagnosis.
- The new questionnaire is published in a peer-reviewed journal JPNS: Gad H. et al. J Peripher Nerv Syst. 2024;1–10.

Raising awareness among the community and simplifying the diagnosis process for physicians is key for a timely diagnosis!



Thank You