Diabetic neuropathy

Correlation with other diabetic microvascular complications

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ABSTRACT

Objective: We studied the frequency of neuropathy in Saudi patients with definite diabetic microvascular complications and compared it to patients without complications. A high frequency of neuropathy in patients with definite microvascular complications would suggest a vascular etiology.

Methods: The study group consisted of 201 type-2 diabetic patients followed in the diabetic clinic of King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia. These patients were screened for microvascular disease. Only symmetrical distal sensory and motor neuropathy cases were included in the study. Screening for retinopathy was carried out according to Klien's criteria and nephropathy was diagnosed if albuminuria, microalbuminuria, abnormal blood urea nitrogen or creatinine was present.

Results: There was a strong correlation between the prevalence of diabetic peripheral neuropathy, retinopathy ($P<0.001$) and nephropathy ($P<0.01$), in patients with type 2 diabetes mellitus. This strong correlation suggests a common underlying pathogenesis.

Conclusion: We conclude that microangiopathy may be a major factor in the pathogenesis of diabetic neuropathy. Major risk factors for microangiopathy are the degree of glycemic control and duration of diabetes.

Keywords: Diabetes mellitus, neuropathy, retinopathy, nephropathy, microvascular complication.

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Diabetic neuropathy is one of the major complications of diabetes mellitus. It affects more than 50% of patients with a history of diabetes for more than 25 years.[1] There is little agreement regarding the underlying pathogenesis of diabetic neuropathy. Whether nerve injury results from the direct metabolic effect of hyperglycemia on nerve fiber or is mediated by nerve ischemia, is not yet clear. The growing consensus is multifactorial. One of the mechanisms is the change in the polyol pathway. The cells adapt to osmotic stress by inducing the formation of organic osmolytes, which allows them to maintain their normal volume while avoiding the accumulation of toxic ions.[2-4] These organic osmolytes include sorbitol, *myo*-inisitol, taurine, and glycerophosphoryl choline. Hyperosmotic stress normally increases the expression of the enzyme aldose-reductase, which in turn converts glucose to sorbitol.[2-5] It also increases the sodium (Na^+) dependent transport of myo-inisitol[2-6] and taurine[2-7] into cells. In the presence of hyperglycemia, the accumulation of sorbitol in the nerves does not result from the hyperosmotic stress, but from the increased provision of glucose, the substrate for aldose-reductase. Microangiopathy and subsequent hypoxia have also been implicated in the development of diabetic neuropathy. Vascular changes suggestive of local vascular disease, such as

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basement membrane thickening, endothelial cell proliferation and vascular occlusion have been demonstrated in nerve biopsies from diabetic patients.[8] It has been demonstrated also that nerve blood flow was reduced in diabetic rats.[9] However, it is not clear whether these intraneural abnormalities are merely a manifestation of generalized diabetic microangiopathy or different from the small vessel disease present elsewhere. Impaired neurotrophic support is another related mechanism in the pathogenesis of diabetic neuropathy. Neurotrophic factors are involved in the development, maintenance and regeneration of responsive elements of the nervous system. Nerve growth factor (NGF) is a protein that promotes the survival of sympathetic and small fibers of neural crest derived sensory neurons in the peripheral nervous system. They are frequently affected in diabetic polyneuropathy. In the diabetic animal models, both NGF production and axonal transport appear to be impaired.[10-11]

The aim of this study is to demonstrate the correlation between diabetic neuropathy and other microangiopathic complications such as retinopathy and nephropathy in patients with type-2 diabetes mellitus. The increased association of neuropathy with these complications are being observed which, may suggest a common underlying pathogenesis. We have also examined the relationship between the prevalence of diabetic microvascular complications and patients' gender, age, duration of diabetes mellitus and the degree of diabetic control as measured by the glycated hemoglobulin (HbA1c) level over the previous 2 years prior inclusion into the study.

Methods. This is a prospective study of patients seen in the diabetic clinic of King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia during the period between March 1997 through March 1998. Patients with chronic debilitating diseases were excluded. Diabetes mellitus was diagnosed in accordance with the World Health Organization (WHO) criteria.[12] At the initial visit, patients' sex and age, as well as their body mass index (BMI), duration of diabetes mellitus, treatment modality, presence or absence of hypertension, hyperlipidemia, smoking history, and family history of diabetes were recorded. Physical examination for the presence of clinical signs of diabetic microvascular and macrovascular complications was performed. Hypertension was diagnosed if blood pressure was >140/90 mmHg. Plasma lipid measurement was performed after 12-14 hours of fasting, using the enzymatic colorimetric method. Low density lipoprotein (LDL) was determined by the homogenous turbimetric method. Hyperlipidemia was diagnosed if the total serum cholesterol was >5.2 mmol/l or the LDL was >3.2 mmol/. Degree of diabetic control was assessed by the average level of the HbA1c as measured over the last 2 years before the patients' inclusion in the study. Glycated hemoglobin was measured using ion-exchange chromatography with a normal range of 6.0-8.5, then the HbA1c was calculated. Urine analysis for proteinuria and screening for microalbuminuria were performed in all patients without overt proteinuria. Microalbuminuria was tested by a quantitative immunoturbimetric method.[10] Nephropathy was diagnosed in the presence of proteinuria and high levels of blood urea nitrogen (BUN) and creatinine.

All patients had a complete ocular examination including direct and indirect ophthalmoscopy, 3 mirror contact lens and slit lamp examination. Color fundus photography and fluorescein angiography of both eyes were performed in all patients with suspected retinopathy on the baseline examination. The overall retinopathy severity was categorized according to the Klein classification.[13] Neuropathy was diagnosed when the patient reported at least one of the following symptoms: pain, tingling, burning or loss of sensation and when one of the following abnormalities was present: impaired or absent tendon reflexes, decreased vibratory sensation in patients less than 50 years-old, decreased sensitivity to pinprick, impaired position sense and abnormal results of neurophysiological studies. In order to increase the accuracy of the diagnosis of peripheral neuropathy, patients with only symptoms, or patients with isolated mono-neuropathy or asymmetrical neuropathy were not included. The neurophysiological tests included motor and sensory conduction studies of the median and ulnar nerves, motor studies of the lateral peroneal and sensory conduction of the sural nerve. Conduction velocity were considered abnormal if they were 2 standard deviation (SD) below of the age- adjusted mean in normal individuals at out neurophysiological laboratory.

Table 1 - Patient demographics and clinical characteristics (results are expressed as mean ± standard deviation).

Patients Gender	Age (years)	Duration (years)	HbA1c	BMI (Kg/m2)
Male	53.4 ± 10.2	10.65 ± 5.54	0.0853 ± 0.0173	28.10 ± 4.24
Female	51.3 ± 8.57	11.00 ± 5.76	0.0864 ± 0.0164	31.76 ± 4.87
All	52.0 ± 9.0	10.80 ± 5.7	0.086 ± 0.017	30.10 ± 4.9

HbA1c - glycated hemoglobulin, BMI - body mass index

Table 2 - Percentage of the frequency of complications in relation to patient characteristics.

Patients Characteristics	Neuropathy*		Retinopathy		Nephropathy	
	% - ve	% + ve	% - ve	% + ve	% - ve	% + ve
Sex						
Female	52.2	60.3	57.6	53.9	56.3	54.8
Male	47.8	39.7	42.4	46.1	43.8	45.2
Total (number)	**92**	**68**	**99**	**102**	**128**	**73**
Age						
<40	16.3	7.4	15.2	5.9	9.4	12.3
40-49	31.5	17.6	31.3	18.6	26.6	21.9
50-59	34.8	41.2	39.4	41.2	41.4	38.4
>59	17.4	33.8	14.1	34.3	22.7	27.4
BMI						
<25	19.6	13.2	17.2	12.7	15.6	13.7
25.0 -30	33.7	42.6	29.3	46.1	39.1	35.6
30.01-35	33.7	23.5	36.4	28.4	31.3	34.2
>35	13.0	20.6	17.2	12.7	14.1	16.4
Duration						
<5	23.9	11.8	33.3	5.9	21.9	15.1
5.01-10	38.0	36.8	39.4	31.4	35.9	34.2
10.01-15	28.3	23.5	23.2	31.4	26.6	28.8
>15	9.8	27.9	4.0	31.4	15.6	21.9
HbA1c						
<6.5	10.9	2.9	12.1	4.9	9.4	6.8
6.5001-8	42.4	33.8	45.5	28.4	39.1	32.9
8.0001-10	19.6	14.7	16.2	21.6	18.8	19.2
10.000-12	21.7	23.5	17.2	29.4	20.3	28.8
>12	5.4	25.0	9.1	15.7	12.5	12.3

* = electromyography was carried out in 160 patients only, BMI = body mass index, HgbA1c = glycated hemoglobulin, -ve = negative, +ve = positive,

Statistical analysis. Correlation was used when evaluating the age of patients, duration of being diabetic and the glycemic control which was assessed by HbA1c values. Degree of significance was measured using Pearsons' correlation test. Multivariate analysis was performed to examine the simultaneous effect of microvascular complications. We considered $P < 0.05$ as statistically significant or as indicated in the text.

Results. This study was carried out on 201 Saudi type-2 diabetic patients. There were 112 (56%) women and 89 (44%) men. Patients' characteristics are shown in **Table 1**. The impact of gender, age, body mass index (BMI), duration, and HbA1c level on the prevalence of neuropathy, retinopathy, and nephropathy is shown in **Table 2**. The association of neuropathy with other microvascular complications were tested using correlation coefficient. Our results showed that 49 (48%) patients with retinopathy ($r= 0.44$; $p<0.0001$) and 50 (35%) patients with nephropathy ($r=0.262$; $p<0.001$) had neuropathy as well. Fifty patients (49%) with retinopathy had

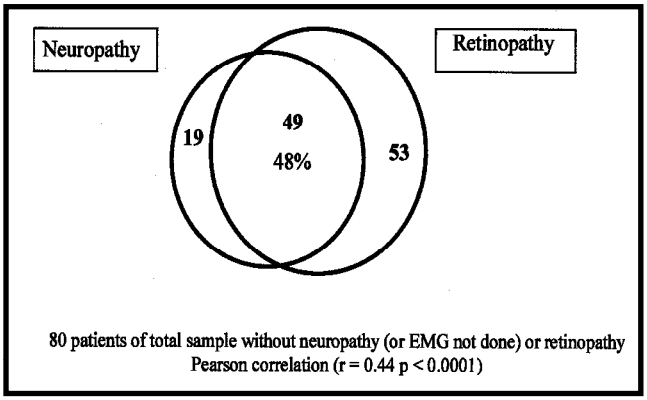

Figure 1 - The association of patients with neuropathy and retinopathy, EMG - electromyography.

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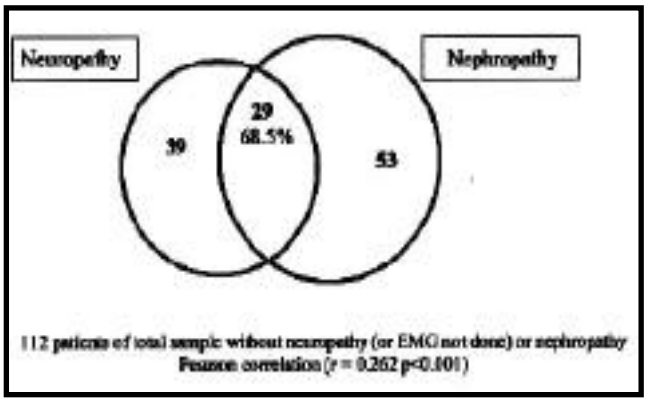

Figure 2 - The association of patients with neuropathy and nephropathy, EMG - electromyography.

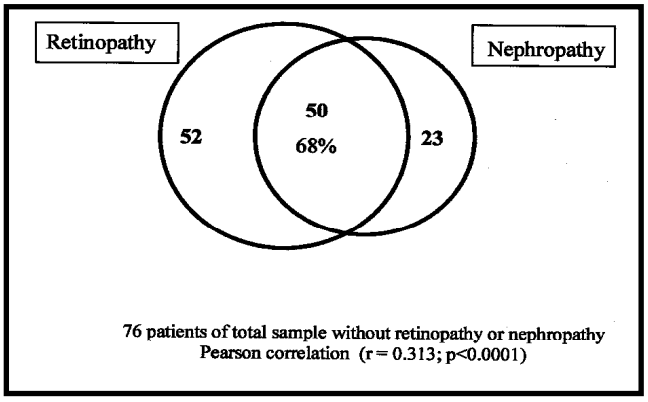

Figure 3 - The association of patients with retinopathy and nephropathy.

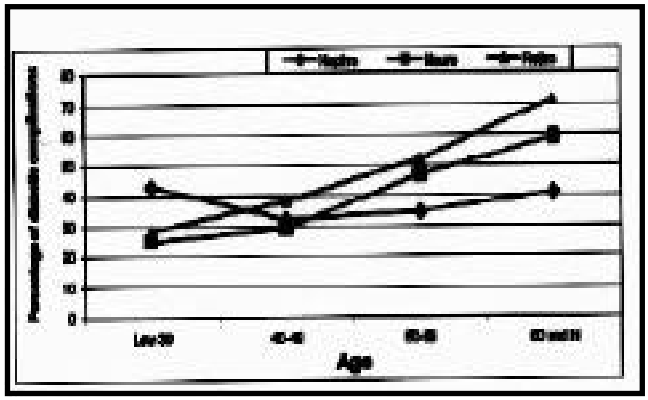

Figure 4 - Diabetic complications correlated to age.

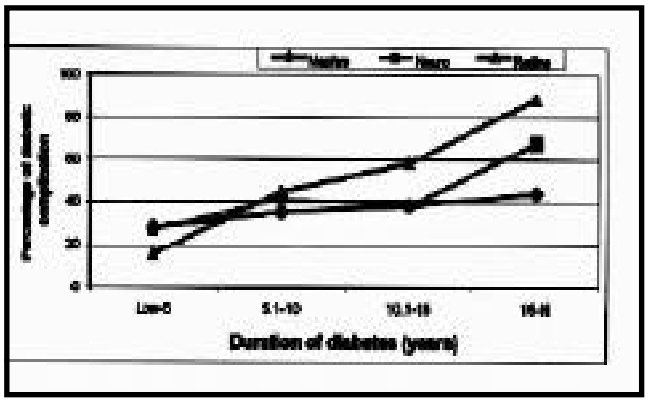

Figure 5 - Influence of duration of diabetes on the frequency of diabetic complications.

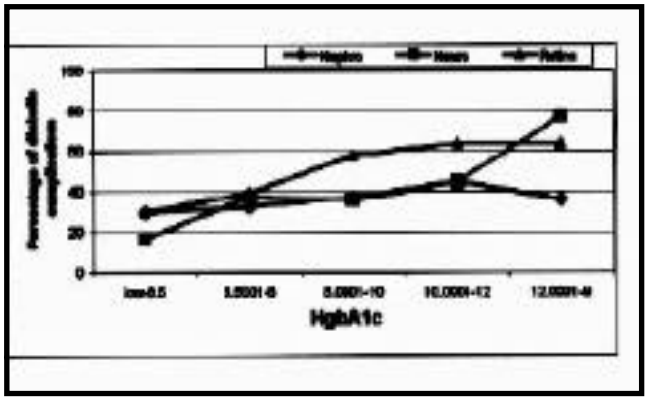

Figure 6 - Influence of glycemic control on the frequency of diabetic complications, HgbA1c - glycated hemoglobulin.

nephropathy (r=0.313; p<0.0001). **(Figures 1,2 & 3).**

Age. The prevalence of neuropathy and retinopathy were significantly related to age as shown in **Figure 4**. The number of patients with these complications increased every 10 years by 14.2% for retinopathy and 11.9% for neuropathy, with a linear regression value of R^2=0.975 for retinopathy and R^2=0.956 for neuropathy. Age had less effect on the prevalence of nephropathy. Nephropathy started with higher frequency and increased thereafter by 4.1% every 10 years (R^2=0.008).

Duration. The progression of microvascular complications correlated significantly with the duration of diabetes mellitus as shown in **Figure 5**. The increment in frequency of these complications was 23.4%, 12% and 5.2% of the diabetic population every 5 years of disease duration with linear regression values of R^2=0.979 for retinopathy, R^2=0.792 for neuropathy, and R2=0.979 for nephropathy.

Glycated hemoglobulin. The average value of the HbA1c measured over the last 2 years prior to inclusion in the study was also found to correlate significantly with diabetic microvascular complications as shown in **Figure 6**. Our data showed that the increase of HbA1c level above the normal value of 0.065, was associated with an increase of 12.9%, 9.4% and 2.5% for the frequency of complication for every 0.015 increase of HbA1c level. Correlation of frequency was applied for the percentage of complications and R^2 was 0.892 for retinopathy, 0.845 for neuropathy, and 0.489 for nephropathy. The BMI, cholesterol, or triglyceride level, smoking or abnormal electrocardiography (ECG) showed no correlation with the prevalence of any of the other microvascular complications when multivariate analysis test was used.

Discussion.

Experimental studies have shown that abnormalities of nerve microcirculation are important factors in the pathogenesis of diabetic neuropathy, but there has been few clinical studies. Features of endoneurial capillary microangiopathy capable of creating hypoxia were observed in both mildly and severely neuropathic patients sufficient to reduce nerve blood flow.[14] Ibrahim and colleagues have shown reduced nerve oxygenation and impaired blood flow in diabetic neuropathy suggesting a central role of microvascular disease in its pathogenesis of diabetic neuropathy.[15] Valensi et al, reported significant independent association between the presence of retinopathy and 11 of the 20 electrophysiological criteria for the diagnosis of neuropathy.[16] In our study a very strong correlation between neuropathy and both retinopathy and nephropathy were demonstrated **(Figures 1 & 2).** Several epidemiological and clinical trials have demonstrated that diabetic duration, poor glycemic control, smoking and hypertension are independent risk predictors of diabetic neuropathy. Pirart reported on more than 4000 patients he evaluated clinically. His results showed that poor control was associated with a higher incidence and prevalence of neuropathy.[1] Earlier, Fagerberg in a population study reported that the prevalence of clinical neuropathy was related to the duration of diabetes.[17] Others have suggested similar conclusions; however, findings were inconclusive for glycemic control.[18,19] Later studies employed newer physiological techniques such as sensory and motor nerve conduction and quantitative sensory testing of thermal and vibration thresholds as surrogate measures of neuropathy. The largest of these studies is the Diabetes Control and Complication Trial (DCCT).[20] In this study, intensive therapy reduced the incidence of appearance of neuropathy from 10% in the conventionally treated group to 3% in the intensively treated patients, a reduction of nearly 70% (p=0.006). Results of the United Kingdom Prospective Diabetes Study Group and the Kumamoto trial[21-22] also supports the relationship between glycemic control and diabetic complications in patients with type-2 diabetes. In the mentioned study performed by Valensi et al,[16] using extensive neurophysiological testing, with a total of 20 parameters, the multivariate analysis showed that 17 electrophysiological parameters correlated with the duration of diabetes, 9 correlated with age, 7 with glycemic control, and only one with gender. In our study, there was a significant positive correlation between age, duration of diabetes, glycemic control and the prevalence of peripheral of neuropathy.

In conclusion, the study has shown that there is a positive independent correlation between the presence of diabetic neuropathy and other microvascular complications. This observation occurs independently of age, duration of diabetes and glycemic control which are also correlated with the presence of neuropathy. Our findings support the hypothesis that microvascular complication of diabetes plays a major role in the pathogenesis of diabetic neuropathy.

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