Abnormal sweating in diabetes — implications for screening for diabetic peripheral neuropathy

John Simpson

Citation: Simpson J (2018) Abnormal sweating in diabetes — implications for screening for diabetic peripheral neuropathy. *The Diabetic Foot Journal* 21(4): 260–4

Article points

1. Diabetic foot disease is a common and serious complication and can lead to foot ulcers, lower-limb amputations and an early death.
2. National guidelines advocate testing that currently does not include screening for evidence of autonomic neuropathy.
3. Clinical signs of abnormal sweating in the feet of people with diabetes is associated with small nerve fibre disease, which is an earlier sign of neuropathy before all-important protective sensation is lost.

Key words

- Abnormal sweating
- Diabetic peripheral neuropathy
- Early screening

Author

John Simpson is Managing Director of Skyrocket Phytophama (UK) Ltd

Distal symmetric diabetic peripheral neuropathy is a common and much feared complication of diabetes. In people with diabetes, abnormal sweating is one of the earliest detectable neurophysiological abnormalities in small fibre peripheral neuropathy. Conventional tests for autonomic neuropathy can be complex and expensive and are not, therefore, routinely available in a primary care setting. Current clinical tests for the detection of neuropathy as recommended by the National Institute for Health and Care Excellence screen for lack of sensation in the feet, which is a proxy for large nerve fibre disease, or the 'at risk foot', which is a late sign of diabetic foot disease, and may lead to ulceration and eventual amputation. Lack of sensation is, therefore, a sign not of moderate risk, but of high risk, as once protective sensation is lost, it cannot be restored and there are few effective treatments. Therefore, the detection of early signs of clinical neuropathy is essential as it provides a better opportunity to educate patients about the importance of optimal metabolic control in order to prevent progression and in some cases reverse disease.

The autonomic nervous system (ANS) regulates fundamental states of physiology, including the heart rate, salivation, digestion, respiration, pupillary dilation, energy utilisation, temperature, sexual arousal and sweating. The ANS creates the equilibrium between relaxation and excitation required to meet environmental demands and comprises three subsystems: sympathetic, parasympathetic and enteric. It has sometimes been described as the 'Cinderella of neurology' and its assessment by clinical examination is difficult. Assessment by signs is preferable so clinicians rely on tests such as the Valsalva manoeuvre, tilt-table test, nerve fibre biopsy, corneal confocal microscopy (CCM), cold-pressor test and the quantitative sudomotor axon reflex test (QSART) to assess functionality.

Estimates vary as to the prevalence of ANS dysfunction among people with diabetes, but it may be present to some degree in 20–40% of patients (England, 2005). The ANS may fail in a number of ways and cause damage to an organ (heart, kidney), to a system (gastrointestinal, cardiovascular) or in case of diabetic peripheral neuropathy (DPN) to nerves, such as the small unmyelinated nerve fibres in the feet. Damage to these nerve fibres may result in denervation of the sudomotors and, therefore, impact on sweating.

Relevance of sweat testing to assess autonomic neuropathy

The first person to describe clinically abnormal sweating in people with diabetes was the distinguished British physician Dr Frederick William Pavy who stated: "I have seen cases … where the subjects of diabetes perspired only on one side of the body. [A] patient said to me … I find that slight mental exertion causes profuse perspiration on the right side of my head and little upon the left. I cannot refrain from simply saying, in passing, that I believe the disordered nerve conditions which may cause [abnormal sweating] have some connexion with the pathological state at the foundation of diabetes mellitus" (Pavy, 1885).

Sudomotoric dysfunction is one of the earliest manifestations of damage to the small nerve fibres and may result either in an increase or a decrease in sweating, but it is more often the decrease in sweating in the feet of people with diabetes that indicates early signs of DPN (Kennedy, 1984).

Small nerve fibres make up 80%–91% of peripheral nerve fibres and damage to these fibres may result in other common symptoms of neuropathy, such as pain and insensation (Malik, 2005; Said, 2008).

Skin biopsies in people with diabetes have shown that there is a relationship between sweat gland nerve fibre density, symptoms of neuropathy and the production of sweat (*Figures 1* and *2*).

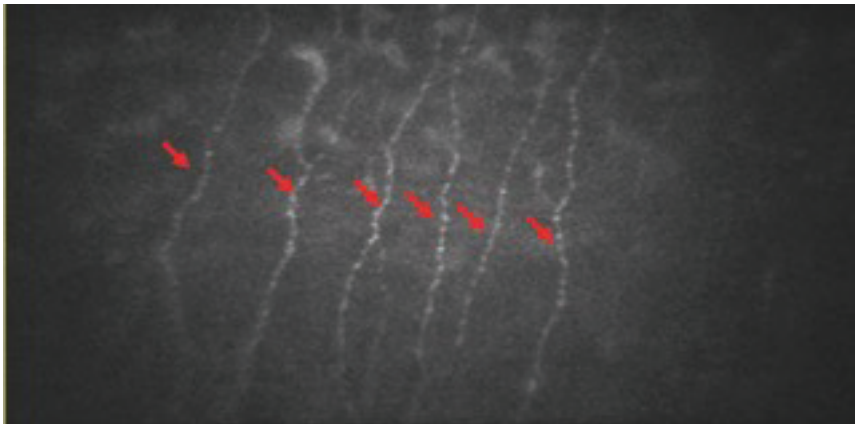


Figure 1. Normal small nerve density in a person without diabetes. Arrows indicate profusions of small nerve fibres in a healthy subject.

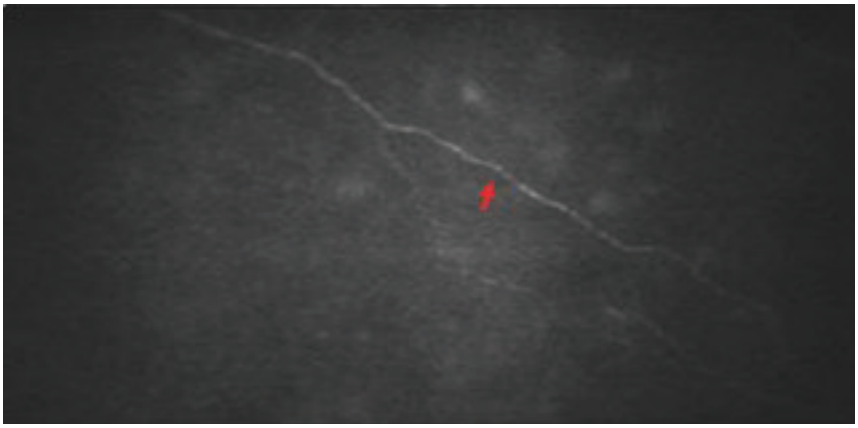


Figure 2. Abnormal small nerve fibre density in a person with diabetes. Arrow indicates the presence of an isolated nerve fibre in an unhealthy subject.

Thermoregulatory sweat testing

In an attempt to improve the diagnosis of autonomic neuropathy in patients, in the 1920s and 1930s two clinicians (Minor, 1928; Roth, 1935) experimented with thermoregulatory sweat testing (TST) by applying anhydrous cobaltrous chloride powder to patients' skin, inducing sweating by elevating the surrounding temperature and measuring the colour change as water from sweat caused the cobalt chloride powder to turn from blue to pink. Although TST was used in several clinics in the United States, and still is (Fealey, 1989), and despite its relative simplicity, clinical usefulness and Roth's own enthusiasm for it, TST did not achieve widespread adoption. However, clinical examination is particularly inadequate for detecting and assessing sweating abnormalities, therefore, a test such as the TST remains a useful screening tool to aid diagnosis. Simplicity, of course, is a relative term and the TST used by Roth (1935) and others employed not only copious quantities of cobalt chloride, but also involved a large chamber being placed over the body of a patient, which was then heated to induce sweating. This was, therefore, only deployed in specialist hospital settings.

The case for improved foot screening

Around 170 diabetes related lower-limb amputations are carried out in NHS England each week and approximately 80,000 people with diabetes have a foot ulcer at any one time with an annual treatment cost in excess of £1 billion (Kerr, 2017). Amputations are at an all-time high, despite efforts to introduce multidisciplinary diabetes foot care teams and there also remains great regional variation in rates of amputation (Kerr, 2017).

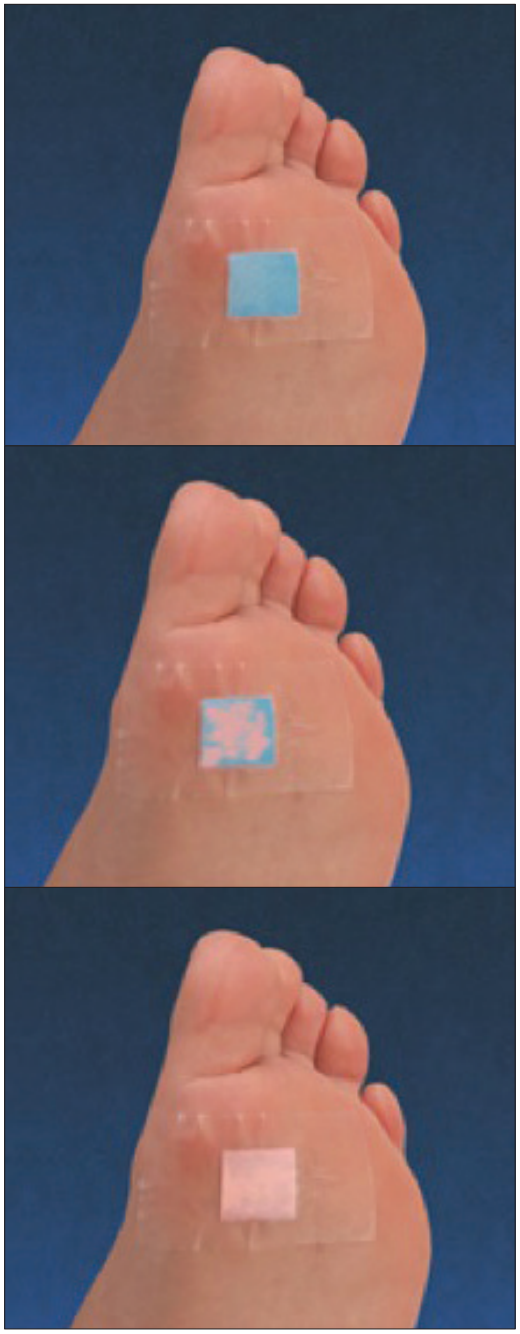
There is controversy around the performance and reliability of commonly used primary care tests for DPN such as the 10-g Semmes Weinstein monofilament examination (SWME) and the 128 MHz tuning fork (TF) for the detection of DPN (Dros, 2009; Wang, 2017). Such tests are subjective rather than objective or categorical and rely on an accurate and discernible patient response. Such tests may only detect established or even advanced neuropathy and, therefore, the 'at risk foot'.

Additionally, the reliance on a patient to healthcare professional verbal communication risks producing both false negatives and false positives, in addition to being inappropriate for patients with significant cognitive or aural deficits, making such tests potentially unreliable (Sanz-Corbalán, 2017). In

Figure 3. Neuropad positioned beneath the first metatarsal. Blue initial colour.

Figure 4. Neuropad partial colour change from blue to pink.

Figure 5. Neuropad complete colour change to pink indicating adequate sweat production.



patients with mild, moderate to severe clinical neuropathy, both the SWME and the TF test fail to diagnose many patients with definite neuropathy. (Perkins, 2001). In fact, the SWME misdiagnoses 29% of patients and the TF in 55%, compared to only 9% of patients being misdiagnosed with nerve conduction studies (NCS) (Perkins, 2001).

DPN is the most common and earliest complication of diabetes and it may occur much earlier in patients with type 1 diabetes (T1D) than in patients with type 2 (T2D) (Won, 2016).

The staging of diabetic neuropathy is crucial. The diagnosis of asymptomatic or preclinical neuropathy is essential in order to stop progression to advanced or irreversible stages and to prevent further complications. Once symptoms appear, there are few effective therapeutic strategies (Javed, 2015).

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complication study (DCCT/EDIC) (Martin, 2014) found that intensive therapy significantly reduced the risk of DPN in patients with T1D by 64% (P<0.01) and that the prevalence and incidence of DPN remained significantly lower in the intensive therapy group compared with the conventional therapy group. The investigators also found that there was a legacy effect of prior intensive therapy on DPN and other complications and that this could still be seen at 14 years. This study provides important information on the influence of glycaemic control and the clinical course of diabetic neuropathy and, most importantly, on how to prevent neuropathy in T1D.

In the landmark United Kingdom Prospective Diabetes Study (UKPDS) (Stratton, 2000), the investigators found that the incidence of clinical complications was significantly associated with glycaemia and that for every 1% reduction in mean HbA_{1c} there were associated reductions in risk of 21% for any diabetes related end point (P<0.0001) and 37% for microvascular complications including DPN. The investigators concluded that "in patients with T2D the risk of diabetic complications was strongly associated with previous hyperglycaemia and that any reduction in HbA_{1c} is likely to reduce the risk of complications, with the lowest risk being in those with HbA_{1c} values in the normal range (<6.0%)".

NICE guideline NG19 diabetic foot problems: prevention and management

It is now generally accepted that symptoms alone have a poor diagnostic accuracy in predicting the presence of neuropathy and that signs are better predictors than symptoms and multiple signs are better predictors than single ones with relatively simple examinations being as accurate as complex scoring systems, such as the Neuropathy Disability Score (NDS) (England, 2005; Vinik, 2016).

Current primary care screening tests for DPN include the SWME developed by Professor Sidney Weinstein, an American neuropsychologist, together with psychologist Dr Josephine Semmes, who created the instrument originally referred to as the Semmes-Weinstein Pressure Aesthesiometer, which is a calibrated series of nylon monofilaments inspired by the Von-Frey horse-hair instrument, which permitted the quantification and classification of sensory loss in blunt trauma brain-injured patients. Other commonly used tests for DPN include the TF.

The National Institute of Health and Care Excellence's guideline *NG 19 Diabetic foot Problems: Prevention and Management* was most recently updated in January 2016. The clinical validity of DPN testing was appraised in NG19 where SWME was recommended despite the lack of clinical evidence for its adoption and use and its moderate to low specificity. In fact, the NICE Guideline Development Group (GDG) considered the predictive accuracy of the different scores and tools and agreed that they would be prepared to accept lower specificity in exchange for higher sensitivity in order to ensure all patients at risk are included in the correct risk categories. The GDG concluded that "false positives were preferable to false negatives given the impact that a foot ulcer can have on a person's life" (NICE, 2016).

Sudomotor function testing

Denervation of both large and small nerve fibres has been implicated in in the development of DPN. Sympathetic skin response has been shown to predict the risk of foot ulceration comparable with a Neuropathy Disability Score (NDS) >5 (Tentolouris, 2009), however, a recent systematic review has called into question the validity of this particular technique (Rajan, 2018).

Neuropad® (Penglioglou, 2018) is a small adhesive plaster with a pad impregnated with a small quantity of cobaltous chloride ($CoCl_2$) in its centre. The anhydrous form is sky blue while the hydrated form is pink. Due to the ease of the hydration/dehydration reaction, and the resulting colour change, cobalt chloride is used as an indicator for the presence of water. It is this simple and easy-to-interpret chemical reaction that is used as a proxy for early small nerve fibre damage by applying a Neuropad to the sole of the feet and waiting until the sudomotors produce enough sweat for a chemical reaction to turn the anhydrous blue cobalt chloride into the pink hydrated form. A cut-off point of 10 minutes is used as a reference. A colour change from blue to pink indicates adequate sweating while either a partial colour change or no change indicates inadequate sweating and therefore sudomotoric dysfunction. A positive (blue) Neuropad result correlates well with the development of ulceration of the foot (Tentolouris, 2010) and may help detect DPN in the absence of other clinical signs and a normal physical examination.

Neuropad has been validated against well-established primary care and hospital-based diagnostic tests for neuropathy (Papanas, 2007; Quattrini, 2008). Neuropad has high sensitivity and good to moderate specificity in the screening of patients with early signs of diabetic foot disease. The sensitivity of Neuropad testing is comparable with NCS, the NDS and vibration perception threshold, which significantly exceeds that seen with the SWME and TF test. (Papanas, 2007; Ponirakis, 2014; Tsapas, 2014)

Reproducibility and repeatability are important characteristics of an effective screening test and Neuropad has near 100% reproducibility with, in addition, very high correlation of results between different healthcare professionals and in patients who tested themselves (Papanas, 2005; Tentolouris, 2008).

In a recent prospective cohort study (Sanz-Corbalán, 2017) of mean 3.5 years duration involving 263 patients with diabetes, Neuropad was evaluated as an adjunctive clinical device to improve the risk stratification of diabetic patients at risk of foot ulceration and to assess whether the earlier detection of diabetic foot disease is enhanced by adding sudomotor function testing (SFT) to assessment using SWME or biothesiometer. The investigators found that a strategy of combining SFT with 10-g SWME increased the sensitivity for the prediction of ulceration to 100% with a specificity of around 30% and that it accurately predicted who may develop a diabetic foot ulcer.

SFT is not only performed to detect early DPN, but should also be included when screening for signs of DPN to predict foot ulceration in patients with diabetes. In a study (Tsapas, 2014) of 379 patients with diabetes, 121 of them developed a diabetes-related foot ulcer and, in the multivariate analysis, the risk increased when the SFT was abnormal. The investigators found that SFT correctly assessed the risk of developing diabetic foot ulcer more accurately than

commonly-used screening methods for the detection of DPN.

Conclusion

Current recommendations for primary care testing for DPN with its reliance on SWME is flawed as it is a screening test for the 'at risk' insensate foot, rather than a test for early neuropathy when protective sensation may still remain. The sensitivity of SWME is also poor for the detection of early neuropathy and, therefore, it cannot be relied upon alone as an effective test for DPN. Primary care screening could be enhanced with the addition of a SFT, such as Neuropad, which increases sensitivity and allows for improved risk stratification, potentially also identifying patients not at high risk of foot ulceration and with home self-testing being feasible (Tentolouris, 2008), it may provide a means of accessing patients who do not attend an annual review and, therefore, do not have their feet examined. ■

Declarations of interest

John Simpson is managing director of Skyrocket Phytophama (UK) Ltd, which distributes Neuropad in the UK and Ireland and is chairman and a director of Lantern Health CIC an NHS primary care health provider in east London.

Dros J, Wewerinke A, Bindels PJ, van Weert HC (2009) Accuracy of monofilament testing to diagnose peripheral neuropathy: a systematic review. *Ann Fam Med* 7(6): 555–8

England JD, Gronseth GS, Franklin G et al (2005) Distal symmetric polyneuropathy: a definition for clinical research: Report of the American Academy of Neurology, the American Association of Electrodiagnostic medicine, and the American Academy of Physical medicine and Rehabilitation. *Neurology* 64(2): 199–207

Fealey RD, Low PA, Thomas JE (1989) Thermoregulatory sweating abnormalities in diabetes mellitus. *Mayo Clin Proc* 64(6): 617–28

Javed S, Alam U, Malik RA (2015) Treating diabetic neuropathy: present strategies and emerging solutions. *Rev Diabet Stud* 12(1-2): 63–83

Kennedy WR, Sakuta M, Sutherland D, Goetz FC (1984) Quantitation of the sweating deficiency in diabetes mellitus. *Ann Neurol* 15(5): 482–8

Kerr M (2017) *Diabetic Foot Care in England: An Economic Study. Insight Health Economics for Diabetes UK*. Available at: https://bit.ly/2zZDJf5 (accessed 08.10.2018)

Martin CL, Albers JW, Pop-Busui R, DCCT/EDIC Research Group (2014) Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care* 37(1): 31–8

Minor V (1928) EinneuesVerfahrenzu derv klinischenUntersuchung der Schweissabsonderung. *ZNervenh* 101: 302–8

Malik RA, Tesfaye S, Newrick PG et al (2005) Sural nerve pathology in diabetic patients with minimal but progressive neuropathy. *Diabetologia* 48(3): 578–85

National Institute of Health and Care Excellence (2018) *Diabetic Foot Problems: Prevention and Management. NICE Guidelines [NG19].* Available at: https://www.nice.org.uk/guidance/ng19 (accessed 09.10.2018)

Papanas N, Papatheodorou K, Papazoglou D et al (2005) Reproducibility of the new indicator test for sudomotor function (Neuropad) in patients with type 2 diabetes mellitus: short communication. *Exp Clin Endocrinol Diabetes* 113(10): 577–81

Papanas N, Giassakis G, Papatheodorou K et al (2007) Sensitivity and specificity of a new indicator test (Neuropad) for the diagnosis of peripheral neuropathy in type 2 diabetes patients: a comparison with clinical examination and nerve conduction study. *J Diabetes Complications* 21(6): 353–8

Pavy FW (1885) Introductory address to the discussion on the clinical aspect of glycosuria. *Lancet* 2: 1033–5; 1085–7

Penlioglou T, Papanas N (2018) New diagnostic tools for diabetic polyneuropathy. *J Gen Emerg Med* 3(2): 103e

Perkins BA, Olaleye D, Zinman B et al (2001) Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care* 24(2): 250–6

Ponirakis G, Petropoulos IN, Fadavi H et al (2014) The diagnostic accuracy of Neuropad for assessing large and small fibre diabetic neuropathy. *Diabet Med* 31(12): 1673–80

Quattrini C, Jeziorski M, Tavakoli M et al (2008) The Neuropad test: a visual indicator test for human diabetic neuropathy. *Diabetologia* 51(6): 1046–50

Rajan S, Campagnolo M, Callaghan B, Gibbons CH (2018) Sudomotor function testing by electrochemical skin conductance: does it really measure sudomotor function? *Clin Auton Res*. doi: 10.1007/s10286-018-0540-0.

Roth GM (1935). A clinical test for sweating. *Proc Staff Meet Mayo Clin* 10: 383–4

Said G, Baudoin D, Toyooka K (2008) Sensory loss, pains, motor deficit and axonal regeneration in length-dependent diabetic polyneuropathy. *J Neurol* 255(11): 1693–702

Sanz-Corbalán I, Lázaro-Martínez JL, García-Morales E et al (2017) Advantages of early diagnosis of diabetic neuropathy in the prevention of diabetic foot ulcers. *Diabetes Res Clin Pract* doi: https://doi.org/10.1016/j.diabres.2017.12.018

Stratton IM, Adler AI, Neil AW et al (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321(7258): 405–12

Tentolouris N, Achtsidis V, Marinou K, et al (2008) Evaluation of the self-administered indicator plaster neuropad for the diagnosis of neuropathy in diabetes. *Diabetes Care* 31(2): 236–7

Tentolouris N, Marinou K, Kokotis P et al (2009) Sudomotor dysfunction is associated with foot ulceration in diabetes. *Diabet Med* 26(3): 302–5

Tentolouris N, Voulgari C, Liatis S et al (2010) Moisture status of the skin of the feet assessed by the visual test Neuropad correlates with foot ulceration in diabetes. *Diabetes Care* 33(5): 1112–4

Tsapas A, Liakos A, Paschos P et al (2014) A simple plaster for screening for diabetic neuropathy: a diagnostic test accuracy systematic review and meta-analysis. *Metabolism* 63(4): 584–92

Vinik AI, Casellini C, Nevoret ML (2016) Alternative quantitative tools in the assessment of diabetic peripheral and autonomic neuropathy. *Int Rev Neurobiol* 127: 235–85

Wang F, Zhang J, Yu J et al (2017) Diagnostic accuracy of monofilament tests for detecting diabetic peripheral neuropathy: a systematic review and meta-analysis. *J Diabetes Res* doi: 10.115/8787261.

Won JC, Park TS (2016) Recent advances in diagnostic strategies for diabetic peripheral neuropathy. *Endocrinol Metab (Seoul)* 31(2): 230–8