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Electro diagnostic Evaluation of Autonomic Dysfunction in Diabetes Mellitus in Baghdad, Iraq

NihalMohanadLutfi [*],AbdulnasirHussin Ameer [**]
[*] *M.B.Ch.B, Ministry of Health.*
[**] *M.B.Ch.B, MSc.,Ph.D, College of Medicine, Baghdad University.*
Corresponding author: NihalMohanadLutfi

Abstract
Background: Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes. The most studied and clinically important form of DAN is cardiovascular autonomic neuropathy.
Aim of study: To assess the autonomic dysfunction in diabetics electrodiagnoctically using reliable tests by SSR and R-R interval tests.
Patients and Methods: A cross-sectional study was conducted in the Electromyography unit in Baghdad Teaching Hospital between (Feb/1/2018 – May/15/2018). It included all adult male and female with symptoms of neuropathy or autonomic dysfunction. Pregnant women were excluded from the study. Neurological tests were performed as (Sympathetic Skin Response, and R-R interval including normal and deep breath, Valsalva and tilt tests).
Results: Means of SSR amplitude, R-R interval (Valsalva), and R-R interval (tilt) tests were significantly higher in non-diabetic patients than diabetics (2.19 versus 0.541, P= 0.001; 1.75 versus 1.48, P= 0.017; and 1.44 versus 1.01, P= 0.002 respectively).They were also significantly higher in controlled than in uncontrolled diabetic patients (1.69 versus 0.15, P= 0.044; 1.99 versus 1.31, P= 0.039; and 1.23 versus 0.941, P= 0.022 respectively). Cut points of these tests between controlled and uncontrolled diabetic patients were (0.81, 1.84, and 1.04 respectively).This mean that all patients with testsbelow these values can be considered uncontrolled diabetics.
Conclusion: SSR amplitude, and R-R interval tests are good electro diagnostic tests to evaluate the autonomic dysfunction affected by DM, and to assess the severity of autonomic dysfunction in uncontrolled DM and differentiating them from those with controlled DM.

Keywords: Diabetes, Autonomic Neuropathy, RR Interval, Sympathetic Skin Response.

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I. INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both and the severity of symptoms is due to the type and duration of diabetes[(1)]. DM resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death [(2)].

In 2014, the International Diabetes Federation (IDF) estimated that diabetes resulted in 4.9 million deaths worldwide [(3)]. In both types of DM, metabolism of all the main foodstuffs is altered, blood glucose concentration increases, cell utilization of glucose falls and utilization of fats and proteins increases [(4)]. DM can affect many different organs and over time, can lead to serious complications as microvascular (include neuropathy, nephropathy and retinopathy) or macrovascular (include cardiovascular disease, stroke, and peripheral vascular disease) [(5)].

Diabetic autonomic neuropathy (DAN) is one of the most common complications of DM. Clinical symptoms including; orthostatic hypotension, resting tachycardia, exercise intolerance, pseudomotor dysfunction, erectile dysfunction, constipation, and gastroparesis [(6)]. The prevalence of DAN in both type1 DM and type 2DM, varies from 16.6 to 20%, and it may increase to 65% with increasing age and DM duration, the prevalence may increase up to 38% in type 1 DM and 44% in type 2DM patients aged 40–70 years and up to 35% in type 1 DM and 65% in type 2DM patients with long standing diabetes [(7, 8)]. Several mechanisms, including neurovascular insufficiency, metabolic insult to nerve fibers and autoimmune are related to pathogenesis of DAN [(9)]. The etiology of autonomic impairment is not well-understood yet. A few studies have reported that inflammation markers (C-reactive protein, IL-6) and decreased heart rate variability are related to DAN[(10)].

Diagnosis achieved through an initial laboratory evaluation (complete blood count, metabolic panel, liver function and immunoelectrophoresis) [(11)] and special procedures like tests of autonomic cardiovascular reflexes (Valsalva maneuvers, Deep breathing and Head-up tilt test), testing of sudomotor function (Thermoregulatory sweat test,sympathetic skin response (SSR), quantitative Sudomotor Axon Reflex Test) and Urological and Gastrointestinal dysfunction studies [(12, 13)]. Treatment of autonomic neuropathy includestreating the underlying disease to manage the disease or condition damaging your nerves as DM and managing specific symptoms. Some treatments can relieve the symptoms of autonomic neuropathy. Treatment is based on what part of your body is most affected by nerve damage [(14)]. The aim of this study is to assess the autonomic dysfunction in diabetic patients electro diagnostically by using reliable tests by SSR and RR interval tests.

II. PATIENTS AND METHODS

Study Design and Setting: This is a cross-sectional study that was conducted in the Electromyography unit in Baghdad Teaching Hospital during the period between (Feb/1/2018 – May/15/2018).

Study Population and sample size: The study population included 50 adult male and female individuals who attended the EMG unit after referral from Neurological Department in Baghdad Teaching Hospital due to the presence of symptoms of neuropathy or autonomic dysfunction. Pregnant women were excluded from this study. The data collection was done through unit visits once a week. A questionnaire had been applied to all attendants to collect needed informationon certain socio – demographic variables (age and gender), duration of disease, history of DM with certain details (Type of DM, type of management, and HbA1C level) and information about clinical features (Postural dizziness, palpitation, and dry skin).

Neurological tests performed: All study patients were subjected to the following neurological tests and analyzed by Medtronic Key point 3 (Sympathetic Skin Response (SSR) test, and R-R interval variability (RRIV) test). Four tests were available for RRIV (normal breathing, deep breathing, Valsalva and tilt). Verbal permission was obtained from each participant prior to collecting data. All personal information was kept anonymous. Data were exclusively used for the purpose of this study. Official approval was granted from the scientific committee in the Department of Physiology which was later approved by the Council of the College of Medicine / Baghdad University. Official approval was granted from the Research committee in the Ministry of Health.

Statistical analysis: The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables among study groups accordingly. ROC curve represents sensitivity, specificity and cut point of SSR amplitude, R-R interval (Valsalva), and R-R interval (tilt) tests was used between controlled and uncontrolled diabetic patients. A level of P – value less than 0.05 was considered significant.

III. RESULTS

This study involved 50 patients. All of them had symptoms of neuropathy or autonomic dysfunction. The mean age of the patients was 47.1 ± 15.08 years; 72% were males. Clinical data about DM showed that56% were diabetics; 85.7% of them were type 2; 78.6% were using oral treatment and 25% were controlled (HbA1c ≤ 6%). Duration of DM was more than 10 years in 67.9% of them as shown in table (1).

Table 1: Distribution of study patients by general characteristics

Variable	No. (n=50)	Percentage (%)	
Age (Years)			
< 40	20	40.0	
40 – 59	17	34.0	
≥ 60	13	26.0	
Gender			
Male	36	72.0	
Female	14	28.0	
			DM
Diabetic	28	56.0	
Non-diabetic	22	44.0	
Type of DM			**n= 28**
Type 1	4	14.3	
Type 2	24	85.7	
Treatment of DM			**n= 28**
Oral	22	78.6	
Insulin	6	21.4	

DM Duration (Years)			**n= 28**
	< 5	2	7.1
	5 - 9	7	25.0
≥ 10		19	67.9
HbA1c Level (%)			**n= 28**
≤ 6		7	25.0
>6		21	75.0

Figure 1 shows the clinical presentation of diabetic patients. We noticed that the most common clinical presentation for diabetic patients was postural dizziness (89%).

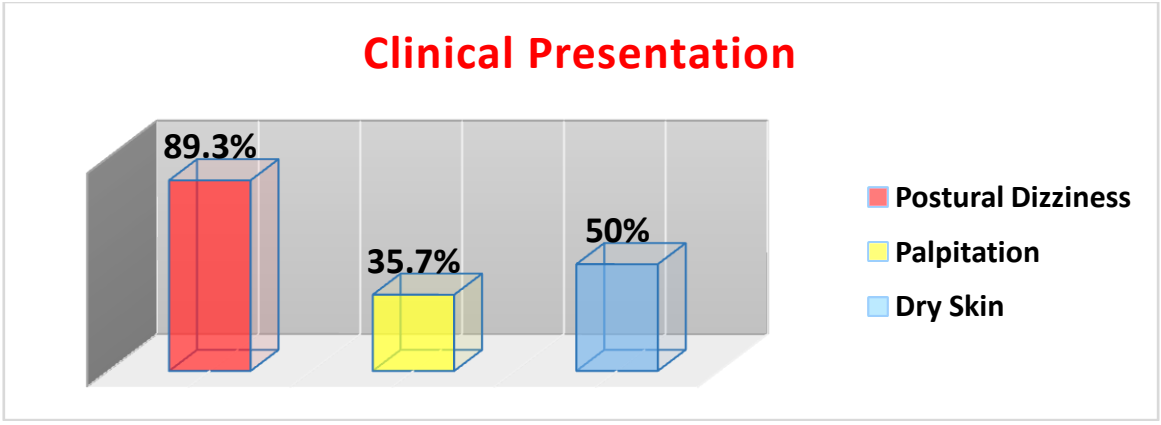

Figure 1: Clinical presentation of diabetic patients

In table 2, we found that Means of SSR amplitude, R-R interval (Valsalva), and R-R interval (tilt) tests were significantly higher in non-diabetic patients than diabetics (2.19 versus 0.541, P= 0.001; 1.75 versus 1.48, P= 0.017; and 1.44 versus 1.01, P= 0.002 respectively).No statistical significant differences in means of SSR latency, R-R interval (normal breath), and R-R interval (deep breath) tests between diabetic and non-diabetic patients (P ≥ 0.05).

Table 2: Comparison between diabetic and non-diabetic patients by certain neurological tests

Neurological Test	**DM**		**P - Value**
	Diabetic Mean ± SD	**Non-diabetic Mean ± SD**	
SSR Latency	1.238 ± 0.7	1.37 ± 0.53	**0.442**
SSR Amplitude	0.541 ± 1.04	2.19 ± 1.15	**0.001**
R-R interval (Normal Breath)	0.254 ± 0.38	0.197 ± 0.13	**0.463**
R-R interval (Deep Breath)	0.452 ± 0.37	0.341 ± 0.09	**0.134**
R-R interval (Valsalva)	1.48 ± 0.51	1.75 ± 0.24	**0.017**
R-R interval (Tilt)	1.01 ± 0.2	1.44 ± 0.56	**0.002**

When we compared the same neurological tests results between patients with controlled and uncontrolled DM, we noticed that means of SSR amplitude, R-R interval (Valsalva), and R-R interval (tilt) tests were significantly higher in controlled than in uncontrolled diabetic patients (1.69 versus 0.15, P= 0.044; 1.99 versus 1.31, P= 0.039; and 1.23 versus 0.941, P= 0.022 respectively).No statistical significant differences in means of SSR latency, R-R interval (normal breath), and R-R interval (deep breath) tests between controlled and uncontrolled diabetic patients (P ≥ 0.05) as shown in table (3).

Table 3: Comparison between controlled and uncontrolled diabetic patients by neurological tests

Neurological Test	**HbA1c Level**		**P – Value**
	Controlled Mean ± SD	**Uncontrolled Mean ± SD**	
SSR Latency	1.36 ± 0.43	1.19 ± 0.77	**0.495**
SSR Amplitude	1.69 ± 1.61	0.15 ± 0.239	**0.044**

R-R interval (Normal Breath)	0.563 ± 0.62	0.15 ± 0.19	**0.134**
R-R interval (Deep Breath)	0.411 ± 0.22	0.466 ± 0.41	**0.663**
R-R interval (Valsalva)	1.99 ± 0.68	1.31 ± 0.29	**0.039**
R-R interval (Tilt)	1.23 ± 0.26	0.941 ± 0.15	**0.022**

ROC curve represents sensitivity, specificity and cut point of H reflex, SSR amplitude, R-R interval (Valsalva), and R-R interval (tilt) tests between controlled and uncontrolled diabetic patients. The cut point of SSR amplitude test was 0.81 with AUC= 88.6%, sensitivity= 95.2%, specificity= 85.7%, accuracy= 92.8%, PPV= 95.2%, NPV= 85.7%, so this mean that all patients with SSR amplitude test < 0.81 can be considered uncontrolled diabetics as shown in figure (2).

Concerning R-R interval (Valsalva) test, the cut point was 1.84 with AUC= 82.3%, sensitivity= 90.4%, specificity= 71.4%, accuracy= 85.7%, PPV= 90.4%, NPV= 71.4%, so this mean that all patients with R-R interval (Valsalva) test < 1.84 can be considered uncontrolled diabetics as shown in figure (3)

About R-R interval (tilt) test, the cut point was 1.04 with AUC= 89.1%, sensitivity= 90.4%, specificity= 71.4%, accuracy= 85.7%, PPV= 90.4%, NPV= 71.4%, so this mean that all patients with R-R interval (tilt) test < 1.04 can be considered uncontrolled diabetics as shown in figure (4).

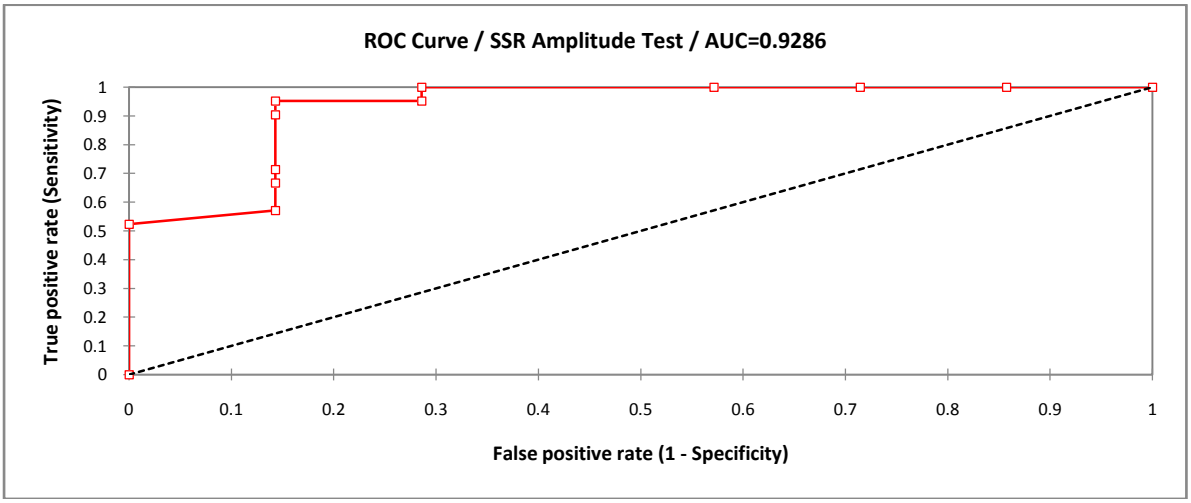

Figure 2: ROC curve represents sensitivity, specificity and cut point of SSR amplitude test between controlled and uncontrolled diabetic patients

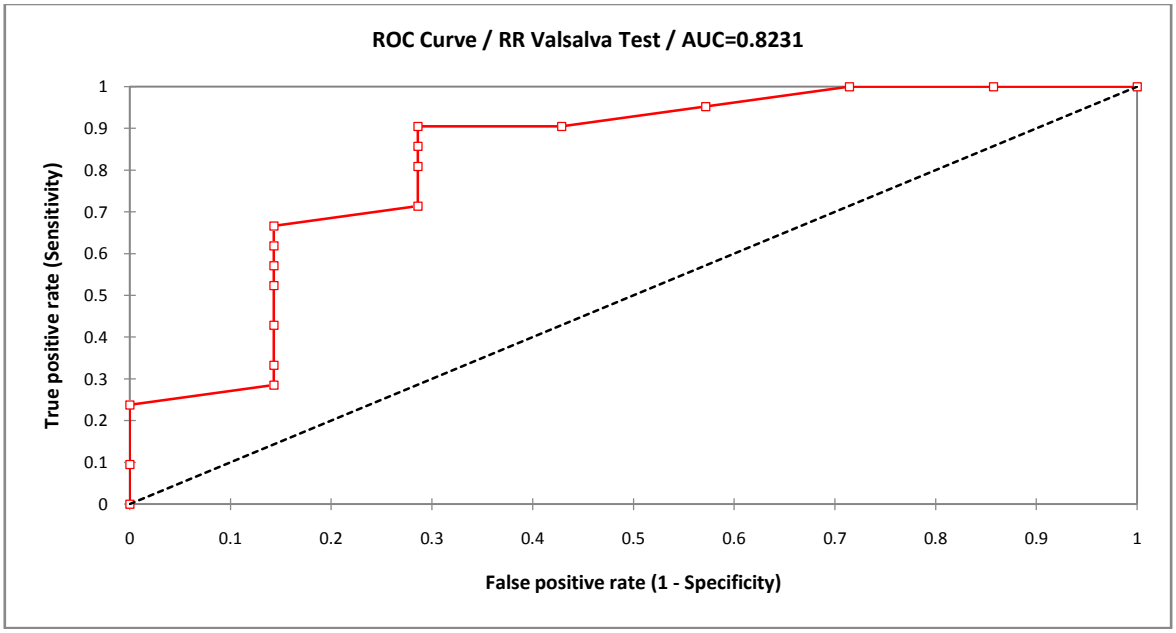

Figure 3: ROC curve represents sensitivity, specificity and cut point of R-R interval (Valsalva) test between controlled and uncontrolled diabetic patients

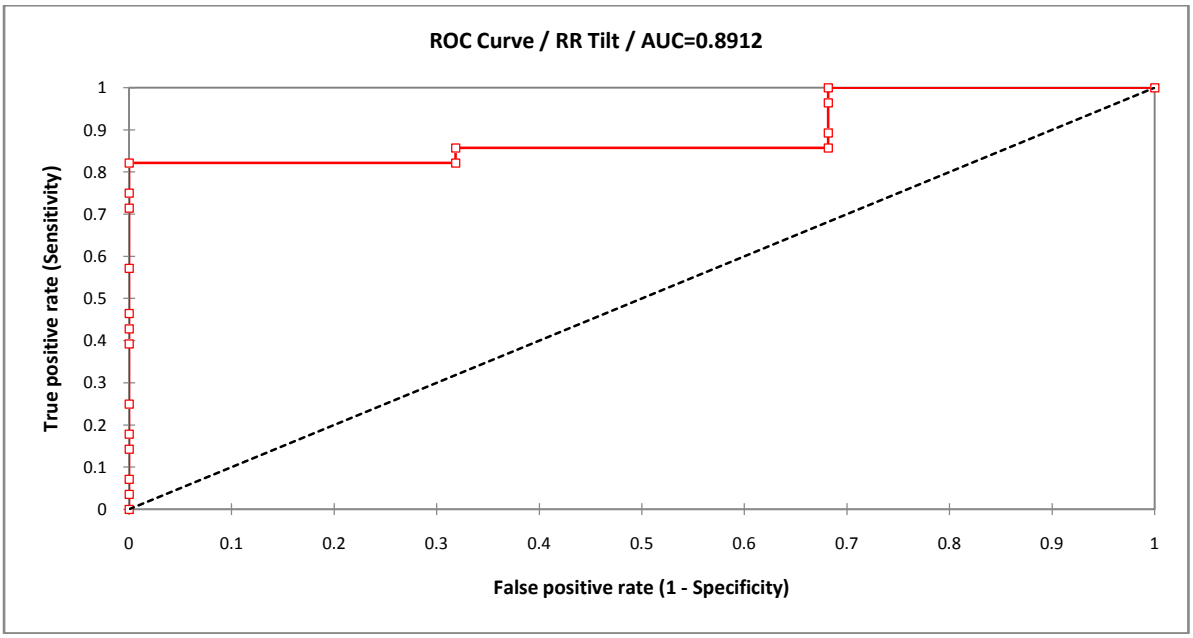

Figure 4: ROC curve represents sensitivity, specificity and cut point of R-R interval (tilt) test between controlled and uncontrolled diabetic patients

IV. DISCUSSION

Although autonomic neuropathy may occur at any stage of diabetes, usually it develops in subjects who have had the disease for 20 years or more with poor glycemic control [(15)]. Thus, early subclinical detection of DAN is important for risk stratification and management [(16)].In this study, 50 patients with symptoms of neuropathy or autonomic dysfunction participated,SSR amplitude wassignificantly higher in non-diabetic patients. Absence of the SSR is an indicator of DAN among patients with DM in Saudi Arabia (2008) [(17)]. Similarity it has been reportedin studies in Thailand (2015) [(18)], USA (1988) [(19)] and Turkey (2002) [(20)] that no correlation could be found with latencies and DM prevalence. In contrast, a study in India, 2012, have reported contradictory results in which the latency of SSR test was found to be significantly prolonged in diabetic patients [(21)].The SSR amplitude in this study among diabetic patients was significantly associated with positive outcomes of poorly controlled DM, also all patients with SSR amplitude test < 0.81 can be considered uncontrolled diabetics, as the cut point was 0.81, the current results differed from a Turkish study in 2002, in which no correlation could be found with HbA1c values [(20)]. These differences may be explained by the fact that large myelinated fibers contribute to the SSR. So, if the number of functional fibers is above a certain threshold, the response will be elicited, albeit with decreased amplitude, and if not, it will be absent [(22)]. In this study, R-R interval (Valsalva maneuver) were significantly higher in non-diabetic group and it was significantly related to outcomes of poorly controlled DM with a cut point of R-R interval (Valsalva maneuver) and R-R interval (tilt) 1.84 and 1.04 respectively, it was in accordance to two studies conducted in India one in (2012) [(23)] and other one in (2017) [(24)]. Regarding R-R interval (tilt), current result and that conducted in Greece (2015) were in agreement, as found that R-R interval (tilt) were significantly higher in non-diabetic patients than diabetics ($P< 0.05$) [(25)]. Many factors might affect the results of the current one and others, as lack of patients (sample size) and a short disease duration, added to that both sympathetic and loss of function in parasympathetic ganglia develops as age advances, and nerve conduction seems to be reduced for various reasons (oxidative damage, decline in neuroprotective agents, synaptic degradation of organelles, extracellular matrix, etc.) on different pathways [(26)].

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