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Impact of Diabetic Polyneuropathy on Ventilatory Function and Respiratory Muscle Endurance

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Abstract--*Diabetic polyneuropathy is one of the most common complications associated with diabetes mellitus. Respiratory neuromuscular function may be affected in diabetic polyneuropathy in type II diabetes. To determine impact of diabetic polyneuropathy on ventilatory function and respiratory muscle endurance. A cross sectional study was performed on ninety type II diabetic patients and thirty matched normal subjects from both genders. Their age ranged from 40 to 60 years. The duration of illness was at least five years. The subjects were assigned into two groups; normal subjects (control group (G1) and diabetic patients (study group (G2). The study group was subdivided into three equal subgroups; (G2a) represented diabetic patients without neuropathy; (G2b) included diabetic patients with clinically diagnosed neuropathy and (G2c) included diabetic patients with confirmed neuropathy diagnosed by nerve conduction studies (NCS). Severity of diabetic polyneuropathy was assessed and rated according to Toronto Clinical Neuropathy Scoring System (TCNS) and confirmed by NCS. Ventilatory function (forced vital capacity, forced expiratory volume in one second and forced expiratory volume in one second / forced vital capacity ratio (FEVI/FVC) and respiratory muscle strength (peak expiratory flow) and endurance (maximal voluntary ventilation) were assessed by Jaeger Vyntus IOS spirometer. revealed significant decrease in all measured variables in both (G2b) and (G2c) comparing with (G1) and (G2a) except FEVI/FVC ratio which is similar in four groups. A negative correlation was observed between the scores of TCNS and all measures of respiratory functions and between the age and MVV. Diabetic polyneuropathy in type II diabetes has a negative effect on pulmonary function.*

Key words--*Diabetic polyneuropathy, Pulmonary function, Respiratory muscle endurance, Spirometry, Type II diabetes.*

I. INTRODUCTION

Diabetes and its complications represent major and increasing challenges to healthcare systems worldwide. The global prevalence of diabetes in 2019 was 463 million. These numbers are expected to increase to 578 million by 2030 and 700 million by 2045 and almost 50.1% of all people living with diabetes are undiagnosed. Egypt is one of the first 10 countries with the highest number of DM patients in 2019 with 8.9 million diabetic patients. This number is expected to increase to 11.9 million in 2030 and to 16.9 million in 2045 [1].

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Diabetic neuropathy is the most common complication associated with diabetes mellitus. Diabetes causes various types of acute, chronic, focal and diffuse neuropathy syndromes. Diabetic polyneuropathy accounts for 75% of the diabetic neuropathies [2]. It may be present in at least 10%–15% of newly diagnosed patients with type II diabetes with rates increasing to 50% after ten years of disease duration [3, 4].

Diabetic polyneuropathy (DPN) is known as a presence of symptoms and/or signs of peripheral nerve dysfunctions in diabetic patients after the exclusion of other causes [5]. It is a chronic, symmetric, length-dependent sensorimotor polyneuropathy (DSPN) [6]. Patients with diabetic polyneuropathy may have symptoms of abnormal sensations (e.g., numbness or pricking feeling in the toes, feet or legs) or signs (i.e., symmetric decreased sensation or decreased or absent ankle reflexes) [7].

Diabetic polyneuropathy was found to be associated with an impaired respiratory neuromuscular function in type 2 diabetic patients, when non- volitional gold-standard phrenic nerve stimulation is applied. However, volitionally assessed respiratory neuromuscular function is not affected in type II diabetic patients [8]. Also, clinically diagnosed diabetic peripheral neuropathy was found to have a negative impact on respiratory muscle strength and function in type II diabetic patients [9].

Although diabetes was found to decrease lung function [10], data on respiratory involvement in diabetic polyneuropathy are limited [8, 9]. The studies of Kabitz et al and Van Eetvelde et al [8, 9] lack the objective assessment of diabetic polyneuropathy by nerve conduction studies. So, assessment of respiratory neuromuscular function related to patients with diabetic polyneuropathy confirmed by NCS may add to the scope of assessment and therefore management of diabetic polyneuropathy.

The aim of the present study is to assess the effect and impact of diabetic polyneuropathy on ventilatory function and respiratory muscle endurance.

II. MATERIALS AND METHODS

Study design

A cross-sectional study was conducted in Kasr EL-Ainy Hospital, Cairo University from August 2019 to January 2020. Diabetic patients were recruited from the Diabetes and Endocrinology Unit, Department of Internal Medicine**.** The nerve conduction studies were performed in the neurophysiological laboratory, Clinical Neurophysiological Department. The ventilatory function and respiratory muscle strength and endurance were assessed in cardiopulmonary laboratory, Fitness and Rehabilitation Department. The ethical committee at Faculty of physical therapy, Cairo University approved the study. All subjects signed an informed consent before beginning of the study to insure complete satisfaction.

Participants

Ninety patients with type II diabetes and thirty matched normal subjects from both genders; their age ranged from 40 to 60 years participated in the study. All diabetic patients fulfilled the criteria for diagnosis of diabetes [11]. Duration of diabetes started from at least five years ago. All patients received the suitable medical treatment for type II diabetes at the time of the study. Forty five patients were being treated with oral glucose-lowering agents and the remaining fifteen patients with daily insulin injection therapy. All Patients were assessed by neurologist and the diagnosis of DPN was confirmed by nerve conduction studies (NCS).

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Subjects with major neurological conditions, severe cardiovascular disorders, any respiratory diseases, smokers and pregnant women were excluded.

The subjects were assigned into two groups; normal subjects (control group (G1) and diabetic patients (study group (G2). Both groups were matched in the general characteristics including age, height and weight, body mass index and physical activity. Control group (G1) included thirty normal subjects to provide the normal database of ventilatory function and respiratory muscle endurance. Study group (G2) was subdivided into three equal subgroups; (G2a) included diabetic patients without neuropathy; (G2b) included diabetic patients with clinically diagnosed neuropathy and (G2c) included diabetic patients with confirmed neuropathy by nerve conduction studies.

Measurement procedures

Clinical assessment of diabetic polyneuropathy by TCNS:

Toronto Clinical Neuropathy Scoring System (TCNS) [12] was used to assess the severity of peripheral neuropathy in diabetic patients. It is a clinically valid scale for assessment of diabetic polyneuropathy [12]. The TCNS incorporates sensory and motor symptoms as well as signs of sensory and reflex findings [13]. Each patient was asked about the presence or absence of pain, numbness, tingling and weakness in the feet; the presence or absence of similar upper limb symptoms and the presence or absence of unsteadiness on ambulation. For each symptom, one point indicates that it was present and zero indicates that it was not present. Knee and ankle reflexes on both sides are scored as zero if normal; 1point with reduced response and 2 points with absent response. Sensory testing (light touch, pinprick, temperature, position and vibration) was performed at the first toe and was defined as normal (zero) or abnormal (one point)**.** At the end of the testing; all points were summed for each patient.

The score ranges from a minimum of 0 (no neuropathy) to a maximum of 19 points. Score 0–5 indicates no or minimal neuropathy; 6–8 indicates mild neuropathy; 9–11 indicates moderate neuropathy and score of 12 or more indicates severe neuropathy [14]. Patients with TCNS score less than 5 were placed in subgroup (G2a). Subgroup (G2b) included patients with TCNS score more than 5 but not fulfill the full NCS criteria while (G2c) represented patients with TCNS score more than 5 points and fulfill the NCS criteria for confirming DPN diagnosis.

Nerve conduction studies

Nerve conduction studies (NCS) were used to confirm the diagnosis of the diabetic polyneuropathy. A Nihon Kohden; Neuropak M1 (Model; MEB-9200; version 08.11, JAPAN) was used in this study to assess the nerve conduction studies. The NCS assessment protocol included motor NCS for right peroneal, left tibial and right ulnar nerves in addition to sensory NCS for left ulnar nerve. The procedures were conducted according to Preston and Shapiro [15]. Amplitude, latency and conduction velocity of motor and sensory nerves were recorded for (G2) and compared with their normal values [15]. Criterion for diagnosing the DPN in this study was the presence of any abnormality in at least 2 parameters (amplitude, latency or conduction velocity) in at least three different nerves in three different extremities. This criterion was modified from the recommendations of the American Association of Neuromuscular & Electrodiagnostic Medicine [16].

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Assessment of autonomic symptoms

The Survey of Autonomic Symptoms scale (SAS) was used to assess the autonomic symptoms in all diabetic patients. It is a new, valid and easily administered instrument for measurement of autonomic symptoms in diabetic neuropathy. It is composed of 11 questions for women and 12 questions for men. The scale detects the presence and severity of autonomic symptom in the last 6 months. Each patient was asked about the presence or absence of the following autonomic symptom domains: orthostatic, vasomotor, gastrointestinal, urinary, and sexual dysfunction. Yes indicates that the symptom is present and no indicates that the symptom not present. If the symptom was present, the patient was asked to describe the severity of the symptom. Degree 1 indicates that the symptom was not present at all; 2 indicates that the symptom bothers him little; 3 means the symptoms bothers him sometimes; 4 indicates moderate bothering and 5 indicates a lot harassment. The total symptom impact score is 0-55 for women and 0-60 for men [17].

Assessment of ventilatory function and respiratory muscle strength endurance

Ventilatory function and respiratory muscle strength and endurance were assessed by Jaeger Vyntus IOS (CareFusion, Hochberg, Germany) spirometer. This PC based spirometry system runs on Sentry Suite and measuring program. It is used for the measurement, recording and assessment of Slow and Forced Spirometry, Maximum Voluntary Ventilation (MVV) and pre/post handling [18]. Ventilatory function included forced vital capacity (FVC); forced expiratory volume in one second (FEV1) and FEV1/FVC ratio. Respiratory muscle strength and endurance were measured by peak expiratory flow (PEF) and maximal voluntary ventilation (MVV) respectively [19, 20]. Respiratory function testing and spirometry calibration was conducted according to European Respiratory Society/American Thoracic Society (ERS/ATS) standards [21]. Assessment procedures were conducted at the morning for all subjects.

Each subject was instructed to inhale completely and rapidly with ahold less than one second then to exhale maximally at least for six seconds until no more air can be expelled while maintaining an upright posture. The spirometer measured the maximal volume of air exhaled with maximally forced effort from a maximal inspiration as forced vital capacity (FVC). The forced expiratory volume in 1 second (FEV1) was measured as the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration. The ratio between FEV1 and FVC was measured as FEV1/ FVC ratio. The spirometer also measured the highest flow achieved from a maximum forced expiration started without hesitation from a position of maximal lung as peak expiratory flow (PEF). After that, each subject was instructed to perform resting breathing for six seconds then breathe as rapidly and deeply as possible (as in running) for at least 12 seconds and then return to resting breathing. The spirometer measured the maximum volume of air a subject can breathe over for at least 12 sec in litter per minute as MVV. Normal values of all measured pulmonary variables were obtained from European Respiratory Society/American Thoracic Society (ERS/ATS) standards [21].

Statistical analysis

Descriptive statistics were utilized in presenting the subjects demographic and clinical data. Quantitative variables were summarized using mean and standard deviation while categorical variables were summarized using frequencies and percentage. Pearson Correlation Coefficient was conducted to determine the correlation of respiratory variables with TCNS score and the subjects' age. The level of significance for all

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statistical tests was set at $p < 0.05$. All statistical measures were performed through the statistical package for social sciences (SPSS) version 25 for windows.

III. RESULTS

Participants' characteristics of both groups are shown in Table 1. There was no significant difference between both groups regarding age, weight, height, BMI and sex distribution (P >0.05). Also there was no significant difference between the three study subgroups regarding fasting blood glucose, duration of illness, TCNS and SAS (P >0.05).

Table 1: The mean values of age, weight, height, BMI and sex distribution in the four groups.

Variable		Control group(G1)	Study group (G2)			P-value
			Diabeticpatients withoutneuropathy(G2a)	Diabetic polyneuropathy		
				Clinically diagnosedby TNCS(G2b)	Confirmed by NCS (G2c)	
Age (years)		47±8.075	49.54±5.076	51.73±4.803	51.1±4.959	0.1217
Weight		77.64±16.76	74.54±8.676	78.73±6.057	80.71±11.02	0.4186
Height		167.9±11.30	161.4±5.709	165.7±6.043	168.1±8.654	0.0972
BMI (kg/m2)		27.22±3.298	28.55±2.402	28.66±1.240	28.45±1.935	0.3009
Sex	Male N (%)	10(33.33%)	4(13.33%)	5 (16.67%):	9(30%):	0.1835
	Female N (%)	20 (66.67%)	26 (86.67%)	25 (83.33%)	21(70%)	
FBG (Mean± SD)		-	186.7±67.93	190.4±69.34	220.3±78.91	0.3380
Duration of illness (Median (IQR)		-	10 (10)	8 (6)	11 (9)	0.1183

BMI: body mass index, SD: Standard deviation, P: probability, *significant= $P < 0.05$, N (%): number (percent), FBG: fasting blood glucose.

Clinical tests

Clinical characteristics of all diabetic patients including the TNCS score and total impact score of the SAS are presented in table 2. There were significant differences in the TNCS scores between the three diabetic subgroups (P= 0.0001). Median scores of TNCS in both (G2b) and (G2c) were significantly higher than (G2a) (P=0.0001). There was no significant difference between the three groups in the total impact score of SAS (p= 0.8831).

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Table 2: Median values of TCNS and SAS scores in the three study subgroups:

Variable	G2a (Median (IQR)	G2b (Median (IQR)	G2c (Median (IQR)	P- value
TCNS	4 (2)	8 (2)	10 (5)	0.0001*
SAS	13 (17)	16 (15)	14 (9)	0.8831

Ventilatory function and respiratory muscle strength and endurance

Comparison of the mean values of ventilatory function (FVC, FEV1 and FEV1/FVC), respiratory muscle strength (PEF) and respiratory muscle endurance (MVV) between the four groups revealed a statistical significant difference in all variables except FEV1/ FVC ratio (P=0.2856) (Table 3). Multiple pairwise comparison revealed that the mean values of FEV1, FVC, PEF and MVV were significantly lower in both (G2b) and (G2c) than both (G2a) and (G1) (P≤0.05) however; there were no significant difference either between (G2b) and (G2c) or between (G2a) and (G1) (P>0.05) (Table 3).

Table 3: Mean values of different ventilatory function and respiratory muscle strength and endurance in four groups:

Variable	G1 (Mean±SD)	G2a (Mean±SD)	G2b (Mean±SD)	G2c (Mean±SD)	P- value
FEV1 (% pred)	107.7±11.51	99.45±11.43	84.95±9.589	81.89±13.62	0.0001*
FVC (% pred)	110.7±11.87	105.4±15.06	86.22±13.54	86.01±15.77	0.0001*
FEV1/ FVC (%)	82.73±7.792	80.22±6.219	83.24±5.983	79.64±7.280	0.2856
MVV (% pred)	97.35±8.713	88.15±7.955	75.84±9.577	76.25±12.80	0.0001*
PEF (% pred)	95.25±17.94	84.68±19.85	64.66±10.94	65.43±17.77	0.0001*

FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PEF: peak expiratory flow; MVV: maximal voluntary ventilation; % pred: percent predicted.

Pearson rank correlation (r) between respiratory variables with TCNS score and age revealed a significant weak negative correlation between TCNS score and all measured variables except for FEV1/FVC (P=0.2982) and a significant negative correlation between the age and MVV (r= -0.3064, p=0.0216) (table 4).

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Table4: Pearson rank correlation between respiratory variables with TCNS score and age:

Variables	**TCNS**		**Age**	
Pulmonary functions	**R**	**P – value**	**r**	**P - value**
FEV1	-0.3773	0.0041*	-0.1947	0.1505
FVC	-0.3605	0.0063*	-0.1764	0.1934
FEV1/ FVC	0.1415	0.2982	0.007414	0.9568
MVV	-0.33030	0.0129*	-0.3064	0.0216*
PEF	-0.3840	0.0035*	-0.2137	0.1137

r: pearson rank correlation; *significant: $P < 0.05$.

IV. DISCUSSION

The key findings in this study were significant decrease in FVC, FEV1, MVV and PEF in both subgroups (G2b) and (G2c) when compared with group (G1) and subgroup (G2a), a negative correlation between the scores of TCNS and the variables of respiratory functions (FVC, FEV1, MVV and PEF) and a significant negative correlation between the age and MVV.

Looking more in detail to the results, FVC and FEV1, MVV and PEF were lower in diabetic polyneuropathy in both (G2b) and (G2c) than diabetic patients without neuropathy (G2a) and control subjects (G1). These results agree partly with Van Eetvelde et al who found that the PEF was lower in diabetic patients with neuropathy than diabetic patients without neuropathy. However, FVC, FEV1 and MVV were not assessed in his study [9].

The underlying pathology responsible for affected respiratory neuromuscular function in association with diabetic polyneuropathy has not yet been conclusively investigated. However, there are number of mechanisms that can be proposed. The phrenic nerve neuropathy may be one of the most attributed mechanisms to these changes in respiratory function. The phrenic nerves innervate the diaphragm and respiratory muscles. Deficiency of these nerves may cause weakness of diaphragm and respiratory failure. Phrenic neuropathy is an important complication of diabetes and coexists with the presence of diabetic polyneuropathy. It can occur unilateral or bilateral. Although unilateral diabetic phrenic neuropathy is common and usually recovers spontaneously, bilateral one is not common and difficult to treat, resulting in death or the need for long-term respiratory assistance [22].

Sensory and motor nerve conduction studies of phrenic and peripheral nerves in prediabetics, diabetics and normal controls were compared [23]. The phrenic nerves were found to be affected consistently with the peripheral nerves in prediabetic and diabetic patients suggesting that the phrenic neuropathy should be considered diabetic and prediabetic patients dyspnea and orthopnea [23]. The occurrence of phrenic nerve palsy associated with diabetic polyneuropathy was reported as single cases. Four different type II diabetic patients with DSPN having diaphragmatic paralysis due to bilateral phrenic neuropathy were reported [22, 24-26] and the phrenic nerve and peripheral nerve conduction studies were consistent suggesting the prevalence of phrenic

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neuropathy in DSPN. Also, a patient with type II diabetes diagnosed as distal symmetric polyneuropathy with unilateral diaphragmatic paralysis was reported [27]. All these findings suggest that phrenic neuropathy coexisting with DPN in diabetic patients should be considered in any diabetic patient with unexplained breathlessness and orthopnea.

Cardiovascular autonomic neuropathy (CAN) may be also considered as an underlying mechanism for affected pulmonary functions in diabetic polyneuropathy. It is the most common type of diabetic autonomic neuropathy and is highly associated with the presence of diabetic polyneuropathy. Bhuyan et al found that all the patients with CAN in his study had coexisting peripheral neuropathy and the peripheral neuropathy was detected in 88% of all type II diabetic patients included in the study [28]. Moreover, severity of CAN increases with increasing severity of peripheral neuropathy in type II DM [29]. The CAN was reported to affect the pulmonary function tests in diabetic patients. The FVC, FEV1 and PEF were found to be significantly lower in patients with CAN compared to healthy controls [30]. Also, the CAN in type II diabetes can cause respiratory muscle weakness measured by maximum static inspiratory pressure (PImax) [31].

The results of the current study contradicted with Kabitz et al [8] who reported that volitional tests (FVC and FEV1) were preserved in diabetic with or without neuropathy when compared with normal controls. However, his study provided evidence that diabetic polyneuropathy affects respiratory neuromuscular functions in patients with type II diabetes when measured by non-volitional tests (twitch trans-diaphragmatic pressure and twitch mouth pressure). The MVV and PEF were not measured in his study [8]. The discrepancy between the results might be explained that Kabitz et al subdivide the diabetic patients in his study into: diabetic patients with no or mild polyneuropathy compared with those with moderate or severe polyneuropathy. So, the estimation of differences between diabetic patient with and without neuropathy could be misjudged in the diabetic patients with no or mild polyneuropathy group. Also, the smaller sample size of diabetic patients with and without neuropathy (n=21) in his study compared to their number in the current study (n=60) could explain the variability in the outcomes.

A negative correlation between the scores of TCNS and the mean values of FVC, FEV1, MVV and PEF was found in the present study. This means that high scores of TCNS are associated with low values of FVC, FEV1, PEF and MVV. So, the severity of diabetic polyneuropathy may affect the ventilatory function (FVC and FEV1), respiratory muscle endurance (MVV) and strength (PEF). This provides strong evidence that diabetic polyneuropathy affects respiratory neuromuscular function, strength and endurance in patients with type II diabetes. This result agrees with Kabitz et al [8] who found that twitch trans-diaphragmatic pressure (TwPdi) and twitch mouth pressure (TwPmo) were significantly lower in diabetic patients with moderate or severe polyneuropathy than in those with no or mild polyneuropathy.

The current study showed a negative correlation between the age of subjects and MVV. So, the respiratory muscle endurance (MVV) is affected by increasing the patient's age in type II diabetes. Aging is accompanied with reduced skeletal muscle capillary density [32]. Furthermore, old age and type II diabetes were found to cause fewer capillary contacts and a lower individual capillary-to-fiber ratio in both type I and type II muscle fibers compared with the young and these changes are associated with decreased muscle endurance and strength [33]. Also, the respiratory muscle endurance measured by MVV seems to be associated with micro-

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vascular complications in type II diabetic patients [34]. So, the age and diabetes itself may be attributed factors for MVV affection in this study.

V. CONCLUSION

In conclusion, both clinically diagnosed and confirmed diabetic polyneuropathy negatively affect the ventilatory function and respiratory muscle strength and endurance in type II diabetic patients. Furthermore, severity of diabetic polyneuropathy is related to values of the pulmonary function tests.

This study has certain limitations, which need to be addressed. First, the severity of diabetic polyneuropathy was rated clinically only by TNCS. Future studies are needed to determine the effect of severity of diabetic polyneuropathy measured by more objective methods e.g. nerve conduction study or intraepidermal nerve fiber density (IENFD). Second, effect of different subtypes of diabetic polyneuropathy (small fiber and large fiber neuropathies) on ventilatory function and respiratory muscle endurance was not explored in the current study. We recommend for other studies to differentiate between effects of small and large fibers neuropathies on different respiratory functions.

Conflict Of Interest

There are no conflicts of interest relevant to this article.

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