# Predictive Value of Peripheral Neuropathy for the presence of Ischemic Heart Disease in Diabetic Patients

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# القيمة التنبؤية لالتهاب الأعصاب المحيطية في وجود مرض جلطة القلب لمرضى السكري

**الخلاصة:**

- من أجل تقييم مدى انتشار مرض قصور الشرايين التاجية للقلب في مرضى السكري المصابين باعتلال الأعصاب المحيطية، فحص ١٠٥ من مرضى السكري الذين كانت أعمارهم (٥٢ ± ٧.٨) سنة، ٥٤ من الذكور و ٥١ من الإناث.
- كان معدل انتشار مرض قصور الشرايين التاجية للقلب في مرضى السكري المصابين باعتلال الأعصاب المحيطية ٥٨.٧٥ ٪.
- إن ارتفاع ضغط الدم له اثر بشكل ملحوظ للغاية على انتشار الاعتلال العصبي المحيطي ($P < 0.001$)، في حين التدخين، فصائل الدم ونظام Rh لن تؤثر على انتشار الاعتلال العصبي المحيطي ($P > 0.05$).
- العجز الجنسي كان له اثر ($P < 0.05$) و قصور الشرايين التاجية للقلب كان له اثر بشكل ملحوظ للغاية ( $P < 0.001$) بالاشتراك مع اعتلال الأعصاب المحيطي السكري.

**Abstract:**

- In order to assess the prevalence of ischemic heart disease (IHD) in diabetic patients with peripheral neuropathy, 105 type 2 diabetic patients aged (52 ± 7.8) years, 54 males and 51 females were investigated.
- Prevalence of ischemic heart disease in diabetic patients with peripheral neuropath was 58.75 %
- Hypertension highly effects the prevalence of peripheral neuropathy ($P < 0.001$) while smoking, blood group and Rh system not effect the prevalence of peripheral neuropathy ($P > 0.05$).
- Impotence significantly ($P < 0.05$) and IHD have highly significantly ($P < 0.001$) association with diabetic peripheral neuropathy while overt proteinurea, serum creatinine and retinopathy do not have any association with diabetic peripheral neuropathy.

**Keywords:** Type 2 diabetes mellitus, Peripheral neuropathy, Ischemic heart disease, Nerve conduction study

## Introduction:

Peripheral neuropathy is a common microvascular complication of diabetes.(1) Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes". (2)

Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies. More than 80% of amputations occur after foot ulceration or injury, which can result from diabetic neuropathy.(1) Peripheral neuropathy implies a heavy burden of morbidity of people with diabetes and increases the economic cost of diabetes management. (3)

The prevalence and pattern of PN vary from country to country, from as low as 1.5% to as high as 100% in patients with type 2 diabetes depending on the differences in screening approaches, diagnostic criteria and the study population. The neuropathy may be silent and go undetected. Up to 7.5% of patients with type 2 diabetes have clinical neuropathy at the time of diagnosis. This rate increases to 50% among patients with diabetes who have had diabetes for 25 years.

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system.

**Diagnosis of ischemic heart disease:** (4)

1- Past history of IHD (previous myocardial infarction, angina, coronary bypass grafting).

2- Abnormality in two or more of the 12 – lead ECG (A depression of $\geq 1$ mm of the ST segment horizontally or down sloping below the baseline ( i.e. PR segment) or ST segment elevation 1mm (2 mm in V1 to V3) in two or more contiguous leads was considered as a positive ECG result.

3- Evidence of a previous myocardial infarction (e.g., pathological Q waves) on the ECG.

**Diagnosis of diabetic peripheral neuropathy:**

The assessment of patients with diabetic neuropathy begins with a detailed neurologic and medical, history and examination and continues with electrodiagnostic studies. Up to this date nerve conduction studies (NCS) remain the most reliable, accurate and sensitive measure of peripheral nerve function in diabetic neuropathy. (5)

**Diabetic peripheral neuropathy diagnostic criteria:**

NCS abnormalities + neurological symptoms (including numbness, acupuncture, pain, burning pain, etc.) or a simple check exception.(6) The electrodiagnosis protocol recommended by the American Diabetes Association was used for the NCS. Median, ulnar and peroneal motor fibers, median and ulnar sensory fibers and sural nerves were studied.(7)

Nerve conduction studies (NCS) are the most sensitive and specific DPN detection method.(8) The information is extremely detailed to the extent that the cellular pathology of a patient's neuropathy is usually defined best by physiological testing rather than by biopsy.

## Patients and Methods:

**Study population:**

This study involved 105 type 2 diabetic patients, 54 males and 51 females, their ages ranged from 35–60 years with a mean of (52 ± 7.8) years.

The patients are classified into two groups: those with peripheral neuropathy (80 patients), their ages ranged from 35 – 60 years and those without peripheral neuropathy (25 patients), their ages ranged from 35 – 60 years.

## Materials:

### Micromed system-plus EMG machine

Micromed System-plus EMG machine was used for electrophysiological analysis of sensory and motor nerve fibers conduction studies. This system includes eight channels preamplifiers and built-in two isolated stimulators with separate jacks.

The stimulus intensity can be manually adjusted (0 – 99 mA), and the evoked responses can be displayed on the monitor, on which four channels can be displayed at the same time .The machine also contains an audio-amplifier which helps to localize the site of stimulation of the nerve in case of the NCS.

### Accessories of the Micromed system-plus EMG machine

**1- Grounding electrode:** A Velcro ribbon strap surface – grounding electrode was used to protect the subject against electrical hazard and to reduce the artifact and interference. The ground electrode should be placed between the stimulating electrode and the recording electrode. (9)

**2- Stimulating electrode:** A bipolar surface stimulating electrode was used to stimulate the nerve. The electrode consists of two felt tips mounted in stainless steel holders in a plastic frame; a negative (–) mark point to the cathode and a positive (+) mark point to the anode of the stimulating electrode. The center to center distance of these felt tips was 23 mm and each felt tips diameter is 6 mm. They were applied manually on the skin over the nerve to be tested. (10)

**3- Recording electrodes**

**Active electrode**

The active electrode (sometimes called the E1 or G1) should be placed over the muscle belly (preferably over the motor point, where the nerve enters the muscle) during motor studies. During sensory studies, the active electrode should be placed directly over the nerve (where the nerve is as superficial as possible).

**Reference electrode**

The reference electrode (sometimes called the E2 or G2) should be placed on a nearby tendon or bone away from the muscle when attempting to record a Compound muscle action potentials (CMAP). When performing sensory nerve action potentials (SNAPS), it has been shown that 3 – 4 cm is the optimal inter-electrode separation. If SNAP electrodes are placed too close to each other, decreased amplitude resembling an axonal lesion can occur. CMAP are less affected than SNAPS when electrodes are placed less than 3 – 4 cm apart. (10)

## Methods:

**History:** Full history about therapeutic regimen, duration, smoking status (never, current), hypertension, history of ischemic heart disease (IHD) and impotence (in male diabetics) is recorded.

Neuropathy was evaluated using a questionnaire on neuropathic symptoms and Neuropathy Symptoms Score (NSS) like presence of neuropathic pain, parasthesia and anesthesia. The calculation was done as present [1] or absent [0]. (11)

**Clinical examination:**

The subject should lie flat on the examining couch in a quiet environment for at least 5 minutes for a steady state (heart rate changing by less than 2–3 beats in consequent minutes). (12)

Blood pressure was measured in all patients in supine position by auscultatory method (Korotkoff phases)(13) using First phase (the appearance of the sound) as systolic blood

pressure and fifth phase (the disappearance of the sound) as diastolic blood pressure.(14) Hypertension defined as blood pressure more than 140/90 mmHg. (15)

Changes in fundi were confirmed by an Ophthalmologist. The diagnosis of retinopathy was confirmed (or not) by fundoscopy. The term " retinopathy " refers to both nonproliferative and proliferative retinopathy.

Three clinical tests were carried out including **ankle reflexes** bilaterally (most sensitive to early diabetic peripheral neuropathy (DPN), performed while the patient is sitting or kneeling, the examiner dorsiflexes the foot and gently strikes the Achilles tendon with the reflex hammer), **joint position** sense (of the interphalangeal joint of the big toe and thumb) and sensation to **pinprick** over the centre of the palm and sole. The latter was compared to pinprick sensation at the midsternal area as reference. Abnormality of the physical sign was defined as absence of joint position sensation, an absent reflex and reduced sensation in the test compared to the reference area over the sternum. (16)

**Biochemical analyses:**

All patients were investigated for serum creatinine, Lipid profiles (Total cholesterol, HDL, LDL and Triglyceride), HbA1c, Blood group, Urine protein and ECG.

**Measuring the variables of NCS:**

1. Sensory nerve fibers measurements including: latency, conduction velocity and amplitude for (median, ulnar, and sural nerves).
2. Motor nerve fibers measurements including: distal motor latency, motor conduction velocity and amplitude for (median, ulnar, posterior tibial and common peroneal nerves).
3. F–wave measurements including the latency.

►The preferred criteria for diagnosis of distal symmetrical polyneuropathy are abnormalities in two of three areas: symptoms, signs, and electrodiagnostic studies. (6)

► Decreased conduction velocity indicates demyelinating neuropathies (decreased motor conduction velocity in motor demyelinating neuropathies and decreased sensory conduction velocity in sensory demyelinating neuropathies) while decreased amplitude of the CMAP or SNAP indicates axonal neuropathies (decreased CMAP amplitudes in motor axonal neuropathies and decreased SNAP amplitudes in sensory axonal neuropathies). (17)

**Results:**

This cross–sectional study involved 105 diabetic patients aged (52 ± 7.8) years, 54 males and 51 females. All subjects were exposed to nerve conduction study.

According to the results of history, clinical examination and nerve conduction study, they were classified into those with peripheral neuropathy (80 patients) and those without peripheral neuropathy (25 patients).

**Effect of hypertension, smoking, blood group and Rh system on the development of peripheral neuropathy.**

There was a statistically highly significant effect of hypertension on the development of peripheral neuropathy ($P < 0.001$) (Table 1) but there was no statistically significant effect of smoking, blood groups and Rh system on the development of peripheral neuropathy ($P > 0.05$) (Table 1).

**Table 1:** Effect of smoking, hypertension blood group and Rh system on the development of peripheral neuropathy.

| **Variables** | **With neuropathy** No. (%) (n = 80) | **Without neuropathy** No. (%) (n = 25) | **P value** |
|---|---|---|---|
| **Hypertension** | | | |
| Normal | 37 (46.25) | 22 (88) | P < 0.001 |
| Hypertensive | 43 (53.75) | 3 (12) | |
| **Smoking** | | | |
| Never-smoker | 43 (53.75) | 17 (68) | P > 0.05 |
| Current-smoker | 37 (46.25) | 8 (32) | |
| **Blood Group** | | | |
| A | 23(28.75) | 2 (8) | |
| B | 19(23.75) | 7 (28) | P > 0.05 |
| AB | 3(3.75) | 2 (8) | |
| O | 35(43.75) | 14 (56) | |
| **Rh System** | | | |
| Rh-negative | 5 (6.25) | 1 (4) | P > 0.05 |
| Rh-positive | 75 (93.75) | 24 (96) | |

**Association between peripheral neuropathy and overt proteinurea, serum creatinine, retinopathy, impotence and ischemic heart disease.**

There was no significant association between peripheral neuropathy and overt proteinurea, serum creatinine and retinopathy (P > 0.05) (Tables 2) but there was a statistically significant effect of peripheral neuropathy on the development of impotence and IHD (P < 0.05) (Tables 2). From table 2, it has been concluded that the prevalence of IHD in diabetic patients with peripheral neuropath was **58.75 %** (Figure 1).

**Table 2:** Association between peripheral neuropathy and overt proteinurea, serum creatinine, retinopathy, impotence and IHD.

| Variables | With neuropathy (n = 80) | Without neuropathy (n = 25) | P value |
|---|---|---|---|
| **Proteinuria**<br>Absent<br>Present<br>No. (%) | 64 (80)<br>16 (20) | 21 (84)<br>4 (16) | P > 0.05 |
| **Creatinine (mg/dl)**<br>Mean ± SD | 0.87 ± 0.36 | 0.79 ± 0.23 | P > 0.05 |
| **Any retinopathy**<br>No<br>Yes<br>No. (%) | 61 (76.25)<br>19 (23.75) | 23 (92)<br>2 (8) | P > 0.05 |
| **Impotence**<br>No<br>Yes<br>No. (%) | 11 (26.8)<br>30 (73.2) | 9 (69.2)<br>4 (30.8) | P < 0.05 |
| **Ischemic heart disease**<br>No<br>Yes<br>No. (%) | 33 (41.25)<br>47 (58.75) | 22 (88)<br>3 (12) | P < 0.05 |

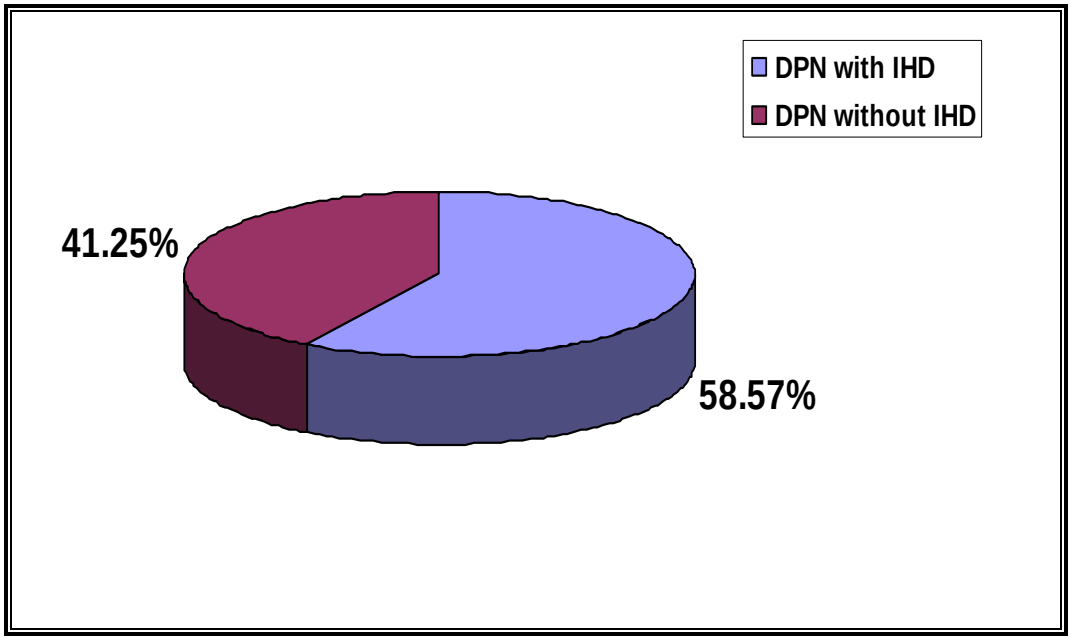


**Figure 1:** Prevalence of IHD in diabetic patients with peripheral

**Discussion:**

In this study, hypertension has been associated with the development of diabetic neuropathy ($P < 0.001$), this agree with other studies(18), while other studies were not able to find associations with PN for blood pressure.(19)

In this study, smoking (classified in two simple categories of never, and current) was not related to prevalence of PN ($P > 0.05$). Although data from some studies suggest a positive relationship between cigarette smoking and PN(20), other studies have failed to confirm this relationship.(21) This lack of association may reflect some pattern of survivorship. Those who smoked may have died of a smoking-related illness, including cardiovascular disease, neoplasia and other causes of death before having opportunity to develop PN.

Smoking narrows and hardens the arteries, reducing blood flow to the legs and feet. This makes it more difficult for wounds to heal and damages the integrity of the peripheral nerves. (22)

This study tried to find the association between Blood Group (ABO System) or Rh System and development of diabetic neuropathy but did not find any association ($P > 0.05$), and didn't come across any such study of this parameter.

Diabetes can cause damage to the kidneys, which may increase the toxins in the blood and contribute to nerve damage.(23) This study was unable to find associations with PN for overt proteinurea and Serum creatinine ($P > 0.05$), and this is consistent with (Janghorbani et al., 2006)(21) in respect to serum creatinine but reverse to the same study in respect to overt oproteinurea.

Significant association between PN and the presence of background or proliferative diabetic retinopathy was not found in this study ($P > 0.05$), while other studies show significant association of PN and the presence of background or proliferative diabetic retinopathy. (24)

Impotency has been used for the evaluation of autonomic nervous system complications in many studies.(25) This study showed a significant association of PN and the presence of impotency ($P < 0.05$) and this is consist with the finding of Mansour, (2009).(26)

The presence of neuropathy is a marker of individuals at increased risk for mortality.(27) Mortality in patients with neuropathy is high, and the cause of death is often coronary heart disease. (28)

Forsblom et al. (1998)(29) in a prospective study of type 2 diabetic patients followed for 9 years observed 29% mortality in subjects with diabetic neuropathy, the majority of whom died from cardiovascular disease suggesting common risk factors. These findings have been supported by data from the Pittsburgh Epidemiology of Diabetes Complications Study. (30)

This study has been found that the prevalence of IHD in patients with diabetic peripheral neuropathy is more than in those without diabetic peripheral neuropathy ($P <0.001$) and it was 58.75%. This finding agrees with other observations. (21)

Although the pathophysiology of PN in DM is not completely clear(31), diabetic polyneuropathy is supposed to be primary a disorder of sensory nerves. Hypoxic neuropathy has been held as important pathogenetic factor. (32) Yokoyama et al., 2007 study hypothesis: (1) Diabetic Polyneuropathy starts before any sign of micro- or macroangiopathy is detectable, and (2) sensory and motor dysfunction occurs concurrently and not sequentially. Hypoxic neuropathy, caused by disturbances in the microvasculature supplying the nerve, has been held as important pathogenetic factor.

This would imply a relation between angiopathy and the appearance of PNP.(33) The presence of microvascular disease is a predictor of coronary heart events. (34)

All the electrophysiological parameters were significantly more abnormal in patients with macroangiopathy than in patients without these complications. (35)

The link between neuropathy and arterial stiffening and/or thickening are: hyperglycaemia which can induce increased polyol pathway activity, dyslipidaemia, formation of advanced glycation end products, and increased protein kinase C activity, leading to increasing oxidative stress and endothelial dysfunction.(33) These mechanisms would affect impaired blood flow and endoneurial hypoxia, which play a major role in causing diabetic neuropathy in human and animal models.(33) They would also increase the inflammatory fibroproliferative response, which damages the endothelium and smooth muscle of the arterial wall, i.e., initiation of the atherosclerotic process.

Polyol pathway hyperactivity has been associated with the progression of intimal thickening of coronary arteries, which was prevented by aldose reductase inhibition in experimental dogs. (36)

## Conclusions:

From the results of this study, it is concluded that:

Nerve conduction study is important method to evaluate peripheral nerve function. They help in the diagnosis, extent and distribution of peripheral neuropathy.

Hypertension significantly affect the prevalence of diabetic peripheral neuropathy while smoking, blood group and Rh system on prevalence of diabetic peripheral neuropathy have no significant effect on diabetic peripheral neuropathy.

Diabetic peripheral neuropathy is significantly associated to the ischemic heart disease and impotence but there is no significance associated with over proteinurea, serum creatinine and retinopathy.

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