WITHINGS

The Science Behind

Body Pro 2

Electrochemical Skin Conductance

The Importance of Electrochemical Skin Conductance Measurement within the Medical Community

What is the link between electrochemical skin conductance and the sudomotor function?

Electrochemical skin conductance is a non-invasive measurement of the sudomotor function[1]. In other words, it measures sweat gland innervation and assesses disorders of the autonomic nervous system, which is a component of the peripheral nervous system[2,3].

What is the autonomic nervous system ?

The autonomic nervous system is a component of the peripheral nervous system that regulates involuntary physiologic processes including heart rate, blood pressure, respiration, digestion, and sexual arousal. It contains three anatomically distinct divisions: sympathetic, parasympathetic, and enteric[3]. Sweating is under the control of the sympathetic nervous system, which orchestrates the body's reaction to stressful situations and emergencies.

What is the sudomotor function and how can it be impaired?

Sweat glands produce water to regulate body temperature and evacuate small molecules. Specific eccrine sweat glands without hair are located on hands and feet and are innervated by thin, unmyelinated sympathetic C nerve fibers. In patients with diabetes, studies have shown a reduction in those C fibers leading to sudomotor dysfunction[4,5] . This type of peripheral autonomic neuropathy (PAN) is one of the earliest detectable abnormalities in distal small fiber neuropathies affecting sudomotor function. Consequently during the last two decades, assessing sudomotor function became furthermore important in the early detection of peripheral autonomic neuropathy in diabetes[6] but also other diseases[7].

What is peripheral autonomic neuropathy?

Peripheral autonomic neuropathy refers to the damage to the nerves of the peripheral nervous system (nerves located outside the brain and the spinal cord). The prevalence of peripheral neuropathy is estimated at 1% of the adult population and over 10% of the population over 55 years old[8]. Peripheral neuropathy often causes weakness, numbness, loss of sensation or pain, usually in the hands and feet, and is independently associated with increased mortality.

What can cause peripheral autonomic neuropathy?

The most common cause of autonomic neuropathy is diabetes, especially when sugar levels are poorly controlled[9] for type 1. This is known as diabetic peripheral neuropathy (DPN). The blood sugar high concentration damages blood vessels that cannot bring nutrients and oxygen to small nerves, that then die. Peripheral autonomic neuropathy is the most prevalent chronic complication of diabetes[10–12] with an estimated prevalence of more than 50% among patients with diabetes[2,11,12]. Of these patients, 50% are asymptomatic[13]. But diabetes is not the only cause of neuropathies. There are diseases like cystic fibrosis or neurodegenerative diseases that can cause neuropathy symptoms.

How can peripheral autonomic neuropathy cause sudomotor dysfunction?

The small fibers innervating sweat glands are the smallest in the body, have slower conduction, and are unmyelinated, which makes them more vulnerable. Naturally, because the small fibers located in the feet are the longest and some of the most fragiles within the body, small fiber neuropathies tend to affect the feet first and then progress upward. The degeneration of these small fibers, one of the first signs of peripheral autonomic neuropathy, reduces sweat gland innervation. The loss of nerves in the sweat gland turns off the gland function and its ability to react to nerve stimuli by producing sweat in appropriate situations.

Why does it matter?

Diabetic wounds

If an individual is experiencing poor sweat gland function, it will lead to drier skin on the feet, making the skin crack easily, and increasing the risk of wounds.
In diabetic wounds, issues like tissue ischemia, hypoxia, high glucose microenvironment and skin dryness disrupt the healing process, leading to delayed or nonhealing wounds and clinical complications. In some cases it leads to amputations and in the worst cases to death. Generally, the loss of sudomotor function is a signal that nerves have been damaged. It can be diseases directly related to the nervous system or a consequence of a decreased vascularisation, as in diabetes. In every case, it is a strong signal that a disease is developing and should be checked before aggravation or unrepairable wounds appear.

Risk of developing a Diabetic Foot Ulcer (DFU)

In diabetic wounds, issues like tissue ischemia, hypoxia, high glucose microenvironment and skin dryness disrupt the healing process, leading to delayed or non healing wounds and clinical complications such as Diabetic Foot Ulcer[14,15].
Diabetic Foot Ulcer is among the most common complications of diabetes when the disease is not well controlled. Usually caused by poor glycemic control, underlying neuropathy, peripheral vascular disease, or poor foot care[16].

The lifetime risk of a person with diabetes developing a foot ulcer may be as high as 25%, whereas the annual incidence of foot ulcers is 2%[17]. The life expectancy of patients with neuropathic foot ulceration is approximately 50% at 5 years. This outcome is worse than many of the major cancers, including breast, colon, and prostate[10].

Diabetic neuropathy is common but often misdiagnosed and undertreated[12]. Whilst acute diabetic neuropathy nearly always presents with clear symptoms easily recognized by diabetes specialists, it is the gradually progressive neuropathy with a silent onset that predominates, causing the bulk of the morbidity and mortality, and is often noticed at a well-advanced stage[10].

Early detection and appropriate treatment of these foot ulcers may prevent up to 85% of amputations according to AAFP (American Academy of Family Physicians)[18]. Indeed, one of the disease prevention objectives outlined in the “Healthy People 2000” project of the U.S. Department of Health and Human Services is a 40% reduction in the amputation rate for patients with diabetes[19].

What are the other approaches than ESC to evaluate nerve health?

Diabetes peripheral neuropathy is a crucial indicator of foot ulcer risk, yet there is a lack of reliable, non-invasive, rapid, and easy-to-use tools to identify this neuropathy[4,20].

Current tools include:

- **Monofilament test** - This test is performed by having patients close their eyes while a physician presses the monofilament to the skin until it bends. If the patient doesn't feel it, it means that they have a high risk of developing ulcers. Monofilament test has limited sensitivity for screening diabetic peripheral neuropathy—47% of patients with neuropathies will be misdiagnosed as having no neuropathy with the monofilament test[21].
- **IEFND / SGNFD tests** - Intraepidermal or Sweat Gland Nerve Fiber Density testing is considered the gold standard for diagnosing small fiber neuropathy. Both tests consist of doing a skin biopsy to quantify and evaluate the integrity of the nerves in a laboratory with results in about 7 days. Even though they are widely accepted techniques, IEFND & SGNFD are invasive procedures[22].

Diabetic peripheral neuropathy can be detected by a complete patient history and clinical exam. However, it is insufficient to diagnose it during early asymptomatic stages[22].
No cure exists for diabetic peripheral neuropathy. Treating DPN mainly consists in controlling blood sugar levels to prevent further nerve damage, and various medications can be used to decrease the pain associated with it. Some behavior changes such as regular physical activity may also help prevent it, curb progression, and reduce pain[22].
Knowing that 50% of patients with neuropathy may be asymptomatic,[1] it is critical to detect diabetic peripheral neuropathy early and monitor it regularly[22].

The Electrochemical Skin Conductance in Body Pro 2

Withings implemented Sudoscan® technology in Body Pro 2 to bring electrochemical skin conductance to an at-home setting.

Introducing Sudoscan®

Sudoscan®, manufactured by Impeto Medical, now part of Withings, is a simple, non-invasive, easy-to-perform sudomotor test that was recently developed to measure sweat gland function. This test is based on the electrochemical reaction between the chloride ions in sweat and stainless steel-based plate electrodes, on which the subject's hands and feet are placed (Figure 1). The patient is asked not to move for 3 minutes and a low-voltage current (< 4 V) is applied through the electrodes, attracting chloride ions from the sweat glands, which are densely concentrated on the palms of the hands and soles of the feet. Sudoscan® provides a quantitative measure of chloride conductance—measured in µsiemens—and its results serve as a biomarker to assess sweat gland function in relation to sweat gland innervation. As the degeneration of small nerve fibers reduces sweat gland innervation and impairs sudomotor function, high conductance means no dysfunction of sweat glands whereas low conductance means dysfunction of sweat glands reflecting neuropathy.

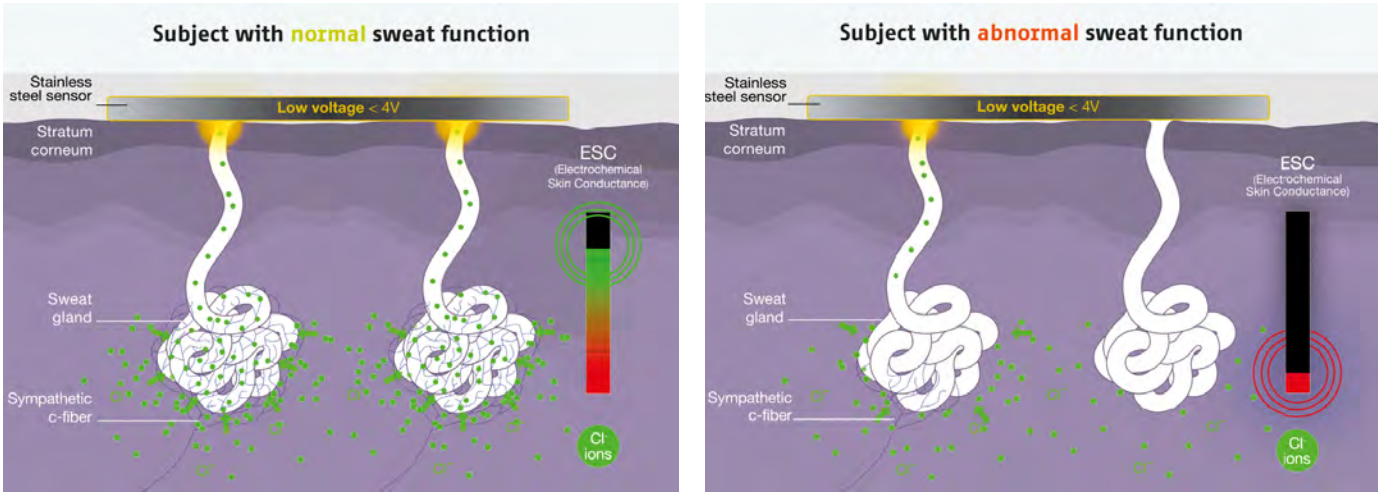
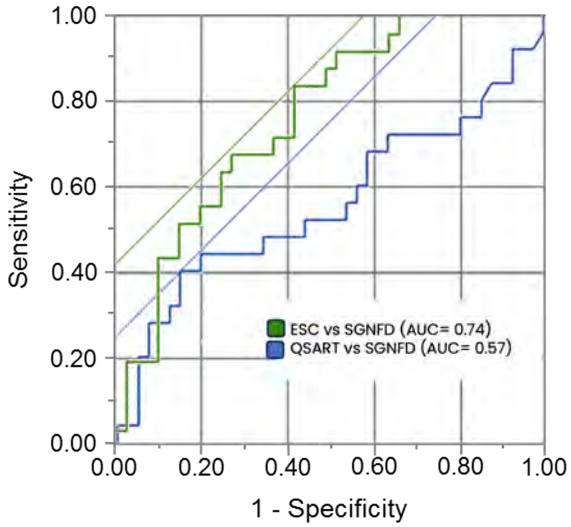


Figure 1. Sweat conductance normal and abnormal sweat function (Impeto, 2021)

Sudoscan® measurement performance

Comparison study between Sudoscan® and Skin Biopsy

A study of 200+ patients was conducted to compare Sudoscan® and Sweat Gland Nerve Fiber Density (SGNFD), assessed by a skin biopsy. In parallel, the comparison was also made between the QSART technique (Quantitative Sudomotor Axon Reflex Test) created and used by the Mayo Clinic[23] and the skin biopsy (SGNFD). It is proven that Sudoscan® has a good correlation with SGNFD (AUC = 0.74) compared to other types of measurement such as QSART (AUC = 0.57)[1].



As stated before, skin biopsies such as IEFND & SGNFD are invasive techniques compared to Sudoscan® which has proven to be a reproducible and repeatable method for screening and monitoring diabetes neuropathy[23–25].

In conclusion, Sudoscan® is a non-invasive and sensitive tool to detect diabetic peripheral neuropathy.

Implementation of Sudoscan® measurement in Body Pro 2

Body Pro 2 measures the electrochemical skin conductance using Sudoscan® 's technology enabling healthcare professionals to detect early signs of diabetic peripheral neuropathy[24–26].

Accuracy of Body Pro 2

An equivalence study tested the performance of Withings scales versus Sudoscan® for patients across 4 leading Parisian Hospitals. The study was made using a Body Scan® which integrates the same algorithm used in Body Pro 2.

The study was conducted with patients suffering from diabetes with or without neuropathy or non-diabetic patients suffering from lower-limb neuropathy. The diagnostic performance of the Withings measurement was assessed by calculating its sensitivity (Se) and specificity (Sp) to detect at least moderate SFN (Se70 and Sp70), defined by a value of feet ESC ≤70µS and >50µS on the Sudoscan® measure, or severe SFN (Se50 and Sp50), defined by a value of feet ESC ≤50µS on the Sudoscan® measure. The agreement between the two devices was assessed with the analysis of Bland-Altman plots, mean absolute error (MAE), and root mean squared error (RMSE) calculations. The repeatability of the measurements was also compared between the two devices.

A total of 147 patients (52% men, mean age 59 years old, 76% diabetic) were included in the analysis. The sensitivity and specificity to detect at least moderate or severe SFN were: Se70=0.91 ([0.83, 0.96]), Sp70=0.97 ([0.88, 0.99]), Se50=0.91 ([0.80, 0.98]), and Sp50=0.99 ([0.94, 1]), respectively. The bias and 95% limits of agreement were 1.5 [-5.4, 8.4]. The MAE was 2.9 and the RMSE 3.8. The intra-sample variability was 2.0µS for the Withings scale and 2.3µS for the Sudoscan®.

The ESC measurements provided by the Withings scale were in almost perfect agreement with those provided by the reference device, the Sudoscan®, which validates the accuracy of the Withings scale for the detection of SFN. By enabling simple, rapid and autonomous use by the patient at home, this new technique will facilitate screening and monitoring of SFN in daily practice.

The results are very conclusive in terms of equivalence, repeatability, and reproducibility[27].

Intended use (FDA)

FDA - Withings Body Pro 2 is intended for the measurement of electrochemical skin conductance to aid in the assessment of sudomotor function. The results are intended to be transmitted to the user via the companion app. The results are also transmitted to a web server for remote review by clinicians or researchers.

The benefits of having the ESC measurement in the at-home setting

Body Pro 2 can help with readily identifying diabetes complications and offering timely interventions on a consistent basis.

While Sudoscan® tests are conducted at the medical clinic once or twice a year, and allow a more in-depth measurement thanks to the asymmetry assessment and the measurement of hands in addition to feet; Body Pro 2 is here to enable physicians to remotely monitor their patients on a daily basis and offers long-term monitoring to identify any decline in patient ESC measurements, which may indicate early-stage small fiber neuropathy, and act on it early.

In the case of peripheral neuropathy, early detection is crucial for the following reasons:

- Early identification of the etiology may allow for a focused screening and prevent further damage to nerves by potentially reversing nerve damage[10,13,28].
- Small fiber dysfunction can be present even in the absence of disordered pain sensation[10].
- SFN may precede large fiber neuropathy, especially in type 2 diabetes and in states of impaired glucose tolerance such as prediabetes[10].

Treatment of peripheral neuropathy focuses on managing the underlying etiology. Small fiber reinnervation has been observed in prediabetic patients[29] and even in stages of established diabetes[10], proving that it is possible to reverse diabetic peripheral neuropathy, especially in its early stages. Unfortunately, neuropathic pain may be the first abnormal sign that prompts patients to seek medical care[30]. If polyneuropathy is diagnosed late in the course after a significant axonal loss has occurred, the neurologic deficits may be irreversible[28].

Body Pro 2 is adapted for frequent measures:

- It is fast
- It is non-invasive
- It is objective/provides quantitative results
- It is user friendly

In terms of clinical benefits:

- **It contributes to early detection of peripheral autonomic neuropathy. It facilitates patient screening and helps physicians treat the disease earlier thus reducing the impact of the disease on the population.**
- **It allows users to monitor disease advancement or regression. For example, If a patient has already been diagnosed with peripheral autonomic neuropathy, the device can help in the follow-up of the disease. It may, for instance, reflect the effects of treatment.**
- **It also increases awareness of physiological conditions in the general user population.**

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