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### RESEARCH ARTICLE

## RISK FACTORS FOR EARLY DEVELOPMENT OF POLYNEUROPATHY AMONG TYPE II DIABETIC PATIENTS.

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Diabetic polyneuropathy, risk factors, type II diabetes.

### Abstract

Polyneuropathy is one of the commonest complications of diabetes and the commonest form of neuropathy in the developed world. The development of neuropathy was associated with potentially modifiable risk factors such as serum lipids, hypertension, body mass index, and cigarette smoking. The aim of this study was to investigate the risk factors for distal symmetric sensory-motor polyneuropathy (DSP) in patients with type 2 diabetes mellitus (DM). **Method:** One hundred patients with type 2 DM (65 males and 35 females) were included in the study. In addition to a detailed neurological examination, the Michigan Neuropathy Screening Instrument was administered to all patients and nerve conduction examinations were performed for all patients.

**Results:** Significant correlation between early development of DPN and BMI, hypertension, high serum cholesterol and poor glycemic control (high serum HbA1c). **Conclusion:** high BMI, hypertension, high serum cholesterol and poor glycemic control are risk factors for early development of polyneuropathy in type 2 diabetes mellitus.

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### Introduction:-

Diabetic peripheral neuropathy (DPN) is a common complication estimated to affect 30–50% of individuals with diabetes mellitus (DM).<sup>1</sup> DPN defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with DM after exclusion of other causes of polyneuropathy.<sup>2</sup> Chronic distal sensorimotor symmetrical neuropathy is the most common form of diabetic peripheral neuropathy and accounts for 75% of the diabetic neuropathy syndromes.<sup>3</sup> The primary symptom of DPN is loss of sensation in the toes, which extends to involve the feet and leg in a stocking distribution. Some patients complain numbness and pain, but most frequently the disease progresses insidiously and undetected.<sup>4</sup> DPN results in loss of protective sensation in the feet<sup>5</sup> and may be associated with foot ulcers, amputations, non-healing skin wounds, and sexual dysfunction<sup>6</sup>. The prevalence of DPN is estimated to be about 8% in newly diagnosed patients and greater than 50% in patients with longstanding disease<sup>7</sup>. In Europe the prevalence is found to be between 20-60 % in patients who have had the DM duration between 4 and 10 years<sup>8</sup>. DPN of the limbs increases with both age and duration of diabetes, and seems more common in those with suboptimal glycemic control and obesity<sup>9</sup>. The pathology of PN is not fully understood, but factors that seem to contribute to its development include, but are not limited to, sustained hyperglycemia, inflammation, inherited traits, and smoking<sup>10</sup>. Several studies reported that age, duration of diabetes and poor

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glycemic control are recognized as risk factors for DPN, while cigarette smoking, retinopathy, hypertension, obesity, hyperlipidemia and microalbuminuria has been pointed out as potential risk indicators. The most important ones among these factors include HbA1c level which reflects poor diabetic control, diabetes duration and demographic parameters including age, height and male gender <sup>11,12,3</sup>

#### Aim of the study:-

The study aimed to identify the risk factors for early development of DPN in type 2 DM patients.

#### Patients and Methods:-

The study was carried out on the patients with type 2 DM according to the criteria of the American Diabetes Association <sup>13</sup> received oral hypoglycemic drugs who presented with clinical picture suggestive polyneuropathy from patients attended the outpatient clinic or admitted to Medical or Neurology Department of Al Azhar University Hospitals during the period from December 2016 to the end of May 2017. This study has been approved by ethical committee consent of Al Azhar University Hospitals. Patients who had type 1 DM, other morbidities leading to neuropathy including uremia, malnutrition, hepatic failure, alcoholism, drugs induce neuropathy and vitamin deficiency or patients refuse to participate in the study were excluded from the study. All patients included in the study were subjected to complete medical and neurological history regarding to detailed history about age, gender, weight, height, BMI, diabetes duration, duration of neuropathic symptoms, antidiabetic therapy used, hypertension, smoking and family history of diabetes. The patients are generally examined for vital signs, extremities, cardiovascular, hepatic, renal, respiratory system and skin. Neurological examination including mental state, cranial nerves, motor, sensory systems, cerebellum, gait, back, spine and bone. Interrogation for neuropathy was made in all patients using the Neuropathy Screening Questionnaire of the Michigan Neuropathy Assessment Scale <sup>14</sup>. Mean glycated hemoglobin (HbA1c) levels, serum cholesterol, triglyceride and uric acid of all patients were recorded. Nerve conduction studies were performed using Medelec- Oxford Synergy EMG device with 20 Hz- 10 kHz filter setting and 50 ms analysis time. All recordings were made using superficial electrodes and the extremity temperature was kept above 31 degrees. In accordance with the polyneuropathy protocol <sup>15</sup>. Median and ulnar nerves motor and sensory (finger-wrist, wrist-elbow) examination was performed in one upper extremity, posterior tibial and peroneal nerves motor conduction study was performed in one lower extremity and sural nerve conduction studies were performed bilaterally. Deceleration or failure to obtain action potential or low-amplitude action potential in at least two nerves was defined as polyneuropathy.

Appropriate statistical methods were applied and the results were tabulated and graphically presented accordingly. P <0.05 was considered significant.

#### Results:-

The study was carried out on 100 patients with type 2 DM presented with clinical pictures of polyneuropathy. They were 65 males (65%) and 35 females (45%) with mean age was  $55.4 \pm 10.19$ , mean age at onset of DM  $45.05 \pm 7.89$  and the mean duration of DM was  $7.17 \pm 4.4$ . Family history of DM was positive in 74% of patients, 37% had sedentary life, 29% were smoker and 59% were hypertensive (**Table: 1**). There was insignificant correlation between early onset of polyneuropathy and age of patients at onset of DM. Also the development of polyneuropathy was early among female patients, patients with sedentary life, smokers and patients with positive family history of DM without significant difference (**Table 3**). There were significant correlations between early onset of polyneuropathy and patients with hypertension, high BMI, hypercholesterolemia and poor glycemic control (high serum level of HbA1c), while height of the patients and serum triglyceride showed insignificant correlation (**Table 4**).

**Table 1:-** Demographic data of the studied patients

Variable	number	percent
Sex	65	65%
Male	35	35%
Female		
Age (years) Mean $\pm$ SD	$55.4 \pm 10.19$	
Age at onset y (Mean $\pm$ SD)	$45.05 \pm 7.89$	
Height cm (Mean $\pm$ SD)	$166.67 \pm 7$	
Duration of DM y (Mean $\pm$ SD)	$7.17 \pm 4.4$	

Positive FH of DM	74	74%
Sedentary life	37	37%
Smoking	29	29%
HIN	59	59%

**Table 2:** Laboratory results

Variable	(Mean $\pm$ SD)
Cholesterol	190.57 $\pm$ 39.95
Triglyceride	171.43 $\pm$ 70.19
HbA1c	8.62 $\pm$ 1.94

**Table 3:** Correlation between duration of DM at onset of PN and demographic and clinical data

	Duration of DM (Mean $\pm$ SD)	P value
Sex		
Male	7.38 $\pm$ 4.57	0.515 (IS)
Female	6.77 $\pm$ 4.12	
Sedentary life		
Positive	7.92 $\pm$ 4.93	0.392 (IS)
Negative	9.17 $\pm$ 4.92	
Family history		
Positive	6.76 $\pm$ 4.93	0.125 (IS)
Negative	8.31 $\pm$ 4.59	
Smoking		
Positive	6.16 $\pm$ 4.29	0.144 (IS)
Negative	7.56 $\pm$ 4.23	
Hypertension		
Positive	5.42 $\pm$ 4.01	0.001* (S)
Negative	8.38 $\pm$ 4.28	

**Table 4:-** Correlation between duration of DM at onset of PN and clinical and laboratory results

	(Mean $\pm$ SD)	Duration	P value
Age at onset of DM	45.05 $\pm$ 7.89	7.17 $\pm$ 4.4	0.192 (IS)
Height	166.67 $\pm$ 7	7.17 $\pm$ 4.4	0.181 (IS)
BMI	30.85 $\pm$ 5.31	7.17 $\pm$ 4.4	0.012* (S)
Cholesterol	190.57 $\pm$ 39.95	7.17 $\pm$ 4.4	0.022* (S)
Triglyceride	171.43 $\pm$ 70.19	7.17 $\pm$ 4.4	0.798 (IS)
HbA1c	8.62 $\pm$ 1.94	7.17 $\pm$ 4.4	0.016* (S)

## Discussion:-

The most accurate diagnosis of DPN is made with association of neuropathic symptoms, signs and abnormal electrophysiological findings<sup>16</sup>. In the present study, one hundred patients presented with DPN were included in the study. The result of the study showed that, the onset of DPN was early among female patients than males without statistically significant difference that agree with<sup>17,18,19,20</sup>. Also no significant difference development of DPN and age at onset of DM that agree with<sup>21</sup>.

The result of the study showed that the development of DPN was early among patients with sedentary life than patients with good physical activity without significant difference.<sup>22</sup> reported that, lack of physical activity was not directly associated with peripheral neuropathy while<sup>23,24</sup> found that there are association between lack of physical activity and early development of peripheral neuropathy. Also<sup>24-26</sup> observed that, physical activity was associated with lower rates of PN development. One potential strategy to delay or prevent the progression of diabetes to diabetic PN is regular physical activity. Physical activity may attenuate the progression of diabetic PN through the established role that physical activity has on modulating inflammation<sup>27, 28</sup> and controlling glucose levels<sup>29</sup>. Our study showed that the development of DPN was early among smoker patients than non-smokers without significant difference.<sup>30</sup> reported that smoking isn't risk factor for DPN while<sup>31-34</sup> reported that smoking is risk factor for DPN.

Regarding to hypertension, the result of the study showed that there was significant correlation between hypertension and early development of DPN that supported by several studies<sup>31-37</sup>. In rodents, the additive effect of hypertension on diabetic neuropathy was attributed to damages in Schwann cells and myelin sheaths around axons. These results endorse the relationship between diabetic neuropathy and its microvascular complications<sup>38,39</sup>.

The result of the study showed that, there were insignificant correlation between age of patient at onset of DM and height and development of DPN.<sup>33,34</sup> reported that, the severity of DPN is usually linked to patient's age. Height may act in concert with poor glycemic control, which is postulated to contribute to capillary basement membrane thickening, possibly due to greater pressure and decreased capillary blood flow in the lower extremities<sup>40,41</sup>. As regard to BMI, the result of the study showed that, there were significant correlation between BMI and development of DPN that supported by several studies<sup>30-34</sup>. The metabolic syndrome and obesity are risk factor of neuropathy. Proposed mechanisms for this nerve damage include fat deposition, extracellular protein glycation, mitochondrial dysfunction, oxidative stress and activation of counter-regulatory signaling pathways leading to chronic metabolic inflammation<sup>13,42</sup>. As regard to serum cholesterol, the result of the study showed that, there were significant correlation between serum cholesterol and development of DPN and insignificant with serum triglyceride that agree with several studies as<sup>30-34</sup>.

The result of the study showed that, there were significant correlation between poor glycemic control (high HbA1c level) and development of DPN, that agree with several studies as<sup>32,43,44</sup> they reported that, among adults with diabetes, the progression of PN can be slowed when glycemic state is controlled. In the European Diabetes Perspective Complications Study, the rate of deterioration of glycemic control contributed markedly to the risk of neuropathy, independently of the glycosylated hemoglobin value at baseline<sup>37,45</sup> suggested that modest levels of moderate-to-vigorous intensity physical activity, coupled with glycemic control (via physical activity, diet, and/or medication), may help prevent or slow the progression of diabetic end-organ damage, particularly diabetic neuropathy.

### Conclusion:-

Early development of DPN associated with increase of BMI, hypertension, high serum cholesterol and poor glycemic control (high serum HbA1c).

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