

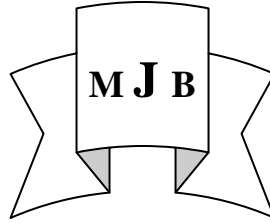
Some Physiological and Clinical Changes in Patients with Diabetic Peripheral Neuropathy

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Abstract

This study was designated to estimate some clinical, biochemical and electrophysiological changes in patients with diabetic peripheral neuropathy, since the changes in these parameters are important in detecting, quantifying, identifying some possible risk factors and assessing patient's response to treatment. The study lasted from November/2008 to May/2009. The total number of study group was 225 persons who fell into 105 patients and 120 controls. The patients were classified into two groups according to the type of DM into: patients with type 1 DM (35 patients), their age range between 16-34 years and patients with type 2 DM (70 patients), their age range between 45-72 years. While control group was classified into diabetic patients without neuropathy (60 patients), their age ranged between 18-52 years and normal healthy control (60 persons), their age ranged between 18-70 years. The patients were recorded in Marjan's teaching hospital center of diabetes and had monthly visits. The patients and control were examined by specialist doctors. The patients and controls enrolled in the study had undergone full assessment that included:- clinical assessment (history and full examination), biochemical assessment (measurement of fasting blood sugar, serum selenium and vitamin E), measurement of glycosylated hemoglobin and electrophysiological assessment that included sensory and motor nerve conduction studies. Results of this study showed that fasting blood sugar and HbA1c level were higher in patients with neuropathy than controls with statistically significant differences ($p < 0.05$). While serum selenium and vitamin E level show significant decrease ($p < 0.05$) in patients with diabetic peripheral neuropathy than controls. Regarding electrophysiological changes patients had shown significant increase in latency for sensory and motor nerves and significant decrease in amplitude and conduction velocity for sensory and motor nerves in patients with peripheral neuropathy than controls.

The study found out that hyperglycemia due to deficiency of insulin or resistance to its metabolic effect is the most important and correctable risk factor for peripheral neuropathy, in addition to the role of hyperglycemia, oxidative stress also plays role.

الخلاصة

تضمنت هذه الدراسة معرفة التغيرات التي تحدث لبعض المعايير الطبية والكيميوية والفسلجية الكهربائية في مرضى السكري المصابين باعتلال الأعصاب وذلك لأهمية هذه المعايير في تشخيص، تحديد، معرفة بعض عوامل خطوره ألممكنه و تقدير استجابة المريض للعلاج.

استمرت الدراسة من تشرين الأول ٢٠٠٨ حتى أيار ٢٠٠٩. كان العدد الكلي لمجموعة الدراسة ٢٢٥ شخصاً تم تقسيمهم إلى ١٠٥ مريض و ١٢٠ شخص في مجموعة السيطرة. تم تصنيف المرضى إلى مجموعتين اعتماداً على نوع السكري المصابين به: المرضى المصابين بداء السكري من النوع الأول (٣٥ مريض) تراوح معدل أعمارهم بين ١٦-٣٤ سنة و المرضى المصابين بالسكري من النوع الثاني (٧٠ مريض) تراوح معدل أعمارهم بين ٤٥-٧٢ سنة. أما مجموعة السيطرة فقد تم تقسيمهم إلى مرضى مصابين بداء السكري وغير

مصابين باعتلال الأعصاب (٦٠ مريض) تراوح معدل أعمارهم بين ١٨-٥٢ سنة ومجموعة الأشخاص الأصحاء (٦٠ شخص) تراوح معدل أعمارهم بين ١٨-٧٠ سنة. المرضى مسجلين في مركز السكري في مستشفى مرجان التعليمي ولديهم زيارات شهرية إلى المركز. تم فحص المرضى ومجموعة السيطره من قبل طبيب اختصاص.

أخضع المرضى ومجموعة السيطره المنخرطين في الدراسة إلى تقييم شامل تضمن: التقييم السريري (التاريخ المرضي و الفحص السريري)، التقييم الكيموحيوي (قياس الجلوكوز في الدم و السيلينيوم و فيتامين E في مصل الدم)، قياس مستوى الهيموغلوبين الجلوكوزي و التقييم الفسلجي الكهربائي المتضمن دراسة توصيل الأعصاب الحسية والحركية. وجدت الدراسة أن مستوى السكر والهيموغلوبين الجلوكوزي في الدم أعلى في المرضى من مجموعة السيطره مع فروقات معنوية ($P<0.05$). كذلك وجدت الدراسة وجود فروقات معنوية في مستوى السيلينيوم ($P<0.05$) و فيتامين E ($P<0.05$) في مصل الدم بين المرضى ومجموعة السيطره.

أما فيما يخص التغيرات الفسلجية الكهربائية وجدت الدراسة زيادة في الكمون الحركي والحسي (motor and sensory latency) بين المرضى ومجموعة السيطره مع فروقات معنوية ($p<0.05$) كذلك وجود انخفاض في سرعة التوصيل للأعصاب الحركية والحسية (conduction velocity) والقمة الحركية والحسية (Amplitude) بين المرضى ومجموعة السيطره مع فروقات معنوية. وجدت الدراسة بأن ارتفاع الجلوكوز في الدم بسبب نقص أو مقاومة العمل الأبيضي لهرمون الأنسولين هو من أهم عوامل الخطورة التي يمكن تعجيلها لمرض اعتلال الأعصاب بالإضافة إلى ذلك فان الجهد الأتأكسدي يلعب دوراً مهماً.

Introduction

Diabetes Mellitus (DM) is a clinical syndrome characterized by hyperglycemia due to absolute or relative insulin deficiency [1]. There are 2 types of complications of diabetes mellitus:- macrovascular and microvascular complications. The macrovascular complications include: - cerebrovascular, cardiovascular and peripheral vascular diseases. The microvascular complications include nephropathy, retinopathy and neuropathy and it result from chronic hyperglycemia [2]. Diabetic neuropathy is the most common chronic complication affecting both type 1 and type 2 diabetic patients [3].

The prevalence of diabetic neuropathy varies from 10% within 1 year of diagnosis to 50% in patients with diabetes for 25 years or longer. The average prevalence is 30% [4]. Distal symmetric sensorimotor peripheral neuropathy (DPN) is by far the most common type of diabetic neuropathy, typically presented as a slowly progressive primarily sensory deficit in a

length-dependent fashion, with symptoms starting in the feet and spreading upwards, evoking the classic stocking glove distribution [5].

Diabetic peripheral neuropathy might be presented early with diminished or absent deep-tendon reflexes, particularly the Achilles tendon reflex often indicates mild and otherwise asymptomatic DPN. More advanced neuropathy may be firstly presented with late complications such as ulceration or neuroarthropathy (Charcot's joints) of the foot [6].

Hyperglycemia clearly plays a key role in the development and progression of diabetic neuropathy as well as the other microvascular complications of diabetes. Long term hyperglycemia elicits enhanced polyol pathway, increased nonenzymatic glycation of structural proteins, increased oxidative stress as well as altered protein kinase C activity and poly ADP-ribose polymerase (PARP) activation that are all interrelated for the cause and development of neuropathy[7]. Apart from direct hyperglycemia-induced

damage, ischemia caused indirectly from decrease in neurovascular flow almost certainly plays a role [8].

The duration of diabetes and degree of metabolic control are the two major risk factors of the development of neuropathy and determinant of its severity. Other factors, such as patient's age, sex, type of DM, height, lipid profile abnormalities, and presence of proliferative retinopathy, nephropathy, and cardiovascular diseases, also have been implicated [9].

Enhanced oxidative stress resulting from imbalance between production and neutralization of reactive oxygen species (ROS) is a well recognized mechanism in the pathogenesis of DPN and other diabetic complications. Vitamin E and selenium is a well-known antioxidants and their deficiency in diabetes will result in oxidative stress and aggravate chronic diseases [10].

Diabetic peripheral neuropathy can be diagnosed by variety of ways including: - full history and neurological examination, nerve biopsy and electrophysiological study (nerve conduction study) which shows a pattern of abnormality that reflects the pathological process of DPN. The electrophysiological changes include prolongation of latency (sensory and motor), decrease amplitude and decrease conduction velocity. These changes are elicited first in the sensory nerves of lower limbs [11].

Aims of study

1-Identify some possible risk factors of diabetic peripheral neuropathy in Babylon province.

2-Assessment of patients with diabetic polyneuropathy that includes:-

A-Clinical assessment, that includes taking full history and examination.

B-Measurement of glycosylated hemoglobin (HbA1c).

C-Biochemical assessment, include measurement of blood sugar, selenium and vitamin E measurement.

D-Electrophysiological assessment, by doing nerve conduction study (motor and sensory).

Patients and Methods

Patients and design of study

The study was conducted in diabetes center in Marjan teaching hospital in AL-Hilla City. The total number of subjects involved in the study was 225 (105 patients and 120 controls). The study group consisted of 87 male and 138 female, 50 had Type 1 DM and 115 had Type 2 DM. The age distribution of study group ranged from 16-72 years. The patients with diabetic polyneuropathy included in the study were classified according to the type of DM into:- patients with Type 1 DM (15 male and 20 female, total 35) and patients with Type 2 DM (22 male and 48 female, total 70). The patients were recorded in the diabetes center and had monthly visit. They were asked if they had any symptoms of peripheral nerve dysfunction like parasthesia, numbness, pain, weakness or others. Patients who experienced any of these symptoms were included in the study. The control group had the same sex and age group distribution to the patients. The control group was subdivided into diabetic patients without neuropathy (60 patients) and normal healthy control (60 persons). Diabetic patients without neuropathy were classified into:- patients with Type 1 DM (5 male and 10 female, total 15) and patients with Type 2 DM (12 male and 33 female, total 45). The normal

healthy control group were classified according to the age into those with age group between (16-40 years) to be considered as the control of Type 1 DM (13 males and 9 females, total 22) and those with age group between (50-65 years) that considered as control of Type

2 DM (20 males and 18 females, total 38). The distribution of the subjects according the subgroup is shown in the following table (table 1). The control group underwent the same tests and exams as those for patients.

Table 1 Distribution of study group.

Variable	Diabetic peripheral neuropathy patients		Diabetic without neuropathy		Healthy controls		Total
	Type 1	Type 2	Type 1	Type 2	Type1	Type2	
Age (year)	16-34	45-72	18-26	42-52	16-40	50-65	
males	15	22	5	12	13	20	87
Females	20	48	10	33	9	18	138
Total	35	70	15	45	22	38	225

Methods

All the patients and control groups were assessed clinically, biochemically and electrophysiologically as following:

1-Clinical assessment

a-History

Full history were taken from each patient regarding personal data like name, age, sex,..... etc, history of presenting illness (polyneuropathy) focusing on symptoms like parasthesia, numbness, pain, exaggerated painfully sensation to normal painless stimuli (allodynia), loss of thermal sensation, weakness, shoe slipping, history of foot ulcer or injury, and others distribution of these symptoms, duration of the symptoms, duration of DM, type of treatment of DM, history of other disease, and history of drug intake [12].

b-Examination

It was in the form of general and systemic examination including full neurological examination. The neurological examination consisted of:-

1- Inspection looking for atrophy, abnormal gait, deformity, ulcer, fasciculation and others.

2- Examination of motor system (muscle tone, power, reflexes and coordination).

3- Examination of sensory system (pinprick, thermal, light touch, proprioception and vibration sensation). The neurological examination focused on lower limbs, especially medial malleollus and big toe [13].The same trained examiner tested all participants.

2-Blood Collection

Venous blood samples were aspirated at about 9 a.m. from anticubital fossa. From each person, ten ml of blood aspirated, 4 milliliter of blood (anticoagulated with EDTA) used for glycosylated hemoglobin measurement, and other part placed in centrifuge for 10 minutes after waiting for 45 minutes to separate serum from whole blood. Serum samples stored in refrigerator (-20°C). Serum samples were used for measurement of blood sugar, total serum cholesterol, HDL - cholesterol and

triglyceride, selenium and vitamin E measurement [14].

3-Glycosylated hemoglobin measurement

Whole blood preparation was mixed with a weakly binding cation-exchange resin; the non-glycosylated hemoglobin was bound to the resin, leaving HbA1c. The percent of HbA1c was determined by measuring the absorbance values at 415nm of the HbA1c fraction to the total Hb fraction, according to the procedure explained by the company (Stanbio lab.,USA)[15].

4-Biochemical Evaluation

a-Serum Glucose measurement

Glucose is oxidized by glucose-oxidase to gluconate and hydrogen peroxide. The absorbance of standard and sample are measured against reagent blank at 546nm according to the procedure recommended by the company (Human, Germany) [16].

b-Determination of serum selenium and Vitamin E

Vitamin E was determined by using a Hashim and Schuttringe procedure [17]. The absorbency of standards and sample was read by spectrophotometer at absorbency 460 nm. Then the contents of each tube returned to its tube then ferric chloride was added to each tube then after 45 minutes, the absorbency of standards and sample was read by spectrophotometer at absorbency 510 nm.

Serum selenium measurement was done using atomic absorption spectroscopy method in Ministry of Science and Technology. Samples are pre-treated consists only of dilution (2X) directly into auto sampler cup. Appropriate standards are prepared in 0.1 M nitric acid.

c-Electrophysiological testing

The electrophysiological test was done in the electrophysiological department in Marjan teaching hospital. Each patient had at least four motor nerves tested (median, ulnar, tibial and peroneal), and three sensory nerves (median, ulnar and sural nerves). Limb temperatures were maintained above 33°C in the legs and 34 in the arms, and the skin was prepared when necessary using abrasive skin cleanser and isopropyl alcohol. The nerve conduction studies were performed using a Micromed machine (Japan). Maximal responses were obtained using electrical stimuli. Distal latency, conduction velocity and waveform amplitude, duration and shape were measured and recorded for each nerve at each stimulus site [11].

Results

1: Duration of diabetes mellitus

The duration of DM (in years) of patients with Type 1 DM who was presented with diabetic peripheral neuropathy was 14.4±2 years for males and 13.4±2 years for females, for diabetics without neuropathy was 2±2 years for males and 3±2 years for females. The duration of DM (in years) of patients with Type 2 DM who was presented with diabetic peripheral neuropathy was 10.3±2 years for males and 8.2±1 years for females, for diabetics without neuropathy was 3.5±3 years for males and 2.2±3 years for females. There are significant differences between diabetic peripheral neuropathy patients and diabetic without neuropathy control (P<0.05). These values are shown in Table 2.

Table 2 The duration of diabetes mellitus of diabetic peripheral neuropathy and diabetic without neuropathy according to the type of diabetes and sex.

Variable		Duration(years)	
Type 1 diabetics	Diabetic peripheral neuropathy	Male 14.4±2	Female 13.4±2
	Diabetics without neuropathy	2±2*	3±2*
Type 2 diabetics	Diabetic peripheral neuropathy	10.3±2	8.2±1
	Diabetics without neuropathy	3.5±3*	2.2±3*

Values are mean ± standard error

* Significant at p<0.05

2: Distribution of diabetic patients according to the duration of diabetes:-

Diabetic peripheral neuropathy is more prevalent in patients with longer duration of DM and so patients with DM duration <5 years represent 19% (20 patients) of the study group, between 5-10 years 25% (27), 10-20 years 35%

(37) and > 20 years constitute 20% (21) of the study group, while most of control group (diabetic without neuropathy) have short duration of DM with 91% (55) of controls (diabetic without neuropathy) have duration <5 years. These results are shown in Figure 1.

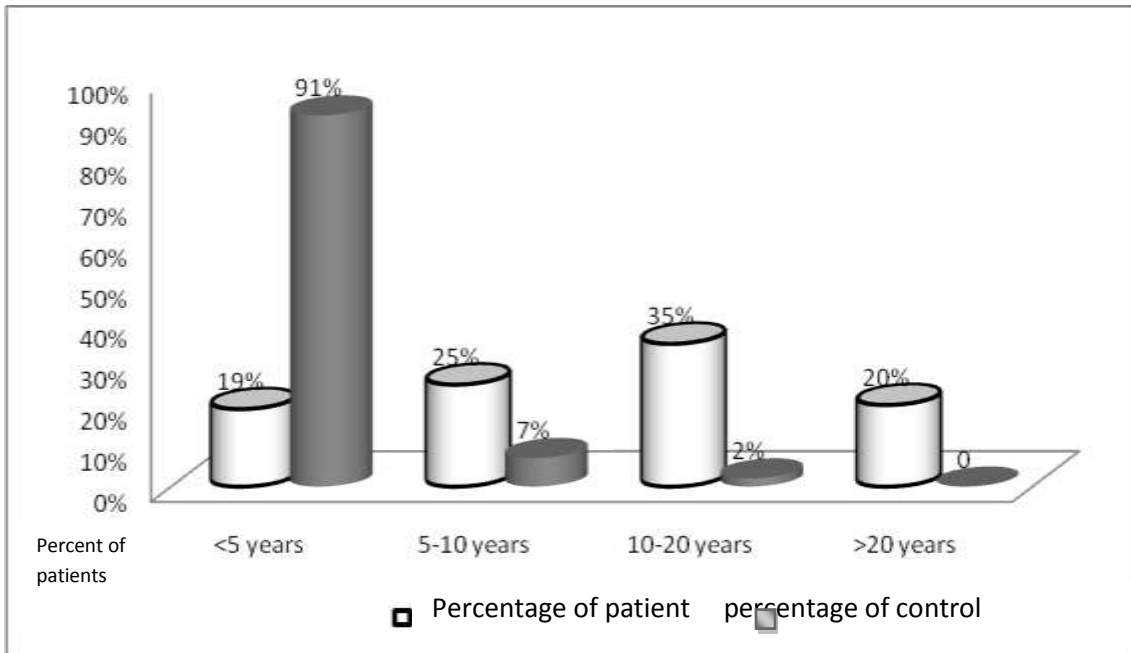


Figure 1 the distribution of diabetic patients according to the duration of diabetes mellitus.

3: Clinical features of diabetic peripheral neuropathy

The study revealed that parasthesia and numbness were the most common symptoms of diabetic polyneuropathy followed by pain (cramping or burning pain) and muscle weakness. While the most common and early sign found during neurological

examination was impaired vibration perception threshold of big toe and medial malleolus followed by diminished deep tendon reflexes of lower limbs joints, then impaired pinprick and thermal sensitivity and finally there was muscle weakness. These results are illustrated in Table 3.

Table 3 the prevalence of each clinical feature in patients with DPN.

Clinical feature		Number and percentage of patients	
		Number	Percentage
Symptoms	Paresthesia	91	84%
	Pain	53	50%
	Weakness	13	12%
Signs	Decrease vibration	81	77%
	Reduced reflexes	74	70%
	Decrease sensation	73	69%
	Decrease power	11	10%

These symptoms and signs do not involve all the limbs at the same time, so the symptoms and signs may involve either lower or upper limbs or both at the

same time, also they may be bilateral or unilateral. These variations are explained in Table 4 (a and b).

Table 4. a The anatomical distribution of clinical features in patients.

Variable	Lower limb	Upper limbs	Total patients
Paresthesia	77	45	91
Pain	38	15	53
Weakness	13	2	13
Vibration	79	22	81
Reflexes	70	20	74
Sensation	61	18	73
Power	11	2	11

Table 4. b- The anatomical distribution of clinical features in diabetic peripheral neuropathy patients according to the side of involvement.

Variable	Bilateral (both sides)		Unilateral (one side)		Total patients
	number	percent	number	Percent	
Paresthesia	69	75%	22	25%	91
Pain	50	95%	3	5%	53
Weakness	11	98%	2	2%	13
Vibration	71	90%	10	10%	81
Reflexes	67	89%	7	11%	74
Sensation	57	88%	6	12%	73
Power	10	98%	1	2%	11

4: Fasting blood sugar (FBS) and Glycosylated Hemoglobin (HbA1c):-

The values of fasting blood sugar and Glycosylated hemoglobin recorded significant increase in DPN patients in

comparison with diabetics without neuropathy at $p < 0.05$ and DPN with normal healthy controls at $p < 0.001$ in both type 1 and type 2 diabetics . These values are shown in Table 5 (a and b).

Table 5 a- The values of fasting blood sugar and Glycosylated hemoglobin between patients and controls of Type 1 diabetics according to the sex.

Variable		Fasting blood sugar (mmol/L)		Glycosylated hemoglobin %	
Type 1 Diabetics	Diabetic peripheral neuropathy patients	Male 12.2±1	Female 13.2±1	Male 8.2±0.7	Female 10.5±1
	Diabetics without neuropathy	7±2*	8±2*	5.6±1*	5±1*
Healthy control of Type 1 diabetics		6.2±2††	5.9±2††	4.5±2††	5±0.7††

Table 5b- The values of fasting blood sugar and Glycosylated hemoglobin between patients and controls of Type 2 diabetics according to the sex.

Variable		Fasting blood sugar (mmol/L)		Glycosylated hemoglobin %	
		Male	Female	Male	Female
Type 2 Diabetics	Diabetic peripheral neuropathy	12.8±1	12.5±1	8.7±0.8	8.6±0.4
	Diabetics without neuropathy	8±4*	8.2±2*	7.2±1*	5.3±1*
Healthy controls of Type 2 diabetics		5.2±2††	5.7±1††	4.3±1††	4±1††

-Values are mean ± standard error.

-* Significant differences at p<0.05 between DPN and diabetics without neuropathy control.

-†† Significant differences at p<0.001 between DPN and healthy control.

5: Serum selenium and Vitamin E levels:-

The values of serum selenium and vitamin E of patients (in both sex) with Type 1 and type 2 DM showed

significant decrease between DPN patients and diabetics without neuropathy at p<0.05 and DPN with normal healthy controls at p<0.001. These values are shown in Table 6 (a and b).

Table 6a- The selenium and vitamin E levels in patients and controls of Type 1 diabetics according to the sex.

Variable		Selenium(mg/L)		Vitamin E(mmol/L)	
		Male	Female	Male	Female
Type 1 Diabetics	Diabetic peripheral neuropathy	61±5	58±8	2.7±0.4	1.8±0.4
	Diabetics without neuropathy	70±4*	74±5*	4±0.3*	4.5±1*
Healthy control of Type 1 diabetics		97±6††	90±5††	7.3±3.5††	7.5±1.9††

Table 6b- The selenium and vitamin E levels in patients and controls of Type 2 diabetics according to the sex.

Variable		Selenium(mg/L)		Vitamin E(mmol/L)	
		Male	Female	Male	Female
Type 2 Diabetics	Diabetic peripheral neuropathy	44±8	62±3	1.7±0.7	2.5±0.4
	Diabetics without neuropathy	63±14*	69±10*	4.2±0.2*	3.9±1*
Healthy controls of Type 2 diabetics		88±6††	99±4††	7.9±2††	6.9±3††

Values are mean ± standard error

* Significant differences at (p<0.05) between DPN and diabetics without neuropathy control .

†† Significant differences at (p<0.001) between DPN and healthy control.

6: Electrophysiological assessment:-

The most commonly affected nerve was sural nerve which is affected in all patients, followed by median sensory which is affected in 84 patient (81%), common peroneal nerve affected in 44 (42%), posterior tibial affected in 40

patients (37%), Median motor nerve affected in 32 patients (30%). Ulnar sensory nerve affected in 32 patients (30%), Ulnar motor nerve affected in 27 (25%). These results are shown in Figure 2.

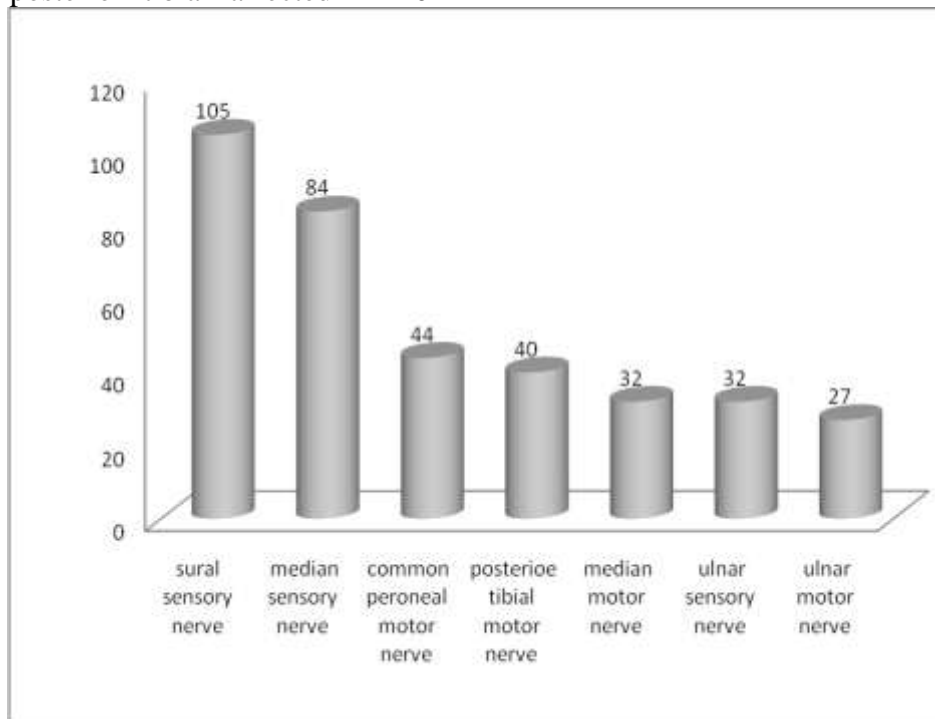


Figure 2 The prevalence of abnormal nerves in patients with diabetic peripheral neuropathy.

As well as the results of study shows that sensory nerves affected earlier and more common than motor nerves, so 51 (48%) patients had sensory neuropathy, 54 (52%) patients had mixed motor and sensory neuropathy. Sensory neuropathy was diagnosed by reduction in conduction velocity and amplitude of sensory nerves with normal

motor nerves parameters. According to the pathophysiology, there are 22 patients had developed axonal neuropathy, 18 patients had demyelinating neuropathy and the remaining (65) had mixed demyelinating and axonal neuropathy as shown in figure 3.

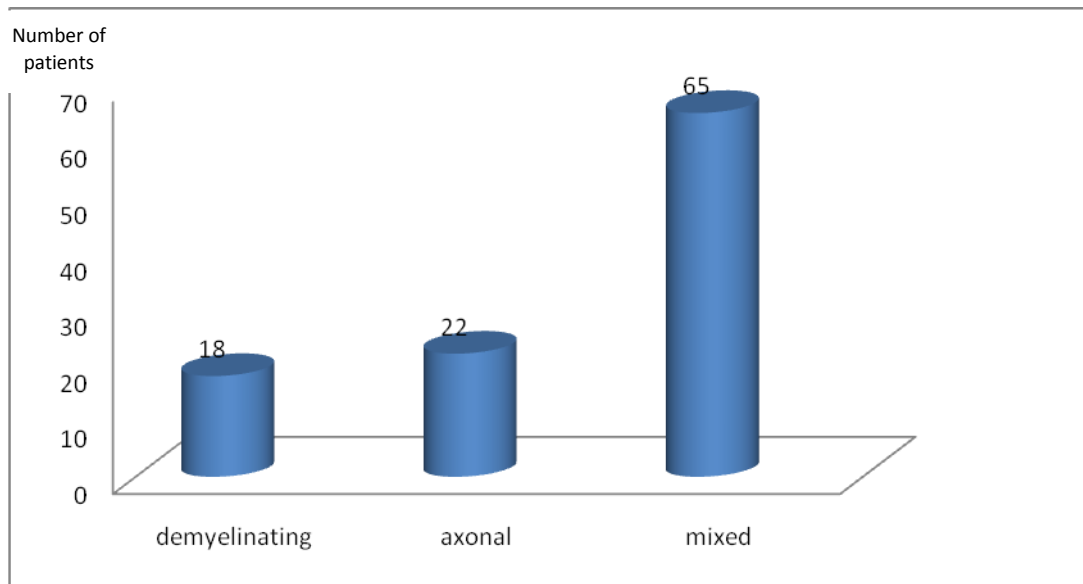


Figure 3 Types of diabetic peripheral neuropathy according to the pathophysiological process.

Discussion

Duration of diabetes mellitus

The study shows that DPN patients have longer duration of diabetes when compared with diabetics without neuropathy (Table 2). The result of study here agrees with other studies [12,18-22] in that longer duration of DM is a risk factor for the development of DPN. Kawano *et al* [23], found out that there is a positive correlation between the prevalence of diabetic neuropathy and diabetes duration. Also, the results of the study shows a higher incidence of diabetic neuropathy in patients with duration of diabetes from 10 to 20 years

when compared with those with duration of diabetes from 5-10 years and in patients with duration of diabetes from 5 to 10 years when compared to those with duration of diabetes below 5 years (figure 1) and so it agrees with a study done by Nather, *et al.*, [13]. These results is assumed to be caused by:- longer duration of DM is associated with poorer control of DM, accumulation of injurious effects of poor metabolic control on peripheral nerves, severer atherosclerosis which results in microvascular insufficiency and accelerates neuropathy [7].

Clinical features of diabetic peripheral neuropathy:-

Symptoms of diabetic peripheral neuropathy:-

Parasthesia and numbness of distal parts of the limbs (fingers and toes) are the main presented symptom followed by pain of muscles or burning pain of distal extremities and weakness of proximal muscles (Table 3). These results agree with results of other studies [21; 2)]. Rubino *et al.*, [24] found that numbness was the most commonly recorded DPN symptom in France, Italy, and Spain. This higher prevalence of paresthesia, numbness and pain are due to the fact that small sensory fibers affected early in the course of disease and these symptoms are due to small sensory fiber dysfunction. While motor weakness is due to large fiber dysfunction which occurs late in the disease [23]. Reduced vibration perception threshold of big toe and medial malleolus were the most common and early abnormalities found during neurological test, followed by reduced deep tendon reflexes and impaired pinprick sensation of distal parts of body (stock and glove sensory loss) and the last abnormality was reduced power of upper or lower limbs (power grade 3 and 4) (Table 4 ,a and b). These results agree with results of other studies [23, 19, 20 21]. Costa, *et al.*, [19] found out that abnormal vibration perception threshold occur early in DPN than other signs and can be used as a useful screening tool for DPN in a symptomatic Type 2 diabetics. Olsen *et al.*, [25] use toe vibration thresholds as a marker for follow up of diabetic neuropathy and it is shown that it is a useful predictor of lower extremity complications. Also the results of the study show that the signs and symptoms of DPN are bilateral because the

pathological process of DPN is systemic and involves all the nerves simultaneously [13].

Fasting blood sugar

The study shows higher fasting blood sugar in DPN patients than control groups with statistically significant difference (Table 5aandb). The study agrees with previous studies [26, 27, 28 , 12] in that hyperglycemia is the most important risk factor for DPN. Chronic hyperglycemia represents the main causative factor involved in the pathogenesis of diabetic neuropathy. Nerve damage may be directly induced by the accumulation of intracellular glucose (the consequences of which include the generation of glycation sugars and advanced glycation end-products (AGE), enhanced oxidative damage and protein kinase C activation). Apart from direct hyperglycemia-induced damage, ischemia caused indirectly from decrease in neurovascular flow almost certainly plays a role [29].

Glycosylated Hemoglobin (HbA1c):-

The results of HbA1c of DPN patients are higher than those of control groups with statistically significant differences (Table 5aandb). These results agree with results of other studies [27, 28, 18, 21] in that higher HbA1c values is reported in DPN patients. High HbA1c values indicate elevated mean blood sugar value over the last 2 months.

Serum selenium level:-

The study shows that selenium level is statistically lower in DPN patients than control groups (Table 6 a and b). Selenium is a trace element with powerful antioxidant effect and the finding of low level of selenium in DPN patients is assumed to the fact that DM is associated with enhanced oxidative stress which causes depletion of these

antioxidants. When the level of selenium and other antioxidants drop, it will reduce the antioxidant defense mechanisms of the body and enhance oxidative stress [30]. Enhancement of oxidative stress is a well known pathological pathway in the pathogenesis of DPN [31].

Serum vitamin E level

The study shows that levels of vitamin-E were lower in patients with DPN than control groups with statistically significant differences (Table 6 a and b). These results agree with result of previous studies [32; 33 ;34]. The finding of low level of vitamin E in DPN patients is due to the fact that DM is associated with enhanced oxidative stress which causes depletion of these antioxidants. Also vitamin E is a fat soluble vitamin and patients with DM are likely to be on diet regimen that excludes fat and so they are more prone to develop vitamin E deficiency [32]. When the level of Vitamin E drops, it will reduce the antioxidant defense mechanisms of the body and enhance oxidative stress. Enhancement of oxidative stress is a well known pathological pathway in the pathogenesis of DPN [35]. Willems *et al.*, [36] found that the level of vitamin E was normal in young Type 1 diabetics with good glycemic control indicating the importance of hyperglycemia in causing deficiency in antioxidants.

Electrophysiological assessment

The study shows that not all nerves involved at the same time and so the patient may have 2 or more than 2 nerve involved (the diagnosis of DPN is based on the presence of 2 or more than 2 nerves affected) according to the severity of the pathological process (figure 2and3). The study shows that the most common nerve involved by DPN is sural

nerve followed by median sensory nerve, common peroneal nerve, posterior tibial nerve, ulnar sensory nerve, median and ulnar motor nerves and so it agree with results of Karsidag *et al.*, [37].

These results shown to be due to the fact that pathological process of DPN starts in the longest nerves of the body and in its distal ends (what is referred to as dying back degeneration) and so the clinical features and electrophysiological changes of DPN start at the nerves of the lower limbs and then ascends up as the disease advances [37]. Also the study shows higher prevalence of median sensory nerve dysfunction indicating the higher prevalence of carpal tunnel syndrome [38]. Moreover the study shows that the nerve involvement is symmetrical because the pathological process is generalized and affects all nerves of the body simultaneously. Furthermore, the study reveals that sensory system is affected more than and earlier than motor system because sensory fibers are affected earlier [39].

Conclusions

- 1- The clinical study of patients with diabetic peripheral neuropathy shows that paresthesia and numbness are the main presenting symptoms, while decrease vibration perception threshold and deep tendon reflexes respectively are the most common and early signs of DPN.
- 2- Duration of DM, type 1 diabetes and male gender are important risk factors of DPN.
- 3- The study shows significantly higher value of fasting blood sugar and Glycosylated hemoglobin in DPN patients than control. In addition to that, the study of selenium and vitamin E shows significant decrease in these

antioxidant parameters indicating that there is a role of oxidative stress in the pathogenesis of DPN.

4- The electrophysiological study shows the following:-

a-The pathophysiological pattern of DPN in the form of demyelination and axonal degeneration.

B-Symmetrical involvement of peripheral nerves.

C-Polyneuropathy start early in the nerves of lower limbs since these are the longest nerves in the body.

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