Investigating the Prevalence of Autonomic Neuropathy in Diabetic Patients with Urinary Irritation Symptoms Without a Known Cause

Anahita Ansari Djafari[1], Babak Javanmard[2]*, Ali Koohifard[2], Fatemeh Hojjati[3], Amir Alinejad Khorram[2], Zahra Razzaghi[1], Seyyed Ali Hojjati[1]

Purpose: Evaluating pseudomotor performance can be a valuable tool for investigating the peripheral autonomic nervous system in diabetic patients. Sudoscan, a simple and non-invasive method for assessing pseudomotor performance, has been developed in recent years. This study aimed to investigate autonomic neuropathy using Sudoscan in diabetic patients with lower urinary tract symptoms (LUTS) of unknown cause.

Materials and Methods: In this cross-sectional study conducted from April 2022 to April 2023, we included 195 patients with type 2 diabetes who were referred to the urology clinic. We extracted demographic, clinical, and laboratory data from the patient files and evaluated urinary symptoms using the International Prostate Symptom Score (IPSS) questionnaire. Patients underwent Sudoscan testing to evaluate autonomic neuropathy in the physical medicine and rehabilitation clinic. To further assess urinary irritative symptoms, patients underwent urodynamic studies (UDS) and ultrasonography.

Results: The Sudoscan test results showed that autonomic neuropathy was present in 77 patients (40%), with 43 (22.1%) having moderate and 44 (22.6%) having severe neuropathy. Patients with autonomic neuropathy were found to be older, had longer diabetes durations, higher average blood glucose levels, and higher creatinine levels. Additionally, we found a significant correlation between autonomic neuropathy and signs of high post-void residue on ultrasound and detrusor contraction disorders on UDS (p-value < 0.05).

Conclusion: Our study found a higher prevalence of autonomic neuropathy in diabetic patients with LUTS using Sudoscan (40%). Longer diabetes duration and poor glycemic control were associated with an increased risk of autonomic neuropathy linked with LUTS, such as urge incontinence.

Keywords: Autonomic Neuropathy; Lower Urinary Tract Symptoms; Type 2 diabetes

INTRODUCTION

Peripheral neuropathy affects up to 70% of diabetic patients over the course of their lifetime. This type of neuropathy often involves the small fibers of the terminal nerves, leading to painful neuropathy. Unfortunately, up to 50% of people with diabetic neuropathy are asymptomatic, which can lead to delays in diagnosis and increased mortality, disability, and decreased quality of life.

Pseudomotor dysfunction is one of the ways to detect neurophysiological disorders in the early stages of peripheral neuropathy. Sweat glands are innervated by small unmyelinated (type C) sympathetic nerve fibers responsible for sweat secretion[(1)]. Due to their unique characteristics, including low thickness, high length, and lack of myelin coating, these fibers are more susceptible to damage caused by metabolic changes such as hyperglycemia[(2)].

Fortunately, the destruction of type C fibers innervating sweat glands has been studied, and pseudomotor dysfunction in diabetic patients has been linked to autonomic neuropathy[(1)]. Therefore, evaluating pseudomotor function can be a valuable tool for investigating the peripheral autonomic nervous system in diabetic patients.

Lower urinary tract symptoms (LUTS) are a common manifestation of diabetic neuropathy. Diabetes can cause dysfunction of the urothelium and smooth muscles, as well as neurological disorders of the bladder through various mechanisms. The progression of urinary tract symptoms and hyperactivity or hypoactivity of the detrusor muscle are related to the progression of diabetes[(3)].

Sudoscan is a non-invasive and simple method for evaluating the function of sweat glands, which has been developed in recent years. The device uses a small, painless probe to capture electrical signals from the skin, which are then analyzed to provide information about sweat gland function, nerve conduction, and other physiological processes. It works by exploiting the electrochemical reaction between chlorine ions in sweat and electrodes on a stainless-steel plate, which are placed on the palms and feet for two to three minutes. By providing a comprehensive picture of sweat gland function and autonomic nervous system activity, Sudoscan has

[1]Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[2]Urology Department, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[3]Physical medicine & rehabilitation research center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
*Correspondence: Urology Department , School of Medicine , Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Tel: 00989126988600. E mail: drbabakjavanmard@gmail.com.
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Table 1. Demographic variables of the groups.

Variables	Sudoscan results			*P* -value
	Normal	Moderate neuropathy	Severe neuropathy	
Age (year)	59.53 ± 8.72	65.49 ± 10.24	66.32 ± 9.20	< 0.001
Gender, female %	82 (59%)	28(20.1%)	29 (20.9%)	0.278
BMI (kg/m^2)	27.94 ± 3.73	28.64 ± 4.17	28.49 ± 4.57	0.713
Diabetes duration (year)	9.26 ± 4.88	13.95 ± 7.60	15.07 ± 7.87	< 0.001
HbA1c (%)	7.08 ± 1.25	8.35 ± 1.55	9.63 ± 2.46	< 0.001
FBS (mg/dL)	131.41 ± 17.89	148.42 ± 26.52	157.76 ± 33.81	< 0.001
Serum creatinine (mg/dL)	1.38 ± 0.27	1.52 ± 0.29	1.61 ± 0.33	< 0.001
IPSS score	16.03 ± 1.99	15.81 ± 1.85	15.05 ± 2.44	0.020
Urinary urge incontinency %	3.7	16.3	22.7	0.001
PVR in ultrasound %	8 (7.4%)	10 (23.3%)	15 (34.1%)	< 0.001
UDS % Normal	100 (92.6%)	27 (62.8%)	25 (56.8%)	< 0.001
Overactive	8 (7.4%)	15 (34.9%)	13 (29.5%)	
Underactive	0 (0%)	1 (2.3%)	6 (13.6%)	

body mass index; kg: kilogram; m2: square meter; HbA1c: Hemoglobin A1c; FBS: fasting blood sugar; mg: milligram; dL: deciliter; IPSS: International Prostate Symptom Score; PVR: post-void residue; UDS: urodynamic study.

been used to diagnose and monitor conditions such as hyperhidrosis, diabetes, and small fiber neuropathy. When a low voltage of 4 volts is applied to the electrodes, chlorine ions are absorbed into the sweat, allowing for the measurement of pseudomotor dysfunction. This is based on the electrochemical conductivity of the skin, which is divided into three subgroups: without impairment (more than 60 microsiemens), moderate impairment (40-60 microsiemens), and severe impairment (less than 40 microsiemens)[1,4].

Objective evaluation of lower urinary tract function can only be achieved through urodynamic studies, which have been extensively researched and validated over years. Urodynamic examination is commonly performed in patients with lower urinary tract symptoms (LUTS) and provides anatomical and functional details of the lower urinary tract[5,6]. The primary goal of this study is to investigate the prevalence of autonomic neuropathy in diabetic patients with unexplained LUTS using Sudoscan and compare its results with

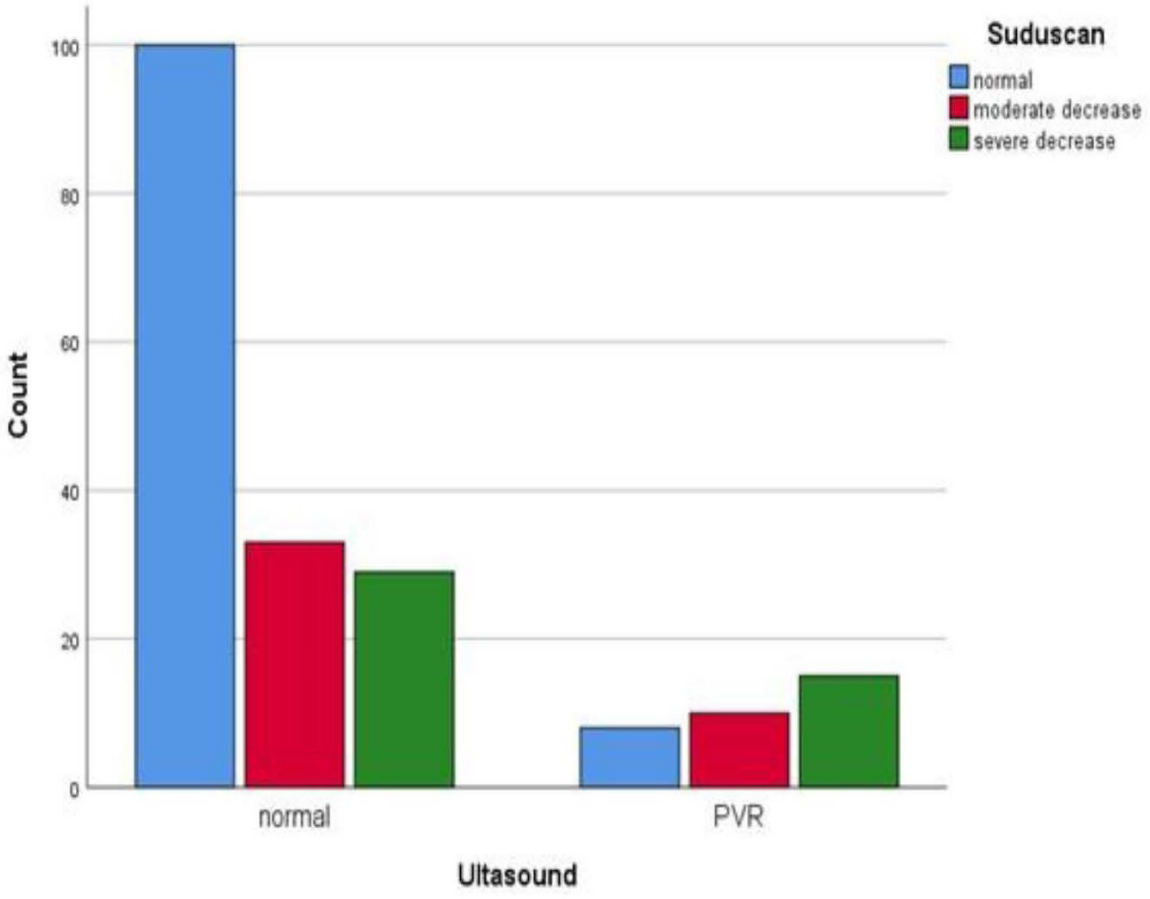

Figure 1. patients with post-void residual (PVR) in ultrasound were found to have a significantly higher frequency of autonomic neuropathy in Sudoscan

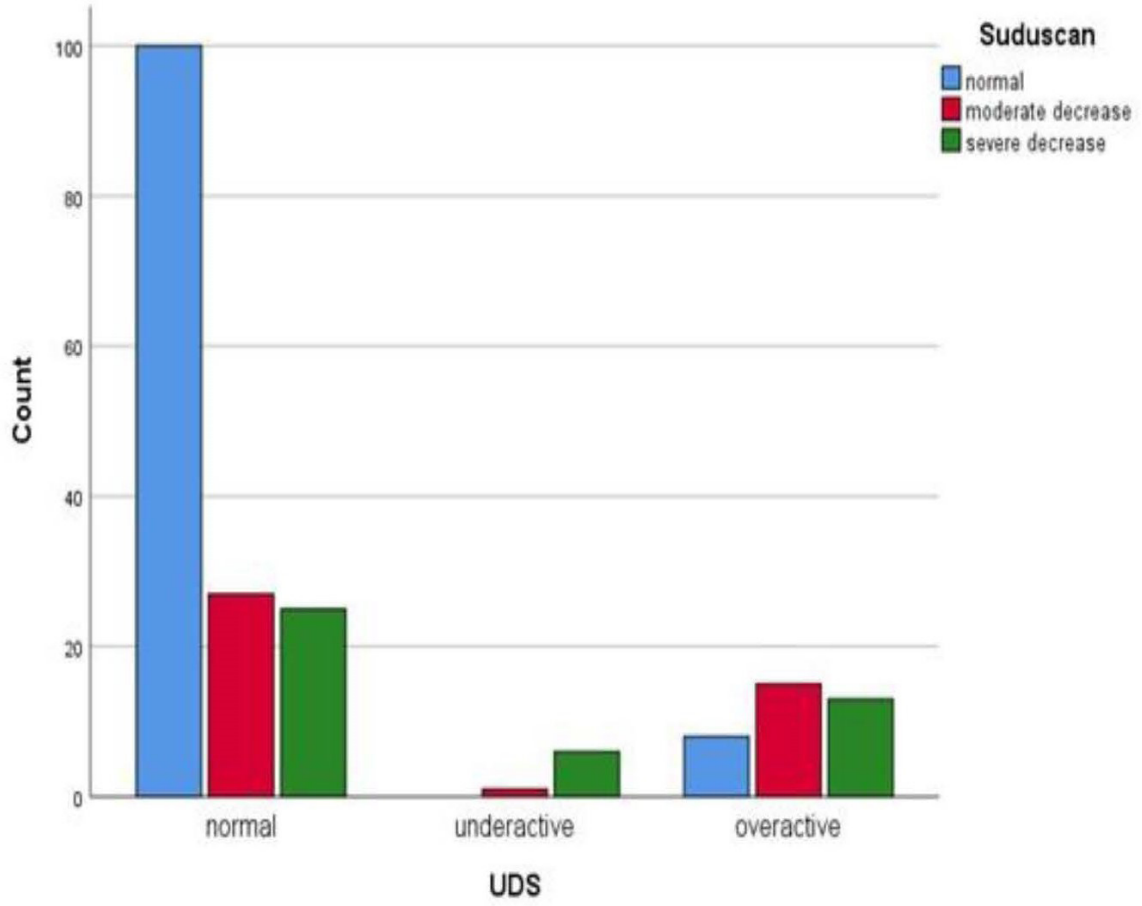

Figure 2. Comparison of Sudoscan and UDS results. No statistically significant relationship was found between underactive and overactive bladder in UDS with Sudoscan results.

ultrasound and urodynamic evaluation. The reason for choosing Sudoscan in this study is that it offers several advantages. Firstly, Sudoscan is a cost-effective and non-invasive option compared to urodynamic studies, which makes it a more appealing choice for this study. Secondly, no previous research has been conducted using Sudoscan to examine the lower urinary tract system, making it a novel and innovative approach in this field.

MATERIALS AND METHODS

This study was conducted as a descriptive cross-sectional survey from April 2022 to April 2023. Patients with type 2 diabetes referred to the Urology Clinic and suffering from lower urinary tract symptoms (LUTS) were eligible to participate. Convenience sampling was used to select patients who met the inclusion and exclusion criteria until the sample size was complete.

The study included type 2 diabetic patients with LUTS, who had a negative urine culture in the last 3 months, were under the supervision of an endocrinologist, and had controlled diabetes, regardless of the duration of their diabetes. Patients with other urological diseases (such as Benign Prostatic Hyperplasia (BPH), nephrolithiasis, urinary tract anatomical disorders, etc.), neurological diseases (cerebrovascular accidents, multiple sclerosis, dementia, Parkinson's, etc.), history of urological and neurological surgeries, and other diseases that cause urinary symptoms (such as diabetes insipidus, untreated diabetes mellitus, etc.) were excluded from the study. Additionally, patients taking medications that induce urinary symptoms or treating urinary symptoms, and those with an obstructive pattern in urodynamic evaluations, were excluded.

Patients' urinary symptoms were evaluated using the International Prostate Symptom Score (IPSS) questionnaire. Then, selected patients were referred to the physical medicine and rehabilitation clinic for Sudoscan (impetomedical) to evaluate the extent of diabetic neuropathy involvement and autonomic dysfunction. Sudoscan was used on both hands and feet equally. For additional evaluation of urinary symptoms, all patients underwent ultrasound of the urinary tract to rule out obstructive diseases that can cause LUTS and to evaluate significant post-void residual (PVR) urine volume of bladder (40 cc and more) and urodynamic studies (UDS) to investigate functional disorders of the bladder. Male patients underwent cystoscopy to ensure the absence of posterior urethral valve, obstructing prostate hyperplasia, and urethral stricture. Female patients were carefully examined for the absence of rectocele, cystocele, and urinary tract abnormalities.

The basic and clinical information of the patients, including age, sex, duration of diabetes, and body mass index (BMI), was extracted from their files. Additionally, fasting blood sugar (FBS), hemoglobin A1c (HbA1c), and serum creatinine were measured in all

patients. After collecting the mentioned information, a statistical analysis was performed to investigate the prevalence of diabetic neuropathy in diabetic patients suffering from LUTS.

A written consent form was obtained from all the patients participating in this study and they were assured that the principle of confidentiality will be observed regarding all information. Data were analyzed with SPSS for Windows 26.0 (IBM Corp Released 2016, NY, USA). Mean ± standard deviation and frequency(percent) were used to describe quantitative and qualitative variables, respectively. The normality test was done with Shapiro Wilks test. For comparing the mean between groups ANOVA or Kruskal-Wallis tests were used based on normal or non-parametric variables distribution. Chi-square test was used to compare the frequency between groups. The p-value less than 0.05 was considered statistically significant.

The study was approved by the ethics committee of the Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1401.254).

RESULTS

In this cross-sectional study, 195 patients with type 2 diabetes with lower urinary tract symptoms were included. The mean age of the participants was 62.37±9.67 and, 139(71.3%) of them were female. The mean BMI was 28.22 ± 4.02 kg/m^2. The diabetes duration, FBS, HbA1c and serum creatinine were 11.61 ± 6.81 years, 141.04 ± 26.57 mg/dL, 7.94 ± 1.96 percent and 1.47 ± 0.30 mg/dL, respectively. 21(10.8%) patients complained of urinary urge incontinence, all of them were females. 34 (60%) of men complained of erectile dysfunction. The mean IPSS score was 15.76 ± 2.10. Grading of patients' symptoms based on the IPSS questionnaire showed that all participants had moderate symptoms. The ultrasound results of urinary tract were normal in 162(83.1%) patients, and significant PVR (40 cc and more) was observed in 33(16.9%) patients. The results of UDS examinations showed that in 152(77.9 %) patients the detrusor contraction was normal and the bladder was underactive in 7 (3.6%) patients and overactive in 36 (18.5 %) patients. The results of the Sudoscan showed autonomic neuropathy in 77 patients, of which 43 (22.1%) patients had moderate and 44 (22.6%) patients had severe neuropathy.

The comparison between demographic and clinical information and results of Sudoscan was duplicated in **Table 1**. Comparison of Sudoscan results with ultrasound results showed that there was a significant relationship between these two diagnostic methods, so that in patients with PVR in ultrasound, the frequency of autonomic neuropathy in Sudoscan was significantly higher (**Figure 1**). Also, the comparison of Sudoscan results with UDS results showed that in patients with bladder detrusor contraction disorder in UDS (either overactive or underactive), the frequency of autonomic neuropathy in Sudoscan was reported to be significantly higher than normal subjects, however, no statistically significant relationship was found between underactive and overactive bladder in UDS with Sudoscan result (p = 0.167) (**Figure 2 and Table 1**).

DISCUSSION

Sudoscan has been shown to exhibit good reproducibility in various physiological conditions. Additionally, its focus on chloride concentration makes it less dependent on sweat rate compared to other methods used to assess sweat performance[1,7-9]. Overall, Sudoscan is a promising tool for assessing pseudomotor function, offering a rapid, non-invasive, and reproducible approach that is less affected by variability in sweat rate.

This study aimed to investigate the prevalence of autonomic neuropathy in diabetic patients with unexplained lower urinary tract symptoms (LUTS) using the Sudoscan device, and to compare its results with ultrasound and urodynamic evaluation. The findings showed that 44.7% of diabetic patients with unexplained LUTS had autonomic neuropathy, with 22.6% of these patients having severe neuropathy. The prevalence of diabetic autonomic neuropathy in previous studies has ranged from 13.5% to 62%, with subclinical cases accounting for 88-22% of cases, and confirmed cases estimated between 2.6% and 11%[10]. The analysis of factors associated with autonomic neuropathy revealed that patients with this condition had a higher prevalence of urinary irritative symptoms and urinary urge incontinence. These findings suggest that the increased duration of diabetes and inadequate glycemic control in diabetic patients are associated with an increased risk of autonomic neuropathy, which leads to urinary symptoms. Additionally, in 60% of male patients in our study, some degree of erectile dysfunction was observed. A review study[11] reported a mean prevalence of erectile dysfunction among all diabetic patients of 52.5%, and a rate of 66.3% in type 2 diabetes patients, which is consistent with our findings and highlights the high prevalence of this disorder in diabetic patients.

The results of ultrasound imaging of the urinary tract system revealed that urinary voiding disorder, characterized by residual urine, was present in 16.9% of patients. Additionally, the urodynamic studies (UDS) showed that 3.6% of patients had decreased bladder detrusor activity, resulting in a significant post-void residual (PVR) volume of 40 cc or above, while 18.5% of patients had increased bladder detrusor activity, leading to urinary irritative symptoms and urgency incontinence. Notably, a significant correlation was found between the ultrasound and UDS findings and the Sudoscan results, indicating a direct and significant relationship between autonomic neuropathy detected by Sudoscan and PVR in ultrasound, as well as bladder detrusor disorder in UDS. Specifically, among patients with PVR in ultrasound, 75.8% showed some degree of autonomic neuropathy in Sudoscan. Moreover, all patients with underactive bladder and 77.8% of patients with overactive bladder in UDS exhibited different degrees of autonomic neuropathy in Sudoscan.

A study by Selvarajah et al.[12] investigated the performance of the Sudoscan device in diagnosing diabetic peripheral neuropathy (DPN) and found that it had excellent sensitivity (87.5%) and good specificity (76.2%) in detecting DPN. In addition, several small studies have investigated the use of Sudoscan to predict microvascular complications other than neuropathy[13]. Freedman conducted a study involving 390 African and European Americans with type 2 diabetes and 166 controls, and found an independent association between ESC and GFR in African Americans, but not in Europeans[14]. The study also notes that pseudomotor dysfunction may have a similar pathogenesis to diabetic nephropathy. Processes downstream of sustained hyperglycemia, in-

cluding activation of protein kinase C, activation of the polyol pathway, and formation of advanced glycosylation end products, are implicated in reduced endorenal blood flow and direct neuronal injury[15].

The study also has limitations. One of the main limitations is the cross-sectional and descriptive nature of the study, which limits the generalizability of Sudoscan results in diagnosing autonomic neuropathy. The absence of a control group means that the findings cannot be extrapolated to other populations. Another limitation is the lack of a gold standard method for diagnosing autonomic neuropathy in diabetic patients, which makes it difficult to evaluate the sensitivity, specificity, and diagnostic accuracy of Sudoscan. However, this study is the first to investigate the relationship between autonomic neuropathy and lower urinary tract symptoms in diabetic patients using Sudoscan.

CONCLUSIONS

The correlation analysis between Sudoscan outcomes and ultrasound imaging revealed a striking association between the two diagnostic tools. In particular, patients exhibiting post-void residual (PVR) in ultrasound scans were more likely to exhibit autonomic neuropathy in Sudoscan assessments. Furthermore, a comprehensive review of Sudoscan results alongside urodynamic studies (UDS) revealed that individuals with bladder detrusor dysfunction in UDS (either overactive or underactive) had a significantly higher incidence of autonomic neuropathy in Sudoscan compared to those with normal bladder function. However, no statistically significant correlation was found between underactive and overactive bladder patterns in UDS and Sudoscan outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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