“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST

DOCTORAL SCHOOL

MEDICINE

EVALUATION OF SUDOMOTOR FUNCTION IN CORRELATION WITH ANTHROPOMETRIC, METABOLIC, AND BIOCHEMICAL PARAMETERS AS A SCREENING METHOD FOR CHRONIC COMPLICATIONS IN TYPE 2 DIABETES PATIENTS

- PhD THESIS SUMMARY -

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Introduction

Sudomotor function is regulated by a subdivision of the sympathetic nervous system, the postganglionic cholinergic fibers that release acetylcholine. Acetylcholine increases skin microvascular flow and sweating. Capillaries mediate vasodilation and increase skin temperature. Sudomotor dysfunction is defined as a decrease in sudomotor activity. Similar to endothelial dysfunction in predicting atherosclerosis, sudomotor dysfunction is the first clinically detectable change of autonomic neuropath (1–3).

Sudomotor function is affected by the reduced density of C fibers in active sweat glands and microcirculation disorders, which can be associated with chronic pain and paresthesias in the lower limbs (4). The main cause of sudomotor dysfunction is diabetes. However, sudomotor dysfunction can also be found in other conditions such as vitamin B12 and D deficiencies, Parkinson's disease, HIV/AIDS, amyotrophic lateral sclerosis, hypothyroidism, chronic kidney disease, chronic ethanol consumption, Alzheimer's disease, and Guillain-Barré syndrome (5). It has also been noted in patients who have undergone chemotherapy or those on antihypertensive treatment with beta and alpha-blockers and calcium antagonists. Rarely, metformin treatment can lead to neuropathy secondary to vitamin B12 deficiency.

The sweat test is a promising method for screening and diagnosing chronic microvascular complications associated with diabetes. This test evaluates sudomotor function, which is influenced by the autonomic nervous system. Since microvascular complications of diabetes, such as peripheral diabetic polyneuropathy, diabetic retinopathy, and chronic kidney disease, can affect sudomotor function, the sweat test provides valuable information about the patient's health status and early identification of these complications.

The utility of the sweat test in screening for microvascular complications of diabetes is even greater because it is non-invasive, easy to perform, and cost-effective. Therefore, it can be integrated into routine clinical practice as part of the general evaluation of diabetic patients, contributing to the early identification of complications and improving their management.

Currently, type 2 diabetes represents one of the greatest public health challenges globally. Although significant progress has been made in understanding the pathophysiological mechanisms of this disease and in developing effective treatments for

glycemic control, type 2 diabetes patients still face major health risks, especially due to associated cardiovascular complications. In the past, clinical approaches focused more on treating advanced stages of the disease and existing complications. However, there is now a significant shift towards preventing these complications. There is growing recognition of the importance of managing risk factors and adopting a healthy lifestyle to prevent or delay the onset of chronic complications.

It is essential to continue research to better identify and understand risk factors and how they influence the progression of diabetes and the development of associated chronic complications. As these mechanisms become clearer, more effective strategies can be developed for preventing and managing type 2 diabetes complications.

Ultimately, it is crucial to focus on primary and secondary prevention of type 2 diabetes complications. Through early interventions and appropriate risk factor management, we can significantly improve the quality of life for patients and reduce the devastating impact of this disease on patients and the healthcare system as a whole.

Currently, knowledge about sudomotor function in diabetes is continuously expanding, although there are still aspects that require research and clarification. Sudomotor function refers to the body's ability to regulate sweating through the autonomic nervous system. This is important because sudomotor dysfunction can be a manifestation of peripheral neuropathy, a common complication of diabetes.

Recent studies have highlighted the utility of the sweat test in screening and diagnosing chronic conditions frequently associated with diabetes, offering a promising perspective on the role of this method in improving patient management.

1. Hypothesis and General Objectives

Main Hypothesis

The sweat test represents an efficient and reliable tool in diagnosing cardiovascular autonomic neuropathy (CAN) in patients with type 2 diabetes. By evaluating the results of this test, a precise and early prediction of CAN can be obtained, facilitating early identification and initiation of appropriate treatment, thus contributing to the prevention of severe cardiac complications associated with type 2 diabetes.

Secondary Hypothesis

The results of the sweat test may have the capacity to predict and diagnose other chronic complications of type 2 diabetes, such as chronic kidney disease, diabetic retinopathy, and symmetric sensitive peripheral diabetic polyneuropathy. Identifying significant correlations between sweat test results and these conditions could lead to significant improvements in clinical practice, facilitating early diagnosis and the implementation of preventive or early therapeutic strategies for the effective management of these complications associated with type 2 diabetes.

Research Objectives

The primary objective of this research is to investigate the predictability of the sweat test in diagnosing cardiovascular autonomic neuropathy (CAN) in patients with type 2 diabetes. Cardiovascular autonomic neuropathy is one of the serious and frequent complications of type 2 diabetes, which can have severe consequences on patients' heart health.

The sweat test is a method used to evaluate the function of the autonomic nervous system and can provide important clues about the presence of CAN. Following the research, we aim to establish whether the results of this test can be used in diagnosing CAN, thus facilitating early identification and appropriate treatment of this complication.

The secondary objective of the research is to evaluate the predictability of the sweat test result in diagnosing other chronic complications of type 2 diabetes. These complications include chronic kidney disease, diabetic retinopathy, and symmetric sensitive peripheral diabetic polyneuropathy. Identifying a correlation between the sweat test results and these complications could provide significant benefits in clinical practice, facilitating more efficient diagnosis and management of these complications. An abnormal sweat test result

could indicate an increased risk for developing a specific complication, thus allowing preventive interventions or early treatment to prevent or slow the progression of the disease.

2. General Research Methodology

Study Sample

The study included 271 patients admitted and evaluated at "Nicolae Malaxa" Clinical Hospital from June 2019 to June 2020. The primary diagnosis of the admitted patients was type 2 diabetes.

Study Design

This research was an observational cross-sectional study. Approval for conducting the research was obtained from the Ethics Committee of "Nicolae Malaxa" Clinical Hospital. Informed consent was obtained from all participating patients.

Inclusion Criteria

- Signing the informed consent
- Patients with type 2 diabetes
- Overweight/obese individuals
- Age over 18 years

Exclusion Criteria

- Patients who did not sign the informed consent
- Patients with other types of diabetes (type 1 diabetes, LADA, MODY)
- Age < 18 years
- Pregnant women
- Patients with diagnosed neoplasms in the last 5 years
- Patients with stroke sequelae
- Patients with a history of myocardial infarction
- Patients with lower limb amputations
- Patients with chronic kidney disease diagnosed before the diagnosis of type 2 diabetes
- Patients identified with another cause of neuropathy (alcoholic, vitamin B12 deficiency)

Clinical Variables

Anthropometric indices such as height, weight, body mass index, abdominal circumference, waist-to-hip ratio, blood pressure values in the supine and orthostatic positions, and ventricular rate in the supine and orthostatic positions will be recorded, along with smoking status.

The urinary albumin-creatinine ratio was measured:

- Under conditions of euglycemia at the time of collection
- In the absence of urinary or systemic infection and outside a febrile episode
- Outside the menstrual period
- After a time interval following intense physical exercise

Outcome Variables

Cardiovascular Autonomic Neuropathy (CAN)

It was evaluated following the performance of:

- Ewing tests

- Sweat test

The sweat test uses a rapid and non-invasive method to evaluate sudomotor function by quantitatively assessing the galvanic skin response, thus early detecting small fiber nerve pathology.

A low-voltage current (<4V) is applied through stainless steel electrodes, attracting chloride ions from the sweat glands richly represented on the palms and soles. The weak current extracts the chloride ions, which pass only through the channels of the sweat glands.

According to the American Diabetes Association (ADA), diabetes is the most common identifiable cause of autonomic neuropathy. Early identification of these complications, which can be asymptomatic in up to 50% of cases, has the potential to reduce or delay complications with timely preventive treatment.

Chronic Kidney Disease (CKD)

The renal status assessment was carried out using:

- The KDIGO 2012 classification. Type 2 diabetes patients were considered to lack renal impairment if they had: eGFR (MDRD) between 90-130 ml/min/173m2 and albuminuria < 30 mg/g

- The nephropathy score generated by Sudoscan, which estimates the current risk of renal dysfunction. It integrates algorithms that combine the electrochemical skin conductance with variables such as body weight, height, age, and HbA1c levels.

Diabetic Retinopathy (DR)

Diabetic retinopathy was evaluated following an ophthalmologic consultation. The fundus examination was performed by a single examiner. The eye with the more severe impairment was used for classification. Diabetic retinopathy was classified as non-proliferative and proliferative. Patients who did not present any of these abnormalities were classified as not having retinopathy.

Symmetric Sensitive Peripheral Diabetic Polyneuropathy

The severity of peripheral diabetic neuropathy was estimated using the Toronto score, sudomotor function, and neurological examination.

The "Toronto Clinical Scoring System" is a protocol validated by comparison with sciatic nerve biopsy results and closely correlated with electrophysiological evaluation.

Peripheral Arterial Disease (PAD)

Peripheral arterial disease was identified using an automated device to measure the ankle-brachial index (ABI MDTM). The interpretation of the result was performed using the ankle index scale. A normal ABI value is between 100 and 140. This shows that the blood pressure in the lower limbs is equal to or greater than in the upper extremities.

Cardiovascular Risk

Cardiovascular risk was assessed using the SCORE2-Diabetes risk score. This is a cardiovascular risk score specifically created for people with type 2 diabetes, extending the SCORE2 score to provide a more accurate assessment of the risk of major cardiovascular events. It includes additional risk factors specific to diabetes, such as disease duration, glycemic control (HbA1c), lipid profile, and the presence of complications that increase cardiovascular risk, such as chronic kidney disease. SCORE2-Diabetes helps individualize and adapt treatment plans to reduce cardiovascular risk in this category of patients.

Implementing SCORE2-Diabetes in clinical practice allows for a more accurate and continuous assessment of cardiovascular risk, facilitating informed therapeutic decisions and effective patient monitoring. This score represents an important advancement in managing cardiovascular risk in people with type 2 diabetes, contributing to improved long-term

outcomes through more effective preventive measures. Depending on the result obtained, cardiovascular risk will be classified into four categories: low (<5%), moderate (5-10%), high (10-20%), very high (>20%).

Statistical Analysis

For this study, statistical analysis was performed using Microsoft Excel and IBM SPSS Statistics 26.0. Primary data were recorded in Microsoft Excel files. Descriptive analysis and graphical representation of parameters were conducted in Microsoft Excel and SPSS using statistical functions and commands such as Functions-Statistical Pivot Tables, Chart, and Data Analysis. Normality tests (Shapiro-Wilks, Anderson-Darling) and complex statistical tests (proportion Z tests, Chi-square, Kruskal-Wallis, Spearman's rho correlation coefficient) were conducted using XLSTAT and SPSS modules. Fundamental statistical indicators (mean, standard deviation) and dispersion indicators (minimum, maximum, median, quartiles) were used to characterize numerical values.

For accurate evaluation of certain statistical tests, data must follow a specific distribution. Normality tests (Shapiro-Wilks, Anderson-Darling, Kolmogorov-Smirnov) were used for this purpose. Student's t-test and ANOVA were used to compare mean values. Interpretation of results is based on p-values: $p < 0.05$ indicates a significant difference, $p < 0.01$ a very significant difference, and $p < 0.001$ an extremely significant difference. For data not following a normal distribution, the Mann-Whitney and Wilcoxon tests were used. Correlation between variables was analyzed using Pearson or Spearman correlation coefficients, depending on data distribution. Linear regression was used to evaluate the relationship between two or more variables. For categorical variables, the Chi-square test was applied to identify associations between risk factors.

Ethical Considerations

The study was conducted with the approval of the local ethics committee of "Nicolae Malaxa" Clinical Hospital. Informed consent explained to and signed by the patient was used.

3. Results

This cross-sectional study was conducted between June 2019 and June 2020. The Ethics Committee of "Nicolae Malaxa" Clinical Hospital, Bucharest, Romania, granted ethical approval for the study (approval number: 2145). All data were obtained according to the hospital's standard of care for type 2 diabetes patients (DZ 2). All patients included in the study provided informed consent for data collection and secondary use of medical data for research purposes.

The study included 271 individuals, of whom 52% (n=143) were women. Significant statistical differences were observed between females and males regarding age, systolic blood pressure, fasting glucose, HbA1c levels, total cholesterol, triglycerides, gamma-glutamyl transferase, and bilirubin levels. It appears that women have better glycemic control than men, but men showed superior control concerning total cholesterol. Additionally, GGT and bilirubin values were significantly higher in men. The prevalence of microvascular complications in the cohort is presented in Fig. 3.1.

Tabelul 3.1. Anthropometric and Biochemical Parameters in the Studied Cohort Stratified by Gender

	Female (n=143)		Male (n=128)		Total (n=271)		
	Mean	SD	Mean	SD	Mean	SD	P-value
Age [years]	**63.31**	**8.58**	**59.67**	**9.25**	**61.59**	**9.07**	**<0.001**
BMI [kg/m²]	32.66	5.28	31.74	5.35	32.23	5.32	0.16
Systolic BP [mmHg]	**132.56**	**19.63**	**136.33**	**16.38**	**134.34**	**18.24**	**<0.001**
DyastolicBP [mmHg]	74.59	10.85	78.59	10.37	76.48	10.79	0.41
HR [bpm]	74.56	10.99	75.62	10.18	75.06	10.61	0.41
FPG [mg/dl]	**180.70**	**81.94**	**198.29**	**85.25**	**189.01**	**83.83**	**0.03**
HbA1c[%]	**7.86**	**1.62**	**8.35**	**2.05**	**8.09**	**1.85**	**0.01**
TC [mg/dl]	**206.35**	**58.62**	**188.76**	**49.36**	**198.01**	**55.03**	**0.01**
HDL-c [mg/dl]	52.41	12.84	48.18	13.63	50.42	13.36	0.80
TC/HDL-c	**4.13**	**1.55**	**4.18**	**1.49**	**4.15**	**1.52**	**0.02**
LDL-c [mg/dl]	115.95	50.41	101.49	46.59	109.11	49.09	0.75

Urea [mg/dl]	**40.08**	**20.24**	**40.74**	**17.53**	**40.39**	**19.00**	**0.01**
Creatinine [mg/dl]	0.87	0.27	1.08	0.33	0.97	0.32	0.59
eGFR[ml/min/1,73m²]	77.18	27.12	77.13	22.26	77.16	24.89	0.21
Bilirubin[mg/dl]	**0.59**	**0.25**	**0.73**	**0.39**	**0.66**	**0.33**	**0.04**
B12 vitamin [pg/ml]	386.26	187.94	476.56	254.40	430.19	224.31	0.23
CRP [mg/dl]	1.38	2.54	0.60	0.90	0.99	1.95	0.99

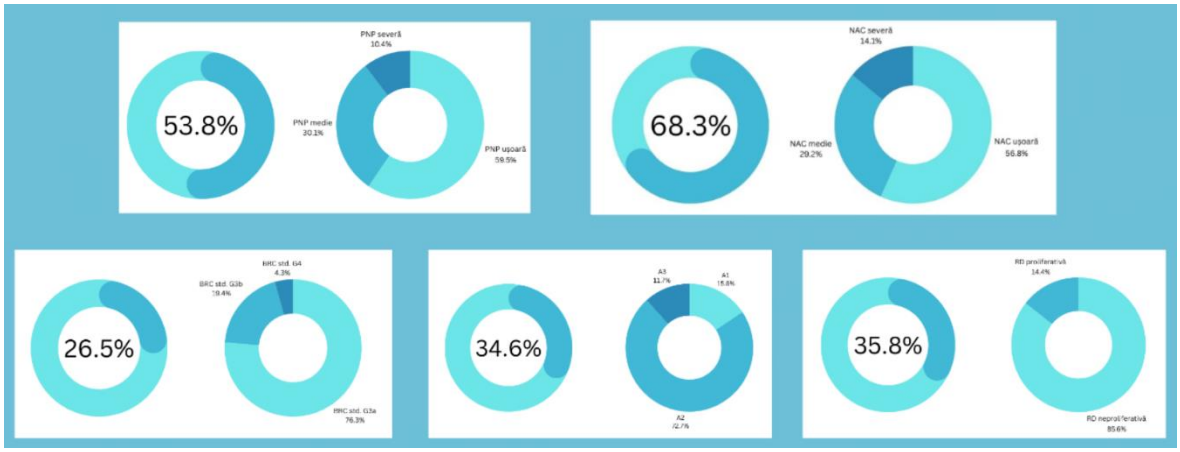


Fig. 3.1. Prevalence of Chronic Complications in the Studied Cohort

The average age for the group with mild CAN was 63.56 ± 8.45 years, for the moderate CAN group it was 61.00 ± 9 years, for the severe CAN group it was 59.50 ± 7.94 years, and for the control group it was 60.20 ± 9.83 years. HbA1c and fasting glucose levels increased proportionally with the severity of CAN, with a mean value of 8.86 ± 2.21 among patients with severe CAN. Total cholesterol and triglyceride levels were significantly lower in patients with mild CAN. Patients with severe CAN had higher urinary albumin-to-creatinine ratios compared to those with mild or moderate CAN (Table 3.2).

Tabel 3.2 Anthropometric Measurements and Laboratory Parameters Stratified by the Presence of Cardiovascular Autonomic Neuropathy (CAN)

Parameters	**CAN (–)**	**CAN(+)**			**P**		
	(n = 51)	**Mild (n =90)**	**Moderate (n =104)**	**Severe (n =26)**	**Pv-1**	**Pv-2**	**Pv-3**
Age [year]	60.20 ± 9.83	63.56 ± 8.45	61.00 ± 9	59.50 ± 7.94	.004	.592	.216
BMI [kg/m²]	30.27 ± 4.18	33.24 ± 5.74	32.95 ± 5.43	33.12 ± 5.24	.012	.265	.371
Height [cm]	167.88 ± 9.2	164.81 ± 10.07	164.48 ± 7.4	164.96 ± 9.06	.193	.269	.656

WC [cm]	101.90 ± 10.2	107.11 ± 13.61	108.26 ± 13.18	108.08 ± 12.48	.167	.107	.331
FPG [mg/dL]	178.84 ± 70.2	185.77 ± 93.73	191.87 ± 64	229.81 ± 108.46	.614	.780	.009
A1c [%]	7.67 ± 1.57	8.13 ± 2.06	8.31 ± 1.49	8.86 ± 2.21	.793	.324	.026
TC [mg/dL]	203.40 ± 49.9	189.40 ± 51.51	203.69 ± 66.69	202.85 ± 56.89	.042	.398	.638
HDL-C [mg/dL]	49.78 ± 13.4	49.93 ± 12.66	52.44 ± 14.8	50.26 ± 13.19	.636	.214	.951
TC/HDL-C	4.38 ± 1.62	3.96 ± 1.29	4.14 ± 1.74	4.20 ± 1.51	.100	.920	.877
LDL-C [mg/dL]	116.80 ± 48.6	104.40 ± 44.69	108.18 ± 57.07	105.32 ± 50.28	.212	.881	.679
TGL [mg/dL]	213.31 ± 136.39	190.85 ± 44.69	237.48 ± 195.94	254.97 ± 126.68	.043	.176	.126
Creatinine[mg/dl]	0.93 ± 0.25	0.99 ± 121.17	0.95 ± 0.32	1.04 ± 0.34	.416	.672	.227
ACR [mg/g]	28.23 ± 91.4	58.01 ± 0.36	72.31 ± 122.78	168.93 ± 435.19	.771	.707	.005
AST [U/L]	24.77 ± 12.3	26.64 ± 14.1	30.34 ± 18.21	26.09 ± 12.69	.936	.040	.815
ALT [U/L]	29.25 ± 15.9	30.03 ± 19.78	35.39 ± 20.5	32.21 ± 15.33	.466	.053	.744
GGT [U/L]	64.20 ± 103.6	43.85 ± 39.17	85.80 ± 106.78	55.68 ± 61.79	.094	.070	.815

Abbreviations: WC — waist circumference; Pv-1 — p-value comparing mild CAN with CAN-, Pv-2 — p-value comparing moderate CAN with CAN-, Pv-3 — p-value comparing severe CAN with CAN-

Electrochemical skin conductance was lower in the CAN+ group than in the CAN- group at the hands (67.34±15.51μS versus 72.38±12.12μS p=0.008) and feet (73.37±13.38μS versus 82.84 ±10.29μS p<0.001). The mean Sudoscan-NAC score was 36.88±8.69 in the CAN+ group and 26.02±36.88 in the CAN- groups (p<0.001).

The prevalence of CAN was higher among females (Fig. 4.2). Non-obese individuals had fewer cases of CAN compared to patients with obesity (Fig. 4.3).

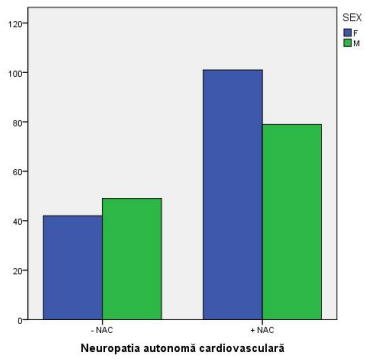


Fig. 3.2.Presence of CAN Stratified by Gender

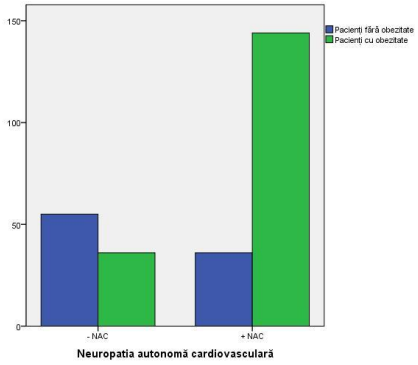


Fig.3.3 Presence of CAN Stratified by Weight Status

The scatter plot shows the relationship between the Sudoscan-NAC score and the Ewing score (Fig 3.4). We identified a significant positive relationship between the Sudoscan-NAC score and the Ewing score. The Pearson correlation coefficient (r) is 0.522, indicating a moderate correlation between the two variables, and the p-value ($p < 0.001$) suggests that this correlation is extremely statistically significant. The analysis suggests that as the Ewing score increases, the Sudoscan-CAN score also tends to increase, indicating a direct association between these two measurements.

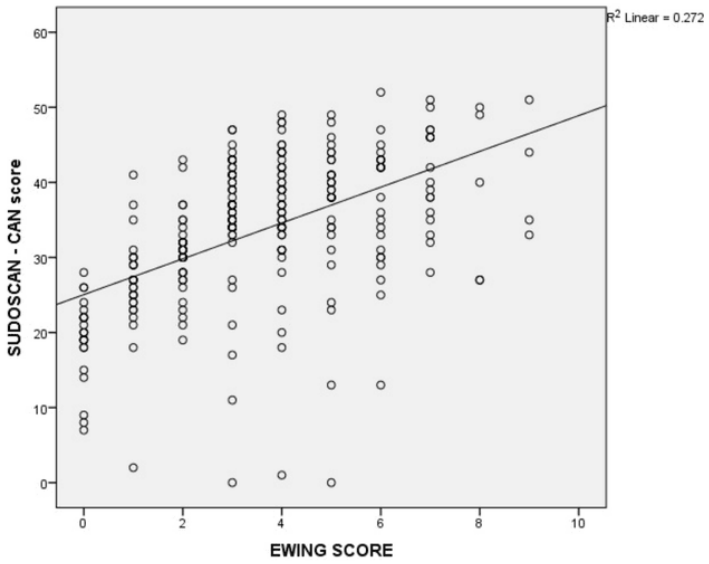


Fig 3.4. Scatter Plot Showing the Relationship Between the SUDOSCAN-NAC Score on the y-axis and the Ewing Score on the x-axis

Performance of Sudoscan in Detecting CAN

The area under the receiver operating characteristic (ROC) curve (AUC) for the Sudoscan-NAC score to predict CAN was 0.864 (OR 0.87 (95%CI 0.819-0.91)) (Figure 3.5). The cut-off score for Sudoscan-NAC was 32.5, and the test had a sensitivity of 81.5% and a specificity of 12.8% for detecting CAN, with a positive predictive value (PPV) of 84% and a negative predictive value (NPV) of 69%.

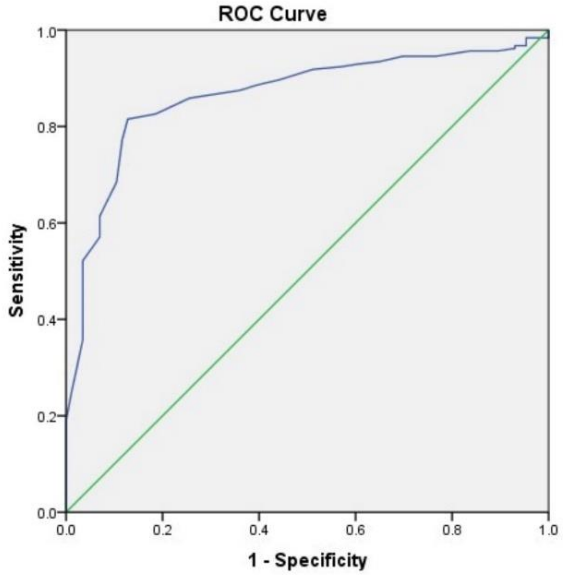


Fig 3.5. ROC Curve of the Sudoscan-NAC Score Used to Detect Type 2 Diabetes Patients with CAN

In multiple linear regression, the Sudoscan-NAC score remained statistically significantly associated with age, increased BMI, diabetes duration, and the Ewing score (Table 3.3).

Tabelul 3.3 Clinical Factors Associated with the Sudoscan NAC Score in Type 2 Diabetes Patients Using Multiple Linear Regression

	Standard β-coefficient	**P-value**
Age	0.256	<0.001
BMI	0.430	<0.001
Diabetes duration	0.074	0.01
Ewing score	0.412	<0.001
BMI - body mass index;		

In the study group, according to SCORE2-Diabetes, four patients (19%) were classified with moderate cardiovascular risk, thirty-five (166%) with high risk, and one hundred seventy-two (815%) with very high cardiovascular risk. The baseline characteristics of the patients are presented in Table 3.4.

Patients with very high cardiovascular risk were older and had a longer diabetes duration. However, there were no notable differences in height, weight, or waist circumference between the risk categories. Higher levels of fasting plasma glucose and HbA1c were observed in the higher risk groups. Lipid levels, including total cholesterol, HDL-c, triglycerides, and LDL-c, did not vary significantly between the risk groups. Lower eGFR was correlated with increased CV risk categories. Although GGT showed a marginal difference between the risk groups, factors such as age, diabetes duration, fasting plasma glucose, HbA1c, and eGFR were identified as key indicators of cardiovascular risk in diabetic patients.

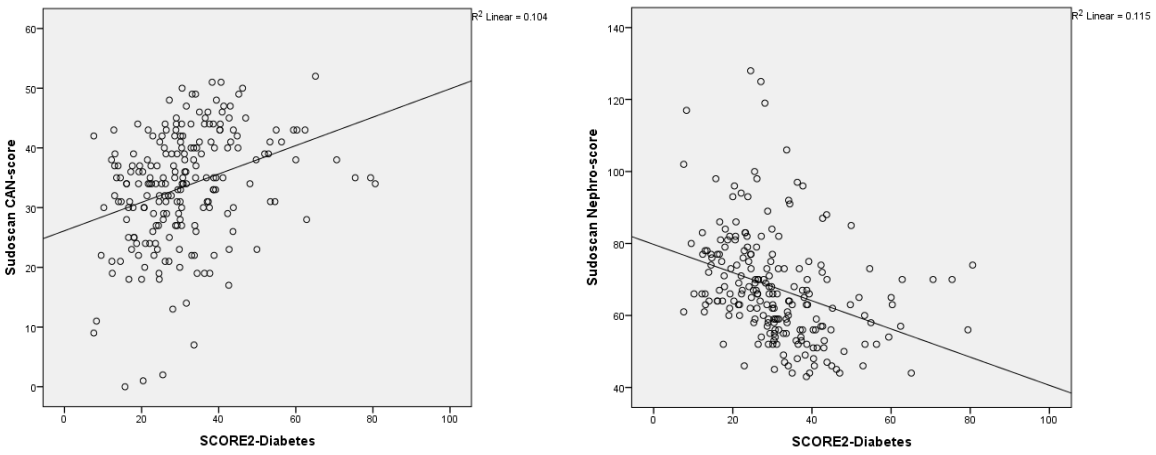
Table 3.4. Anthropometric and Biochemical Parameters Stratified by Cardiovascular Risk

Cardiovascular risk	(5-10%) n=4		(10-20%) n=35		(>20%) n=172		Total		
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	p-value
Age (years)	**45.25**	**4.92**	**52.29**	**5.27**	**59.89**	**6.59**	**58.35**	**7.18**	**<0.001**
Diabetes duration(years)*	**6.50**	**8**	**5**	**5**	**7.5**	**8**	**7**	**8**	**0.036**
Height (cm)	170.00	8.98	167.14	11.00	166.47	8.71	166.64	9.10	0.701
Weight (kg)	95.00	20.70	88.86	17.42	90.55	16.91	90.36	17.00	0.745
WC (cm)	110.25	21.82	105.49	11.98	106.92	12.94	106.74	12.92	0.722
FPG (mg/dl)	**200.50**	**43.93**	**162.11**	**61.97**	**206.06**	**91.39**	**198.67**	**87.85**	**0.025**
HbA1c (%)	**7.26**	**0.52**	**7.17**	**1.19**	**8.61**	**2.04**	**8.34**	**1.99**	**<0.001**
TC (mg/dl)	212.25	44.63	184.89	50.93	200.75	57.15	198.34	56.09	0.277
HDL-c (mg/dl)	54.10	12.55	47.12	14.40	50.32	13.08	49.86	13.30	0.352
LDL-c (mg/dl)	94.63	9.31	101.85	45.22	109.13	50.53	107.73	49.32	0.668
TGL (mg/dl)*	292.5	612.5	173	169	179	132.5	178	138	0.103
eGFR (ml/min/1,73m^2)	**98.43**	**17.87**	**92.74**	**30.69**	**74.61**	**24.27**	**78.07**	**26.27**	**<0.001**
GGT (UI/L)*	52.50	62	34	73	38	50	37.5	52	0.05
ACR (mg/g)*	23.13	39.37	12	28.54	31.25	71.33	26.27	49.12	0.78
B12 vitamine*	889.5	91	427.5	158	350	269	382	364	0.057

Abbreviations: WC = waist circumference, FPG= fasting plasma glucose, HbA1c = glycated hemoglobin, TC= total cholesterol, HDL-c = high-density lipoprotein, LDLc = low-density lipoprotein, TGL = triglycerides, eGFR = estimated glomerular filtration rate, GGT= gamma-glutamyl transferase, ACR= Albumin-to-creatinine ratio, *variables expressed as median, interquartile range [IQR], statistical significance, $p<0.05$

Correlation Between Sudoscan and SCORE 2 – Diabetes

The scatter plot shows the relationship between the Sudoscan NAC score, the Sudoscan Nephro score, and SCORE2-Diabetes (Fig. 3.6). The Sudoscan NAC score showed a significant positive correlation with SCORE2-Diabetes, and the Sudoscan Nephro score showed a significant negative correlation with SCORE2-Diabetes.



A B

Fig. 3.6. Scatter Plot Showing the Relationship Between the Sudocan NAC Score on the y-axis and SCORE 2 – Diabetes on the x-axis (A); Scatter Plot Showing the Relationship Between the Sudoscan Nephro Score on the y-axis and SCORE 2 – Diabetes on the x-axis (B)

The area under the ROC curve (AUC) for the Sudoscan-NAC score to predict very high cardiovascular risk was 0.657 (95% CI: 0.569-0.745) (Figure 3.6). The diagnostic threshold of the Sudoscan-NAC score was 39.5, and the test had a sensitivity of 34.3% and a specificity of 79% for detecting very high cardiovascular risk.

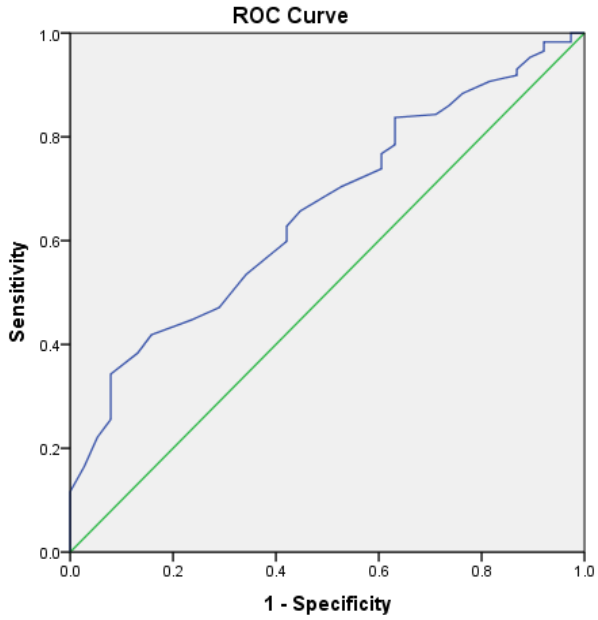


Fig. 3.6. ROC Curve of the Sudoscan-NAC Score in Detecting Very High Cardiovascular Risk in Type 2 Diabetes Patients

Multiple linear regression analysis examining clinical factors associated with SCORE2-Diabetes in type 2 diabetes patients reveals several significant associations. Age and diabetes duration show positive correlations with SCORE2-Diabetes, with standardized β coefficients of 0.413 and 0.179, respectively, both statistically significant ($p < 0.001$). Similarly, HbA1c, LDL-c, Sudoscan lower limb score, Sudoscan NAC score, Ewing test score, and supine systolic blood pressure demonstrate positive associations with SCORE2-Diabetes, with significant p-values (<0.05). In contrast, higher eGFR and Sudoscan Nephro scores are negatively associated with SCORE2-Diabetes, suggesting that higher eGFR and Sudoscan Nephro scores are associated with lower SCORE2-Diabetes values (Table 5.5).

Tabelul 3.5. Clinical Factors Associated with SCORE2-Diabetes in Type 2 Diabetes Patients Using Multiple Linear Regression

	Standard β- coefficient	P-value
Age	**0.413**	**<0.001**
Diabetes duration	**0.179**	**<0.001**
FPG	0.026	0.688
HbA1c	**0.353**	**<0.001**
TC	0.313	0.085
LDL-c	**0.239**	**<0.001**
HDL-c	-0.109	0.069
TGL	0.021	0.795
eGFR	**-0.315**	**<0.001**
Sudoscan feets score	**0.261**	**0.001**
Sudoscan Nephro-score	**-0.389**	**<0.001**

Sudoscan CAN-score	**0.199**	**0.036**
Ewing test score	**0.197**	**0.004**
HRVi	0.008	0.869
SBP supine position	**0.238**	**<0.001**
DBP supine position	-0.058	0.356

Abbreviations: FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, TC= total cholesterol, LDLc = low-density lipoprotein, HDL-c = high-density lipoprotein, TGL = triglycerides, eGFR = estimated glomerular filtration rate, HRVi = heart rate variability index, SBP = systolic blood pressure, DBP = diastolic blood pressure, statistical significance, p<0.05

Statistical analysis of chronic diabetic complications in patients with chronic kidney disease (CKD) at stages G3a, G3b, and G4 shows increasing prevalence rates for diabetic polyneuropathy (DPN) and diabetic retinopathy (DR) with CKD progression (Table 3.6).

Tabel 3.6. Prevalence of Chronic Complications in Type 2 Diabetes Patients by CKD Stage

CKD	G3a (n=55)	%	G3b (n=14)	%	G4 (n=3)	%
DPN	38	69.09	13	92.85	3	100
CAN	32	58.18	11	78.57	0	-
DR	29	52.72	8	57.14	3	100
PAD	11	20	2	14.28	2	66.66

Given the natural progression of CKD, we calculated the risk of progression to dialysis for patients with renal disease using KDIGO (6). Thus, we evaluated anthropometric measurements and laboratory parameters based on groups stratified by the risk of progression to dialysis (Table 3.7).

Table 3.7. Anthropometric Measurements and Laboratory Parameters Stratified by Risk of Progression to Dialysis

Risk of progression to dialysis	Low		Moderately increased		High		Very high		P-value
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	
BMI (kg/m²)	32.05	5.61	32.10	4.92	32.68	4.48	32.96	5.90	0.935
SBP (mmHg)	133.41	17.48	131.91	19.67	141.41	17.99	137.37	18.46	0.143
DBP (mmHg)	76.36	10.52	76.09	10.51	80.72	12.44	73.11	11.12	0.117
HR (bpm)	74.58	10.59	74.42	11.23	77.19	10.85	75.37	8.82	0.654
Diabetes Duration (years)	6.81	5.58	8.88	5.48	10.58	6.92	12.47	6.25	<0.001
FPG (mg/dl)	174.83	77.91	193.04	73.75	222.91	88.65	225.47	135.42	0.01
HbA1c (%)	7.81	1.90	8.34	1.91	8.64	1.47	8.55	2.15	0.071
Potassium (mmol/l)	4.16	0.50	3.96	0.65	4.17	0.52	4.67	0.60	0.024
Urea (mg/dl)	35.61	14.00	39.62	16.70	41.54	13.16	72.66	34.08	<0.001
eGFR (ml/min/1,73m2)	84.41	1.24	72.63	1.34	60.47	1.35	37.97	1.27	<0.001
ACR (mg/g)	6.44	2.90	31.20	3.30	72.04	3.12	133.16	3.46	<0.001

TC (mg/dl)	198.46	51.35	194.44	63.47	197.91	54.36	201.47	58.68	0.964
HDL-c (mg/dl)	50.36	14.06	51.34	14.31	51.73	10.19	45.95	11.40	0.599
LDL-c (mg/dl)	110.64	46.66	105.36	52.35	111.17	52.88	103.62	51.31	0.924
TGL (mg/dl)	207.21	140.79	221.72	131.38	197.49	65.94	265.29	271.29	0.509
Ewing score	2.88	1.89	4.20	2.18	4.34	1.98	4.84	2.22	<0.001
Sudoscan Nephro-score (uS)	66.12	1.27	61.42	1.25	57.98	1.31	53.59	1.25	0.01
Sudoscan CAN-score (uS)	31.21	10.10	34.83	9.07	36.72	7.68	39.68	6.40	<0.001
Cardiovascular Risk Score	26.52	9.18	32.10	12.52	36.99	13.46	48.28	16.83	<0.001

Performance of Sudoscan in Detecting CKD

The area under the ROC curve (AUC) for the Sudoscan-Nephro score to predict CKD was 0.63 (95% CI 0.563-0.696). The diagnostic threshold of the Sudoscan-Nephro score was 60.5, and the test had 55% sensitivity and 30.7% specificity for detecting CKD. On the other hand, the eRFG test (ml/min/1.73 m²) has a higher AUC of 0.787 (95% CI 0.725-0.848). The diagnostic threshold of eRFG was 60.5, and the test had 60% sensitivity and 73% specificity for detecting CKD (Figure 3.7).

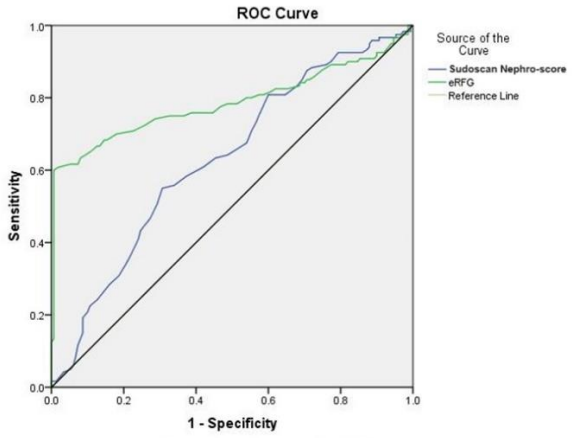


Figure 3.7. ROC Curve of the Sudoscan-Nephro and eRFG in Detecting CKD in Type 2 Diabetes Patients

The area under the ROC curve (AUC) for the Sudoscan-Nephro score to predict CKD (eGFR below 60 ml/min/1.73m²) was 0.664 (95% CI 0.591-0.736), which is statistically significant ($p < 0.001$). The threshold of the Sudoscan-Nephro score was 60.5, and the test had 63.9% sensitivity and 33.3% specificity for detecting CKD defined as eGFR below 60 ml/min/1.73m². These attributes underline the utility of the Sudoscan test as a diagnostic tool, especially in identifying positive cases essential for clinical management (Figure 3.8).

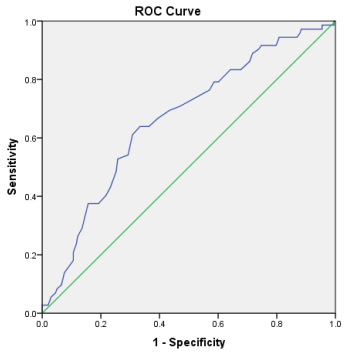


Figure 3.8. ROC Curve of the Sudoscan-Nephro Score in Detecting CKD Defined as eRFG Below 60 ml/min/1.73m²

Multiple linear regression reveals several key findings regarding the factors influencing Sudoscan-Nephro scores. Older age and longer diabetes duration are associated with lower Sudoscan-Nephro scores, highlighting the effects of age and disease duration on neurological and vascular health. In contrast, good glycemic control reflected by lower HbA1c levels and higher eGFR indicates normal renal function correlated with higher Sudoscan-Nephro scores. Additionally, higher diastolic blood pressure in the supine position negatively influences Sudoscan-Nephro scores. Lower scores on tests such as Ewing and Toronto are significantly associated with lower Sudoscan-Nephro scores, emphasizing the importance of neurological and cardiovascular function in determining Sudoscan-Nephro outcomes. These findings highlight the multifactorial nature of Sudoscan-Nephro scores, with age, diabetes control, renal function, blood pressure, and specific test scores all being crucial in evaluating diabetes complications (Table 3.8.).

Table 3.8. Clinical Factors Associated with the Sudoscan-Nephro Score in Type 2 Diabetes Patients Using Multiple Linear Regression

	Standard β- coefficient	P-value
Age	**-0.524**	**<0.001**
Diabetes duration	**-0.271**	**<0.001**
FPG	-0.155	0.303
HbA1c	**0.390**	**0.005**
eGFR	.183	**0.003**
Albuminuria	**-.126**	**0.039**
Creatinine	**-.139**	**0.022**
Uric acid	-.421	0.209
SBP supine position	**-.183**	**0.007**
DBP supine position	**.256**	**<0.01**
Ewing test score	**-.388**	**<0.001**
Toronto test Score	**-0.264**	**<0.001**

Abbreviations: FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, eGFR = estimated glomerular filtration rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, statistical significance, p<0.05

Comparative analysis between the severity of the Sudoscan score for the lower limbs (LL) and various anthropometric variables and parameters obtained from performing Ewing tests are represented in Table 3.9. The analysis reveals that there are significant differences between age and diabetes duration in these categories of patients. All these parameters are already known risk factors for the occurrence of peripheral diabetic neuropathy.**

Table 3.9. Characteristics of patients stratified by the presence and severity of PND established based on the Sudoscan LL score

	Scor Sudoscan MI normal		Scor Sudoscan MI modificat		Scor Sudoscan MI sever		Total		Valoare P
	Medie	DS	Medie	DS	Medie	DS	Medie	DS	
Age (years)	**61.54**	**9.15**	**63.09**	**8.95**	**55.58**	**9.57**	**61.54**	**9.21**	**0.042**
Diabetes duration (years)	**7.96**	**5.92**	**8.39**	**5.83**	**13.08**	**7.73**	**8.26**	**6.06**	**0.016**
Height (cm)	165.57	9.19	166.02	10.06	167.33	8.39	165.73	9.29	0.794
Weight (kg)	**87.41**	**15.96**	**92.17**	**19.59**	**96.00**	**12.25**	**88.60**	**16.61**	**0.060**
BMI (kg/m2)	31.89	5.36	33.24	5.16	34.41	4.53	32.23	5.32	0.102
WC (cm)	**104.65**	**12.23**	**109.04**	**13.55**	**113.25**	**12.63**	**105.78**	**12.64**	**0.011**
Supine SBP (mmHg)	134.44	17.44	133.85	20.22	134.42	25.04	134.34	18.24	0.980
Supine DBP (mmHg)	76.82	10.35	75.67	11.77	73.50	14.57	76.48	10.79	0.502
Supine HR (bpm)	74.61	10.29	75.78	12.03	80.33	9.69	75.06	10.61	0.168
Orthostatism SBP(mmHg)	**130.00**	**17.76**	**128.22**	**21.20**	**114.75**	**16.37**	**129.02**	**18.53**	**0.020**
Orthostatism DBP (mmHg)	76.31	10.27	77.35	14.79	71.17	13.78	76.26	11.33	0.241
Orthostatism HR(bpm)	**78.30**	**11.31**	**80.72**	**13.42**	**86.25**	**7.52**	**79.06**	**11.66**	**0.040**
HR min Ewing (mmHg)	68.90	15.38	69.81	16.17	68.20	17.05	69.02	15.52	0.927
HR max Ewing (bpm)	**95.48**	**26.14**	**97.28**	**28.44**	**118.70**	**52.14**	**96.69**	**28.12**	**0.038**
Handgrip	**1.37**	**0.74**	**1.61**	**0.54**	**1.83**	**0.39**	**1.43**	**0.71**	**0.013**
HRV index	17.94	7.78	14.79	6.29	15.33	7.65	17.33	7.63	0.360
Ewing score	**3.12**	**1.96**	**4.50**	**1.89**	**6.58**	**1.98**	**3.51**	**2.12**	**<0.001**

The area under the receiver operating characteristic (ROC) curve of the Sudoscan score for the lower limbs to predict severe PND (Fig. 3.9.) was 0.845 (95% CI 0.766-0.923). The threshold of the Sudoscan LL score was 72.75, and the test had 80% sensitivity and 23.8% specificity to detect severe PND.

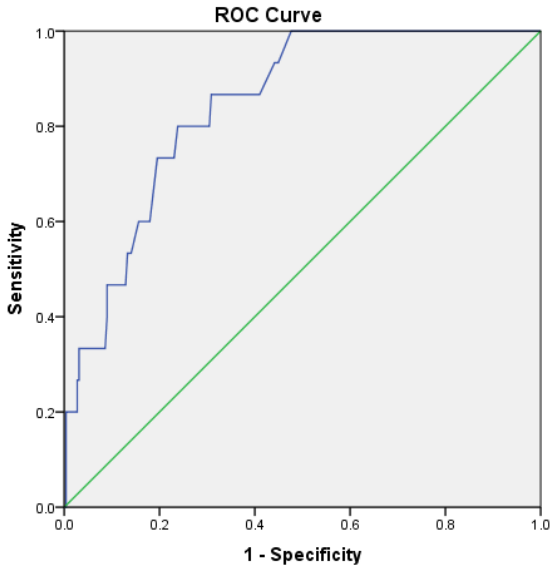


Figure 3.9. ROC curve of the Sudoscan LL score in detecting severe PND in type 2 diabetes patients.

Table 3.10 presents clinical factors associated with the Sudoscan LL score in type 2 diabetes patients using multiple linear regression. Standardized coefficients (β) and P-values for each factor provide information on the direction and significance of the associations.

Table 3.10. Clinical factors associated with the Sudoscan LL score in type 2 diabetes patients using multiple linear regression.

	Standard β- coefficient	P-value
Diabetes duration	-0.173	0.004
BMI	-0.119	0.042
Toronto Score	**-0.285**	<0.001
Ewing Score	-0.41	<0.001
FPG	**-0.205**	**0.001**
HbA1c	-0.22	<0.001
eGFR	**0.123**	**0.049**
ACR	**-0.144**	**0.021**

We divided the patients into three categories based on the presence and severity of diabetic retinopathy: without diabetic retinopathy (RD-), with non-proliferative diabetic retinopathy (RDN), and with proliferative diabetic retinopathy (RDP). The results highlight statistically significant differences between several variables (Table 3.11).

Table 3.11. Clinical characteristics and biochemical parameters stratified by the presence and severity of diabetic retinopathy.

	RD -		RDN		RDP		Total		
	Medie	DS	Medie	DS	Medie	DS	Medie	DS	Valoare P
Age (years)	**60.96**	**9.25**	**63.48**	**8.76**	**58.14**	**6.72**	**61.59**	**9.07**	**0.038**
Diabetes duration (years)	**6.35**	**4.93**	**11.33**	**6.39**	**13.71**	**6.40**	**8.26**	**6.06**	**<0.001**
Height (cm)	165.71	9.17	165.96	9.70	164.64	8.65	165.73	9.28	0.885
Weight (kg)	87.42	16.98	89.89	15.42	95.43	17.70	88.60	16.61	0.154
BMI (kg/m2)	**31.80**	**5.42**	**32.61**	**4.66**	**35.31**	**6.85**	**32.23**	**5.32**	**0.043**
SBP (mmHg)	132.68	17.84	137.77	18.33	134.21	20.90	134.34	18.24	0.110
FPG (mg/dl)	182.25	81.81	198.56	82.20	215.21	111.07	189.01	83.83	0.167
HbA1c (%)	7.99	2.01	8.22	1.51	8.59	1.66	8.09	1.85	0.382
TC (mg/dl)	201.04	56.26	193.62	53.13	186.08	50.81	198.01	55.03	0.435
HDL-c (mg/dl)	49.77	13.31	51.81	13.66	50.00	12.47	50.42	13.36	0.518
LDL-c (mg/dl)	112.31	49.11	103.25	49.99	105.43	42.71	109.11	49.09	0.378
TGL (mg/dl)	212.65	151.46	222.65	139.97	171.43	79.65	213.59	145.11	0.471
eGFR (ml/min/1.73m2)	79.67	22.44	73.04	28.38	70.86	28.81	77.16	24.89	0.083
ACR (mg/g)	**47.51**	**192.81**	**71.34**	**112.03**	**198.93**	**524.38**	**62.68**	**203.59**	**0.032**
Toronto Score	**5.01**	**3.03**	**7.27**	**2.66**	**8.79**	**3.93**	**5.91**	**3.21**	**<0.001**
Ewing Score	**3.02**	**2.03**	**4.32**	**1.96**	**4.57**	**2.34**	**3.51**	**2.12**	**<0.001**
Sudoscan Nephro score	**68.38**	**16.28**	**57.93**	**13.07**	**64.57**	**14.16**	**64.93**	**15.93**	**<0.001**
Sudoscan CAN score	**31.16**	**9.84**	**37.44**	**8.17**	**37.07**	**7.76**	**33.42**	**9.70**	**<0.001**
Susoscan Score LL	**79.24**	**11.30**	**71.92**	**15.32**	**73.89**	**12.66**	**76.69**	**13.15**	**<0.001**
Sudoscan Score UL	69.70	13.80	66.79	15.76	72.54	18.15	68.94	14.69	0.214

Performance of Sudoscan in diagnosing diabetic retinopathy

The area under the receiver operating characteristic (ROC) curve of the Sudoscan Nephro score to predict diabetic retinopathy (Fig. 3.10) was 0.679 (95% CI 0.614-0.743). The threshold of the Sudoscan Nephro score was 69.5, and the test had 84.7% sensitivity and 54.1% specificity to detect diabetic retinopathy.

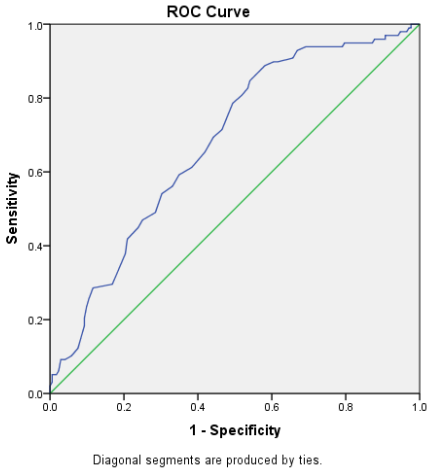


Fig. 3.11 ROC curve of the Sudoscan Nephro score in detecting diabetic retinopathy in type 2 diabetes patients.

The statistical analysis presented in Table 3.12 uses multiple linear regression to investigate the correlation between Sudoscan test variables and diabetic retinopathy in type 2 diabetes patients.

The Sudoscan LL score has a standardized β coefficient of -0.272 and a P-value <0.001, indicating a significant negative correlation between the Sudoscan LL score and diabetic retinopathy. This suggests that a decrease in the Sudoscan LL score is associated with greater severity of diabetic retinopathy.

The Sudoscan CAN score has a standardized β coefficient of 0.214 and a P-value of 0.01, indicating a significant positive correlation. This suggests that an increase in the Sudoscan NAC score is associated with greater severity of diabetic retinopathy.

The Sudoscan Nephro score has a standardized β coefficient of -0.128 and a P-value of 0.142, indicating no significant correlation between the Sudoscan Nephro score and diabetic retinopathy. Variations in the Sudoscan Nephro score do not appear to be associated with the severity of diabetic retinopathy.

Table 3.12. Sudoscan test variables in correlation with diabetic retinopathy in type 2 diabetes patients using multiple linear regression.

	Coeficient standard β	Valoarea P
Sudoscan score LL	**-0,272**	**<0.001**
Sudoscan score UL	0.036	0.571
Sudoscan CAN score	**0,214**	**0.01**
Sudoscan-Nefro Score	-0,128	0.142
Ewing tests Score	**0.313**	**<0.001**
Toronto Score	**0.219**	**<0.001**

4. Conclusions and personal contributions

In this doctoral thesis, we explored and analyzed the efficiency of using the Sudoscan test for diagnosing and monitoring cardiovascular autonomic neuropathy and other complications associated with type 2 diabetes.

Sudomotor dysfunction measured by Sudoscan was correlated with the risk of progression to dialysis in patients with chronic kidney disease and type 2 diabetes. The Sudoscan test had 63.9% sensitivity and 33.3% specificity to detect CKD (7). These results highlight the potential of the Sudoscan test as a predictive biomarker for severe diabetes complications, allowing for earlier and more effective interventions.

The study confirmed the significant role of sudomotor dysfunction in identifying type 2 diabetes patients at high cardiovascular risk. The use of the Ewing test and Sudoscan scores offers a promising auxiliary tool in assessing cardiovascular risk. The Sudoscan test had a sensitivity of 34.3% and a specificity of 79% to detect very high cardiovascular risk(8). Sudomotor dysfunction is closely linked to cardiovascular autonomic neuropathy, which is one of the most dangerous complications of diabetes.

The study results showed that the Sudoscan test proved to be a useful and efficient tool in detecting severe peripheral diabetic neuropathy in type 2 diabetes patients. This underscores the importance of the test in current clinical practices, providing a non-invasive and rapid method for assessing peripheral neuropathy. The study showed a significant negative correlation between the Sudoscan LL (lower limbs) score and the severity of diabetic retinopathy. Thus, a decrease in the Sudoscan score is associated with greater severity of diabetic retinopathy.

Novelty and original contributions of the study

This work brings new contributions to the specialized literature, demonstrating significant correlations between sudomotor dysfunction and cardiovascular risk, as well as between sudomotor dysfunction and the risk of CKD progression to dialysis. These findings have not been previously described in the specialized literature and highlight the potential of using Sudoscan as an innovative tool for early identification of patients at high risk of cardiovascular and renal complications. These correlations underscore the importance of monitoring sudomotor function in the holistic management of type 2 diabetes patients.

Integration of Sudoscan into clinical practice

I have demonstrated that the Sudoscan test can be effectively integrated into routine clinical practice to improve the early identification of diabetic complications. This can guide early therapeutic interventions and contribute to preventing the progression of severe complications associated with type 2 diabetes. Integrating this test into regular patient evaluations can facilitate continuous monitoring of their health status and adjust treatments according to individual needs.

Multidisciplinary evaluation of diabetes patients

We emphasized the importance of a multidisciplinary evaluation of diabetes patients, including monitoring sudomotor function, glycemic control, and renal function assessment. A multidisciplinary approach allows for comprehensive and proactive management of diabetic risks and complications. Collaboration between diabetologists, cardiologists, nephrologists, and ophthalmologists can ensure integrated patient management, maximizing intervention efficiency and improving patient outcomes. This holistic strategy can reduce the incidence and severity of complications, enhancing the quality of life for diabetes patients.

Development and validation of screening methods

We contributed to the development and validation of the method using the Sudoscan test for screening peripheral diabetic neuropathy and other complications. We demonstrated that Sudoscan can be used as a non-invasive additional tool for early identification of these complications. Validating this method showed that Sudoscan can be widely applied to patients, providing an efficient and accessible alternative for assessing nerve function and monitoring the health status of individuals with type 2 diabetes.

Future perspectives

Future studies should focus on validating and expanding these findings through longitudinal studies with larger and more diverse samples. Research should also include evaluating the cost-effectiveness of using Sudoscan in clinical practice and developing clinical guidelines that integrate this test into the standard management of diabetes.

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List of scientific publications

1. **Nica AE**, Rusu E, Dobjanschi C, Rusu F, Sivu C, Parlițeanu OA, Sivu C, Radulian G. The Relationship between the Ewing Test, Sudoscan Cardiovascular Autonomic Neuropathy Score and Cardiovascular Risk Score Calculated with SCORE2-Diabetes. Medicina (B Aires). 2024 May 17;60(5):828., IF= 2.6 (Chapter 4)

Link: https://www.mdpi.com/1648-9144/60/5/828

2. **Nica AE**, Rusu E, Dobjanschi CG, Rusu F, Parliteanu OA, Sivu C, Radulian G. The Importance of Evaluating Sudomotor Function in the Diagnosis of Cardiac Autonomic Neuropathy. Cureus [Internet]. 2024 Mar 29 [cited 2024 May 20];16(3). IF= 1.2 (Chapter 5)

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3. **Nica AE**, Rusu E, Dobjanschi CG, Rusu F, Parliteanu OA, Vinereanu I V., Sivu C, Radulian G. Sudoscan's Effectiveness in Identifying Chronic Kidney Disease in Patients With Type 2 Diabetes. Cureus [Internet]. 2024 May 15 [cited 2024 May 20];16(5). IF= 1.2 (Chapter 6)

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