# Sudomotor Function Assessment by Sudoscan among Diabetic Algerian's Patients

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## Abstract

**Purpose:** To address if there is an increased frequency of abnormal Electrochemical Skin Conductance (ESC) findings in patients with paresthesia, we performed a prospective observational study.

**Methods and Results:** 199 consecutive diabetic Algerian patients were evaluated by sudoscan. 12 patients with T1DM (31% of all with T1DM), 50 with T2DM (43%), and 26 with T2DMI (60%) have abnormal ESC. After multivariable adjustment for potential confounders, analysis of patients with ESC abnormalities showed that women with paresthesia have more Diabetic Peripheral Neuropathy (DPN). Therefore, the diagnostic efficacy of the sudoscan in women is particularly good (AUC: 85.1%), much better than for men (AUC: 69.97%). Overall, the Receiver Operating Characteristics (ROC) curve for sudoscan at 71.9% indicates a poor discriminant between asymptomatic and patients with paresthesia.

**Conclusion:** Sudoscan procedure, which allow a noninvasively assessment of risk of DPN was reliable only in the female patients. The ESC is lower in the group with insulin treatment related to the longer disease duration. The paresthesia group has a worse glycemic control than asymptomatic patients.

**Key Words:** Small Fiber Neuropathy (SFN) • Diabetic Peripheral Neuropathy (DPN) • Electrochemical Sweat Conductance (ESC) • Diabetes Mellitus Type 1 (T1DM) • Diabetes Mellitus Type 2 (T2DM) • Diabetes Mellitus Type 2 Insulin Dependent (T2DMI).

## Introduction

The prevalence of diabetes in the Middle East and North Africa (MENA) is about 11% of the population [1]. The reported incidence of Diabetic Peripheral Neuropathy (DPN) in North Africa ranges from 24% in the Tunisian population and even 45.6% in the Moroccan population [2,3]. Compared to the French population, the incidence of neuropathy in an Algerian group was higher and occurs earlier [4]. As a length-dependent neuropathy, diabetes is characterized by progressive axonal degeneration initially involving distal small unmyelinated fibers whose anatomical changes predict degeneration of epidermal nerve fibers in painful neuropathies [5]. Because the clinical signs of DPN have moderate sensitivity, a range of tools to detect early diabetic neuropathy was proposed including a skin biopsy to assess epidermal nerve fiber density [6]. In contrast, the sudomotor tests have only limited sensitivity but it was shown that sudoscan as a reproducible and quantitative procedure correlates well with clinical signs and symptoms of neuropathy [7-9].

### Objective

Our objective was to evaluate the efficacy of sudoscan device in detecting small fibers involvement in a cohort of Algerian diabetic patients. We hypothesized that inside our cohort, the diabetic patients experiencing paresthesia, as a term that covers all abnormal sensations, would exhibit worse small fiber function than individuals without paresthesia. We also intended to speculate on the potential mechanisms involved.

## Patients and Methods

### Study population

199 outpatients, 85 women and 114 men, ages ranging from 11 to 82 years, mean 52.65, (39 with T1DM, 117 with T2DM, and 43 with TI2DM) were sequentially evaluated (**Table 1**).

The following exclusion criteria were used: limbs amputation, bedridden patients, end-stage kidney disease, or neurologic disorders that could be associated with neuropathy. The goal of the study was explained to each patient and written informed consent was then obtained. Patients were allocated to one of two groups depending on the presence (Y) or absence of paresthesia (N) defined as abnormal limb sensations. Description of the variables: HbA1c, the type of glycated hemoglobin, Hb1 (5% to 7.1%), Hb2 (7.2% to 8.8%), gender, the type of diabetes, (**Table 2**), paresthesia: presence (Y) or absence (N) of paresthesia as a binomial qualitative variable to be explained.

While the patients with DNID are equally divided into the two groups, this is not the case for patients with DID and DiDR patients who have different proportions between the two groups. Patients with DiD are more represented in the non-paresthesia group while patients with DNID appear to be more represented in the paresthesia group.

### Neuropathy assessment

All patients underwent clinical assessment and have had a detailed medical history. Age, duration of disease, sex, and Body Mass Index (BMI) according to weight and height measured on site, were recorded. The sudomotor function was assessed by a sudoscan device (Impeto Medical, Paris, France). The Electrochemical Sweat Conductance (ESC) expressed in micro siemens (µS) was determined in each palm and each sole placed on stainless steel plates which interact with the chloride ions in sweat following an incremental DC low voltage. ESC expressed in micro siemens (µS) is the measure of asymmetry between the two hands and the two feet because of the symmetric and distal characteristics of the DPN.

**Table 1.** Proportions of age groups for both paresthesia groups.

| Age Groups | Paresthesia | Population | % (N or Y) |
|---|---|---|---|
| (11, 42.6) | N | 27 | 24 |
| (42.6, 51) | N | 29 | 26 |
| (51, 58) | N | 21 | 19 |
| (58, 64) | N | 21 | 19 |
| (64, 82) | N | 13 | 12 |
| (11, 42.6) | Y | 13 | 15 |
| (42.6, 51) | Y | 15 | 17 |
| (51, 58) | Y | 17 | 19 |
| (58, 64) | Y | 19 | 22 |
| (64, 82) | Y | 24 | 27 |

**Table 2.** Number and proportions of different types of diabetes by group (absence (N) and presence (Y) of paresthesia).

| Diabetes By Group | N | Y |
|---|---|---|
| Did | 27 (24.3%) | 12 (13.6%) |
| DNiD | 67 (60.4%) | 50 (56.8%) |
| DidR | 17 (15.3%) | 26 (29.6%) |

## Statistical analyses

Statistical analyses were performed with the open-source software "R" (version 3.5.1.). All quantitative variables were described by descriptive statistics. The statistical significance level (p-value) was set at 0.05. The patients were matched for gender, age, BMI, and diabetes types. Two methods were used to explain the presence or absence of paresthesia in patients, a multifactorial descriptive method, and an inferential method. A Principal Component Analyze (PCA) was performed on ranked values (because of non-normality) for all patients, to investigate the relations between the occurrence of paresthesia and all other quantitative measures followed by a Hierarchical Classification of Principal Component (HCPC). The PCA is used to describe the quality of segregation of subjects according to the quantitative variables measured. The diagram of individuals will allow observing if there is a correlation between the individuals, i.e. if some patients are close to each other based on the quantitative variables measured. This analysis also makes it possible to visualize the relationships between the variables and thus to see if there are correlations (positive or negative) between certain quantitative variables measured. The pieces of information are then reunited to identify whether the patient groups are characterized by a high value of one variable or a low value of another. Some variables involved in the analysis have non-normal distributions. Normality of data is one of the conditions of application of the PCA. The PCA was therefore carried out on variables transformed into rows to address this problem.

The PLS-DA was the best model assessed through a confusion matrix, the ROC curve (Receiver Operating Characteristic), and AUC (Area under the Curve). Odds-ratio was assessed for quantitative variables and the chi-squared test was performed on the qualitative variables.

# Results

## Baseline characteristics

The proportions of the age categories are different between the paresthesia (Y) and absence of paresthesia (N) groups, especially for the age groups (11, 51) and (64, 82) as younger patients tend to have less paresthesia than older patients. The mean age of patients with paresthesia is 56 years versus 50.6 years of the patients without paresthesia.

In women the only minor difference between patients with and without paresthesia whereas in men, are very few cases of paresthesia in the youngest subjects.

**BMI:** The mean BMI for individuals with paresthesia was 28.86 *versus* 27.48 for those without paresthesia, greater in women at 29.44 than in men at 27.08.

**Type of diabetes:** The patients with type 2 diabetes with and without paresthesia are equally divided between the two groups, whereas the incidence of paresthesia in the T1DM patients is half of that of patients without paresthesia.

**Patient's age:** The distribution of age of patients is similar for both groups and asymmetrical on the side of the oldest patients **(Figure 1).**

The distributions are similar for both groups. The data are asymmetrical upon the side high values. The median value of patients with paresthesia is higher than the median value of patients without paresthesia.

**Patient's height:** Concerning the patient's height, the distributions are similar and normally distributed (170 cm for the patients without paresthesia versus 165 cm for patients with paresthesia) **(Figure 2)**.

The distributions are unimodal. They are similar and seem normally distributed.

**Patient's BMI:** Depending on BMI, both distributions are similar and multi-modal. The patients with paresthesia have higher BMI values **(Figure 3).**

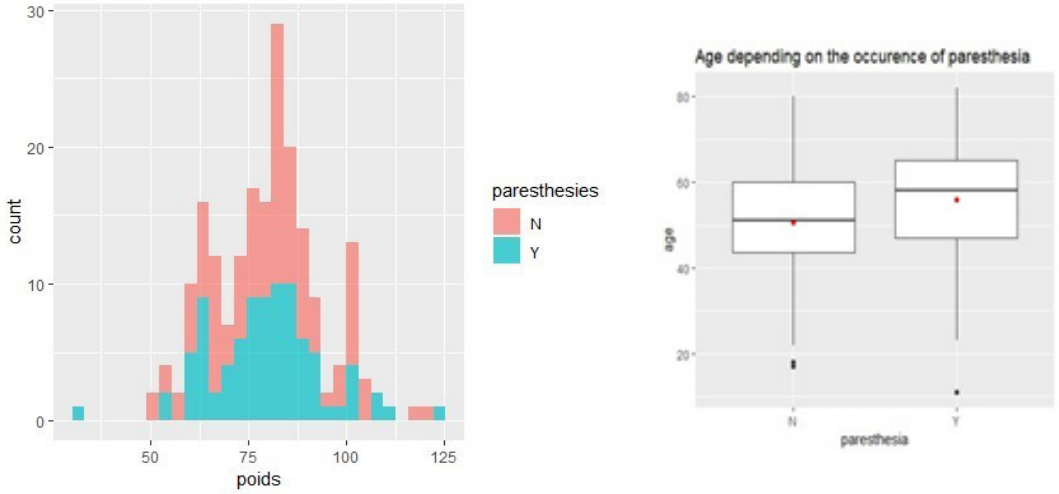


**Figure 1.** Depending on the age of the patients.

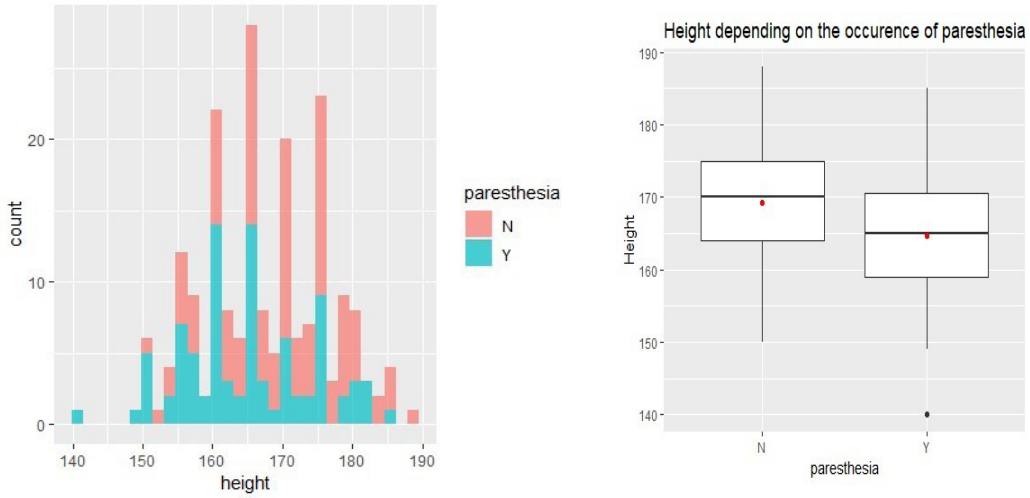


**Figure 2.** Depending on the height of the patients

The patients with paresthesia have higher BMI values, unlike patients without. Only the paresthesia group has non-standard values on either side of the distribution.

**Patient's HbA1c:** Both distributions of glycated hemoglobin are unimodal and asymmetrical with a median of the HbA1c in the Y group (with paresthesia) of 7.55, higher than that of N patients (without paresthesia) of 6.80 **(Figure 4).**

The two distributions are similar, unimodal, and asymmetrical upon the side of low hemoglobin glycated percentage values. The median percentage of glycated hemoglobin in the paresthesia group is higher than that of patients without paresthesia.

Several out-of-norm values in high values are present in both groups and are responsible for the dissymmetry of the distribution.

**Patient's ESC-H and ESC-F:** ESC-H and ESC-F: For ESC-H and ESC-F, the two distributions are also similar and asymmetrical on the side of high levels of electron conductance. The median of ESC-F in Y patients is lower than that in N patients, 80.5 µS versus 83 µS **(Figures 5 and 6).**

The median feet electron conductance of patients with paresthesia is lower than that of patients without paresthesia. Several out-of-norm values in low values are present in both groups.

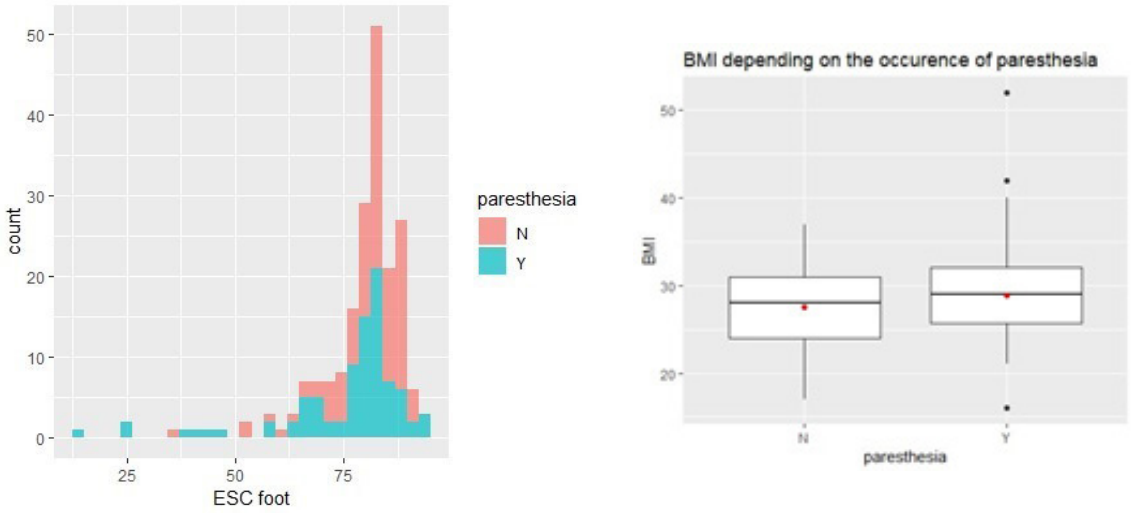


**Figure 3.** Depending on the weight of the patients.

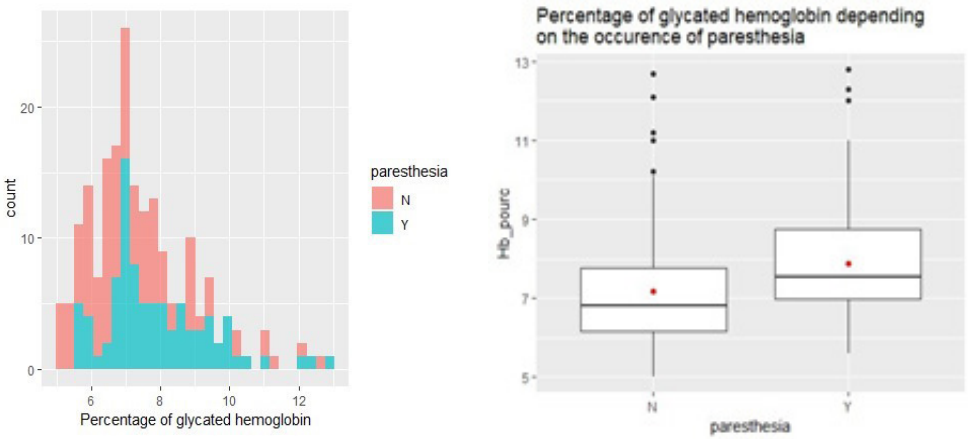


**Figure 4.** Depending on the HbA1c of the patients

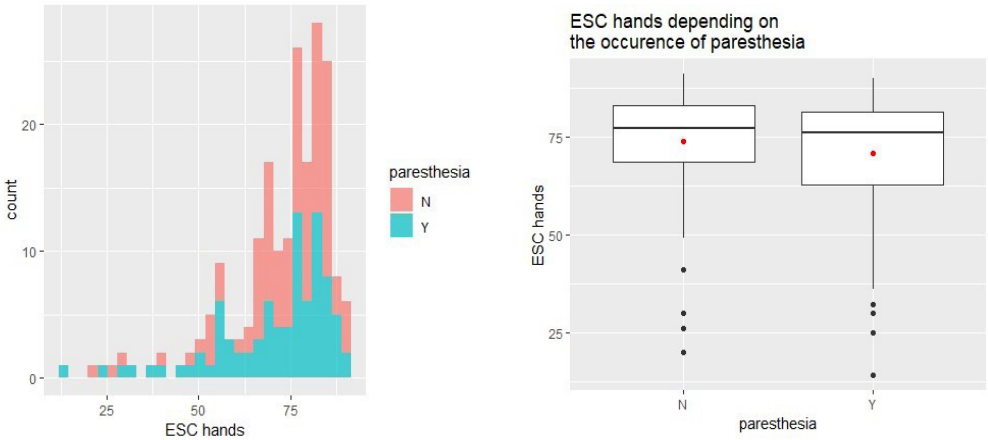


**Figure 5.** Depending on the hands ESC of the patients

## Multifactorial Description of Data

### Principal Component Analyze (PCA)

The Principal Component Analyze (PCA) was performed on ranked values (because of non-normality) for all patients, to investigate the relations between the occurrence of paresthesia in patients and all other quantitative measures **(Figure 7).**

The two groups with paresthesia (Y) and without paresthesia (N) are surrounded by a trusted ellipse using individual coordinates. The color rectangles are at the center of gravity of each group. ESC, height, and HbA1c allow discrimination between Y and N patients. Discrimination between patients with paresthesia (Y) and those without (N) is not visible in the first factorial design as the two clouds of points strongly overlap.

**Hierarchical Classification on Principal Component (HCPC):** This allows discriminating between the subjects with and without paresthesia through the BMI and ESC according to age.

**Inferential statistics:** Of all the models tested the top three are PLS-DA, Random Forest, and SVM **(Figure 8).**

The percentage of good variables classified with the PLS-DA model is 67.8%, statistically significantly; p=0.00034 **(Figure 9)**.

The ROC curve, with 71.9% area under the curve, indicates a distribution between patients with and without paresthesia not better than a random distribution.

The best variables to discriminate among Y and N patients are height, HbA1c, ESC-F, age, and type of diabetes. Group descriptions by quantitative variables (weight, BMI, Hand ESC, Foot ESC, height, HbA1c, and age): the variables are sorted in order of importance of the difference

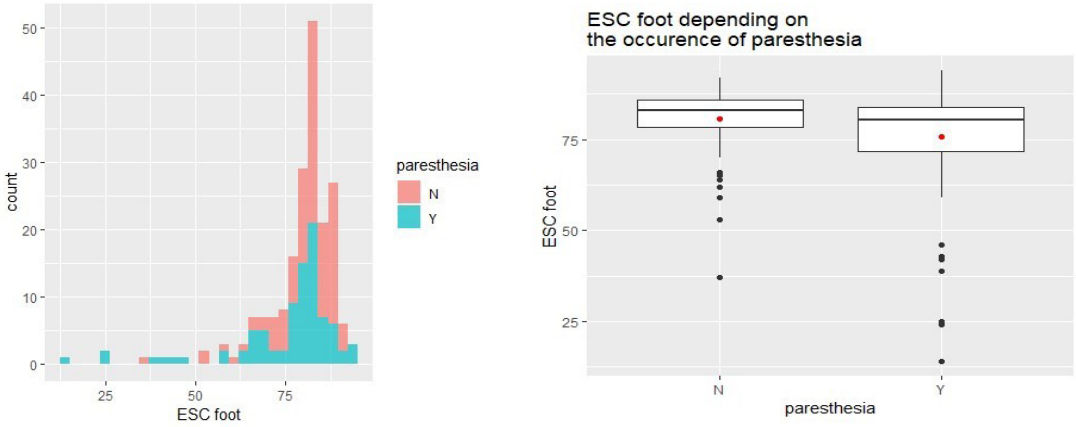


**Figure 6.** Depending on the feet ESC of the patients.

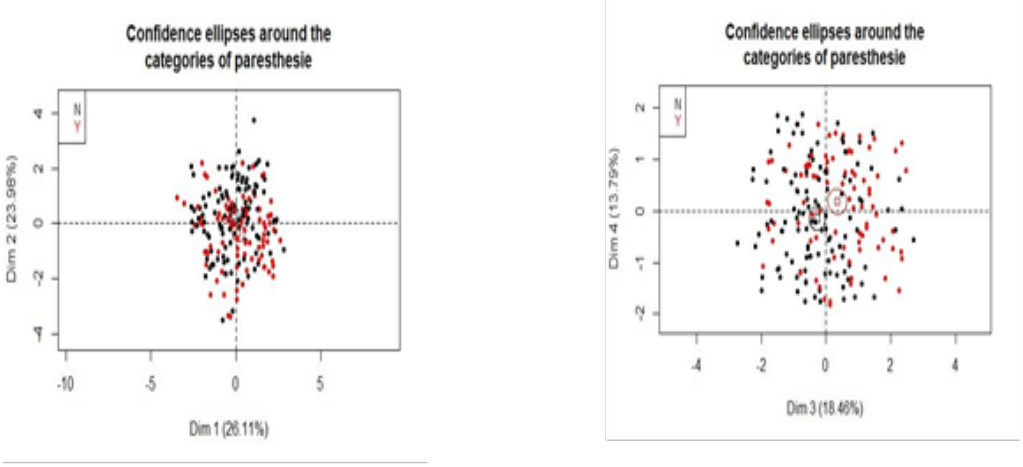


**Figure 7.** Analyze the quantitative variables age, height, weight, BMI, HbA1c, and ESC between patients with and without paresthesia.

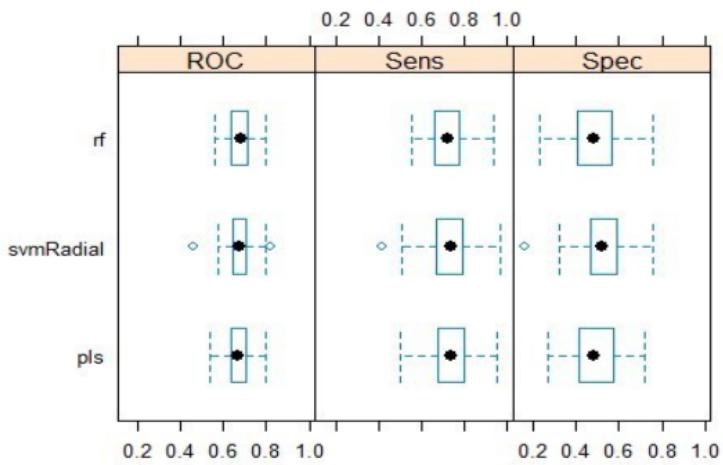


**Figure 8.** Assessment of the ROC, sensitivity (Sense), and specificity (Spec) parameters to estimate the quality of the various pre-selected models.

between groups. The Eta2 value is the result of an ANOVA (variance analysis) between the groups for each variable. A large value of Eta2 indicates a significant difference between the groups. The larger the value of Eta2, the smaller the p-value. The Eta2 values, although significant for all variables except the percentage of glycated hemoglobin, is quite low (< 0.6).

Group 1 presents mean values of conductance variables higher than the general mean (82.0 ± 4.8 µS versus 72.5 ± 14.2 µS, respectively for hands and 85.7 ± 3.3 µS versus 78.5 ± 12.0 µS, respectively for feet) and average values lower than general averages for all other variables, mainly for weight and BMI (72.1 ± 10.0 kgs versus 79.8 ± 14.1 kgs, respectively for weight and 26.0 ± 3.9 units versus 28.1±4.9 units, respectively for BMI).

Group 2 is characterized by a higher mean age value than the general mean (59.9 ± 14.2 years versus 52.9 ± 14.0 years, respectively) and by mean values of all other variables lower than the general mean, especially for conductance in the feet and weight (68.0 ± 15.7 µS against 78.5 ± 12.0 µS, respectively for feet and 67.9 ± 7.7 kgs against 79.8 ± 14.1 kgs, respectively for weight).

Group 3 is characterized by mean values of weight, BMI, and height higher than the general averages (weight: 91.5 ± 9.6 kgs against 79.8 ± 14.1 kgs, respectively, BMI: 31.3 ± 4.1 units against 28.1 ± 4.9 units, respectively and height: 170.3 ± 8.8 cm against 167.2 ± 8.9 cm, respectively). This group has average hand and foot conductance values like the general averages (78.1 ± 10.1 µS and 70.4 ± 12.7 µS, respectively).

The classifications carried out on the main components of the PCA for women and men separately also lead to three groups of individuals. For women, these groups differ in their values from the variables classified, feet and hand ESC, BMI, weight, and HbA1c. For men, they differ by their values of all quantitative variables except age and by the qualitative variables 'classifications_age', 'classifications_BMI', and 'TYPE.DIABETE'.

The data concerning the presence of paresthesia concerns only a little more than 30% of the total variability of the point cloud.

## The Model Applied To The Women Diabetic Patients

The percentage of well-classified patients is 81.2%, which is statistically significant (p =1.65.10-8) (**Figure 10**).

The ROC curve, with 85.1% area under the curve, shows a distribution of Y and N women significantly better than a random distribution. The best variables to discriminate the women with paresthesia from those without are HbA1c, the type of diabetes, ESC-F, ESC-H, and BMI. The Y patients have odds-ratios less than 1 meaning a relationship with small values of height and ESC-F whereas odds-ratios greater than 1 imply a significant association of symptomatic patients with greater values of HbA1c and age.

For the model PLS-DA, the variables which allow discriminating the Y and N women are HbA1c, type of diabetes, ESC-F, ESC-H, and BMI. For the variable TYPE.DIABETES, the chi² test indicates a significant association between the occurrence of paresthesia and the type of diabetes with a p-value of 0.02276 (Chi² =7.57). There is a higher proportion of T1DM in

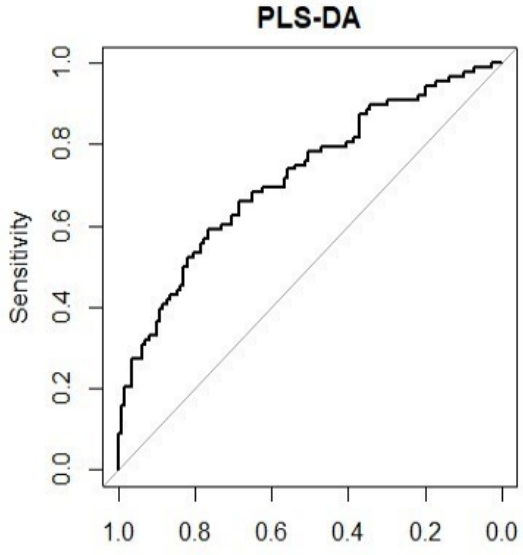


**Figure 9.** ROC curve and Area Under Curve (AUC) for the PLS-DA model.

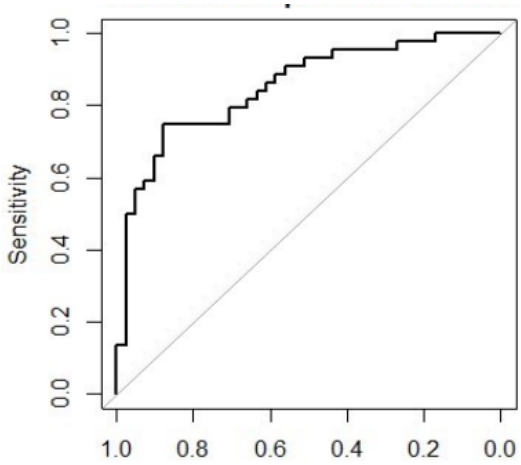


**Figure 10.** ROC curve and Area Under Curve (AUC) for the PLS-DA model studies conducted in women diabetic patients.

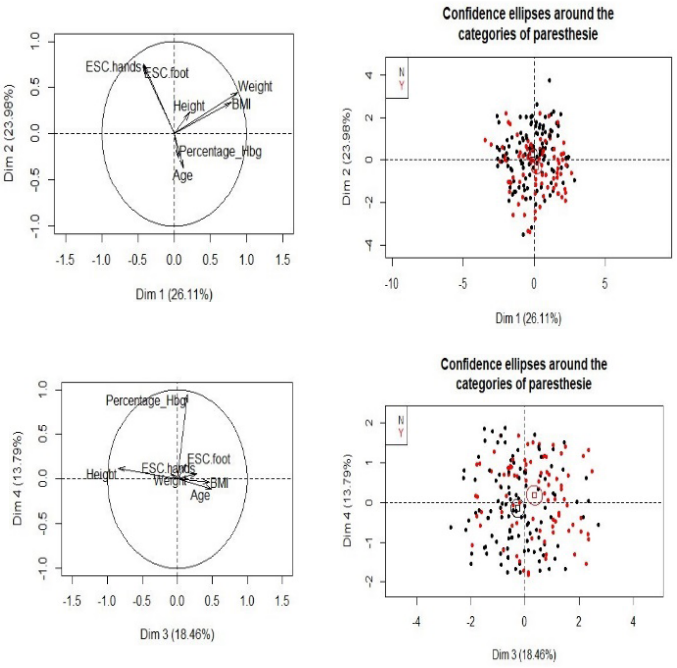


**Figure 11.** PCA with quantitative variables (age, height, weight, BMI, hemoglobin percentage and ESC variables) transformed into ranks. The two groups with paresthesia (Y) and not with paresthesia (N) are surrounded by a trusted ellipse using individual coordinates. The color rectangles are at the center of gravity of each group. At the top: representation of variables (left) and individuals (right) on the factorial plane 1*2. At the bottom: representation of variables (left) and individuals (right) on the factorial plane 3*4.

the Y group compared to N group. The reverse is true for type 1 diabetes.

The results of the PCA on the men's and women's groups separately are very similar to those obtained by considering all patients, regardless of gender, in the same analysis. Indeed, the percentage of variance explained on the first four axes for the total analysis is 82.3% and it is 84.7% for women and 84.1% for men. The variables best represented on these first four axes are slightly different between women and men: we find in common the weight and the ESCs in the hands and the feet. For women, the variables BMI on axis 1 and HbA1c on axis 4 are also well represented. It is on the 1*4 plan that women with paresthesia are best discriminated against by those without it. Women with paresthesia appear to have higher weights, BMI, and glycated hemoglobin percentages than those without paresthesia (Figure 11).

## Discussion

Evidence from previous studies suggests that the incidence of Diabetic Peripheral Neuropathy (DPN) in North Africa is higher and occurs earlier compared in the European population [4]. The point prevalence of PDN in the countries in the MENA region is estimated at 42.2% [10]. The current study intended to assess the sudomotor function in an Algerian cohort

of diabetic patients based on sudoscan procedure. The early detection of SFN is challenging especially for diabetic patients without obvious clinical symptoms and normal neurological examination [11]. It is worth noting that the sensory symptoms alone should not be considered a reliable clinical characteristic [12]. Moreover, the sensory symptoms may occur in the absence of clinical signs of peripheral neuropathy [13]. The assessment of the SFN's degeneration represents a major interest in earlier diagnoses of SNF dysfunction [5]. Punch skin biopsy directly measures pathological changes in intraepidermal nerve fiber [6]. But even so, the unmyelinated sensory fibers density may be normal in about 10% of patients [14]. In turn, assessing the sudomotor function, and therefore of sympathetic C-axons, may be achieved in a noninvasive way using the sudoscan given that feet ESC is significantly correlated with the sural nerve amplitude in diabetic subjects [15]. Moreover, there is evidence to suggest that sweat gland nerve fiber density correlates with neuropathic scores and ESC [16-17]. The sympathetic innervation of sweat glands begins to decline at an early stage of diabetes following a linear progression [13]. Current evidence is that clinical signs of DPN have moderate sensitivity and high variability and tests evaluating sympathetic sudomotor or small-fiber-function have also limited sensitivity and uncertain interpretation [7]. Even with low sensitivity, the quantitative sensory testing by sudoscan based on Sympathetic Skin Response (SSR) could assess early neuropathy [15].

Our study provided the testing of the sudomotor function of a large cohort of 199 Algerian diabetic patients, to discriminate between the groups with versus without sensory positive symptoms of DPN described generically as paresthesia. Our data revealed that the likelihood of DPN was higher among patients with paresthesia than that of asymptomatic ones. Overall, the ESC-F is lower than ESC-H respecting a length-dependent DPN profile. Therefore, feet ESC as a surrogate of DPN followed by height and glycated hemoglobin are the most important discriminant factors between patients with and without sensory symptoms. We confirmed that the patients with paresthesia have worse glycemic control than asymptomatic patients previously reported [18]. It is important to consider gender differences in diabetes, given their potential impact on the outcome. Men are over-represented in the group without paresthesia more likely to contribute to the overall results of group N. The top five variables identified by the model are size, HbA1c, feet ESC, age, and type of diabetes. All these variables show odds ratios differ from 1. The size and feet ESC have odds ratios less than 1, indicating that lower values of these variables tend to increase the risk of paresthesia. Higher HbA1c and age were also significantly associated with the risk of developing paresthesia. The best variables to discriminate between men with and without paresthesia are age, BMI, ESC-F, and type of diabetes. These variables are slightly different from those of women concerning essentially BMI and HbA1c. In this respect, in a large community-based diabetic population women had a 50% increased adjusted risk of painful symptoms compared with men [19]. The variables BMI, HbA1c, T2DMI, and ESC allow for discrimination between the groups of women with and without paresthesia. A higher Body-Mass Index (BMI) in women is linked to a greater incidence of paresthesia whereas the duration of diabetes and age at onset are similar in both gender groups. Strong evidence exists in favor of an etiological association between obesity and neuropathy utilizing chronic metabolic inflammation leading to nerve damage [20]. The patients with peripheral neuropathy were more likely to have a BMI greater than 30 [21]. In agreement with other reports, our data showed that insulin use in T2DM reflects a more advanced stage [22]. It is well known that the duration of diabetes is a critical risk factor for DPN noted in more than a third of the patients with disease duration greater than 10 years [23]. These findings have been reproduced in a cross-sectional study of a large Jordanian cohort validating the duration of diabetes as a risk factor for neuropathy [24]. We also noted a significant difference between women with T2DM and T2DMI: the best variables for discriminating the N group from symptomatic patients are HbA1c, ESC, and BMI. HbA1c as a reliable measure of chronic hyperglycemia correlates well with the risk of long-term diabetes complications, findings that are in keeping with other studies [18]. Earlier observational studies suggested that glucose control is beneficial for neuropathy prevention in both T1DM and T2DM and may help in preventing micro- and macrovascular complications [25-26]. The multifactorial description of data showed that the skin electroconductances and HbA1c allow for better discrimination between Y and N patients. In our cohort, the incidence of neuropathic symptoms in type 1 diabetes was a third lower than that of type 2 diabetes whereas, in other studies, the adjusted risk of neuropathic symptoms in T2DM was double that of the T1DM [19]. It is a paradoxical finding given that an important percentage of abnormal skin biopsy findings were found in patients with paresthesia which could be explained by additional large fibers involvement [26]. Concerning the neuropathic process involving the small fibers, initially, nerve conduction studies are still normal and when large fibers damage becomes symptomatic, the distal sensory axons would be more severely involved [27]. BMI and skin electroconductances, representing about half of the total variance, are the best discriminating factors of the risk of SFN.

Even though the characterization of peripheral neuropathy symptoms is based only on the generic term paresthesia, the number of patients included in our study is sufficient to give insights into the potential utility of these procedures for detecting DPN. The ROC curve, with 71.9% area under the curve, indicates a distribution between patients with and without paresthesia not better than a random distribution and therefore lower than in other studies [8].

There are some explanations for our findings. The diagnosis of DPN was based only on a clinical basis, not all potential clinical measures of neurological impairment could be evaluated. Besides these, we must consider the subjective pattern of neuropathic symptoms (paresthesia) including the involvement of the limbic system in the sensory and emotional components of the painful experience. However, in a cohort of patients with burning foot sensations, more than half had normal findings [28]. Also, the sensitivity of sudoscan procedure is not high enough to confirm the DPN without additional tests. This study's single-center design may limit the generalizability of the results. It is impossible to evaluate, at this moment, how the presence of paresthesia in asymptomatic patients would influence the evolution of neuropathy which requires long-term ascertainment. Moreover, the cut-off value of ESC is recommended by the producer but when we ascertained an ESC feet threshold of 68 µS instead of 60 µS, we obtained a significant rise of a positive diagnosis of neuropathy. We have specifically examined the functional parameters of small fibers only by sudoscan unable to assess them by other methods because of a lack of specific tools.

In conclusion, this technique even if is considered a surrogate marker for diabetic neuropathy, designed to detect early neuropathic abnormalities in diabetic subjects represents just a complementary diagnostic tool with insufficient sensibility. Our major finding is that the assessment of skin electroconductances allows discrimination against the groups of diabetic women with neuropathy. This study as a cross-sectional design, could not evaluate the long-term effects of risk factors on the development of DPN. Consequently, further studies are needed to assess the validity of these procedures to determine the most appropriate combination of tools and whether these results would be replicated in a larger cohort.

## Statement of Ethics

### Ethics approval

Ethics approval and consent to participate: The study complies with the Declaration of Helsinki. The data were gathered without patient identification. This study was approved by the Research Ethics Committee of the University Hospital of Setif. The subjects and in the case of children, participants' parents gave their written informed consent to participate in this study. Furthermore, the author confirms that they accept the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

### Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could represent a potential conflict of interest.

### Funding sources

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

### Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author, upon reasonable request.

### Author contributions

The first author (CP) conceived and designed the study, performed the sudoscan experiments, analyzed the data, wrote, and revised the manuscript. Dr. MCC examined the patients, performed the sudoscan

experiments, analyzed the data, and revised the manuscript. Dr. EP analyzed the data and revised the manuscript.

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### Conflict of interest

Authors reported none.

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