Original Article

DOI: 10.17354/ijss/2016/89

Distal Polyneuropathy in Type 2 Diabetes Mellitus in and Around Jabalpur, Madhya Pradesh, India

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Abstract

Background: Diabetes is a systemic disorder characterized by metabolic abnormalities and angiopathy. Small vessel disease in the form of polyneuropathy contributes the major cause of disability. The relationship between the degree of glycemic control and development of long complication poses an intriguing though vital problem. The magnitude of morbidity calls for a reassessment of the situation and hence this study.

Aims and Objectives: To study the pattern of distal polyneuropathy (DPN) in Type 2 diabetes mellitus (T2DM) and its correlation with duration of disease and degree of glycemic control.

Materials and Methods: Pattern of peripheral neuropathy in 838 cases of T2DM (478 males and 360 females) varying from 25 years to 65 years has been analyzed. The study was conducted over 1 year December 2014 to December 2015. Subjects were put to detailed clinical workup including body mass index, hypertension labeled as per the WHO criteria. A thorough neurological assessment was made.

Results: DPN was encountered in 64% ($P < 0.05$) being more frequent in advancing age ($P < 0.001$) of the long duration (16-20 years) ($P < 0.05$). Autonomic neuropathy was a common accompaniment (43%). The presence of polyneuropathy in patients on the low caloric diet had a higher incidence of polyneuropathy while the blood sugar level has no direct retinopathy. Elevated serum triglycerides and low high-density lipoprotein cholesterol were associated with higher incidence of polyneuropathy. The presence of DPN even after glycemic control (180 out of 296 cases impaired glucose tolerance 60.8%) make us feel that polyneuropathy is regarded as a component rather than a complication of diabetes.

Conclusion: Metabolic decompensation of diabetes has a detrimental effect. No single mechanism appears to explain polyneuropathy, a combination of factors appear to be responsible. Mode of therapy and glycemic control can only lessen the severity. Diabetic polyneuropathy is regarded as a component of and not a complication of diabetes.

Key words: Body mass index, Distal polyneuropathy, High-density lipoprotein, Impaired glucose tolerance, Small vessel disease

INTRODUCTION

There is the global rise of diabetes mellitus (DM) and it has reached epidemic proportions worldwide. Recent estimates suggest that the prevalence of diabetes is rising globally, particularly in developing countries, an estimated 80-85% of the global population with diabetes lives in developing countries.[1] DM has become an important health concern in the South Asian region with a projected rise in the prevalence of diabetes of over 150-160% between 2000 and 2035.[1] Diabetes is a systemic disorder characterized by metabolic abnormalities and angiopathy.[2-6] Neuropathy is considered the most common micro-vascular complications DM.[7,8] Neuropathies in diabetes can impair the normal functioning of the peripheral central and autonomic nervous systems.[9] Diabetic polyneuropathy also called distal peripheral neuropathy and affected the peripheral nervous system and is by far the most common type of neuropathy seen in DM.[10] Distal polyneuropathy (DPN) is considered the major risk factor for amputation, and hence a significant cause of morbidity in DM.[11] The relationship between the degree of blood sugar control

Access this article online

www.ijss-sn.com

Month of Submission : 12-2015
Month of Peer Review : 01-2016
Month of Acceptance : 01-2016
Month of Publishing : 02-2016

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and development of long-term complication poses an intriguing though vital problem. Of these, the neurological complication contributes to the main cause of disability,[12-14] and some of the theories have been proposed for its pathogenesis.[4] The magnitude of morbidity calls for the reassessment of the situation and hence this study.

MATERIALS AND METHODS

838 cases of Type 2 DM attending the OPD of Department of Medicine, Sukh Sagar Medical College and Hospital, Jabalpur between December 2014 to December 2015 contributed a sample of this study. Subjects were put to detailed clinical workup including base metabolic index; the later was calculated as = kg/m^2, hypertension labeled as per the WHO Criteria.[6] A thorough neurological assessment was done of samples. Polyneuropathy was regarded as the bilateral loss of ankle jerks or gross sensory deficit in both feet as per who criteria multinational study. A 75 g oral glucose tolerance test was carried out, and the WHO criteria were adopted.[6] Blood glucose was estimated by the ortho-toluidine, while glycosylated hemoglobin by the modified chemical method of Flickinger and Winterhalter.[15,16] Lipid profile and serum creatinine were determined in the fasting state of patients.

OBSERVATIONS

Observations are shown in Tables 1-14.

The Table 1 shows highly significant increase ($P < 0.001$) in the frequency of DPN with advancing age.

The Table 2 reveals that BMI has no bearing to the incidence of peripheral neuropathy.

The Table 3 shows that duration has no linear correlation though the highest incidence was encountered in disease of 16-20 years duration. However, this rising trend of incidence was not maintained in disease of more than two decades.

It is revealed from the Table 4 that low caloric intake has a significant bearing ($P < 0.05$) in the frequency of polyneuropathy.

Table 5 shows that fasting blood sugar has no linear relationship with incidence of peripheral neuropathy.

It is evident from Table 6 that post-prandial hyperglycemia too does not have a linear relationship.

Thus, no consistent correlation was observed (Table 7).

Table 1: Age versus peripheral neuropathy in T2DM

Age (years)	Cases	Peripheral neuropathy	%
25	10	2	20
26-35	52	25	47.70
36-45	204	83	40.60
46-55	310	159	51.20
56-60	128	112	87.50
61 and above	134	128	95.50
Total	838	509	

T2DM: Type 2 diabetes mellitus

Table 2: Peripheral neuropathy and BMI

BMI	T2DM	Peripheral neuropathy	%
19	250	100	66.60
19-23	294	200	68.02
Above 23	294	209	71.06

BMI: Body mass index, T2DM: Type 2 diabetes mellitus

Table 3: Peripheral neuropathy and duration of diabetes

Duration (years)	Cases	Peripheral neuropathy	%
0-5	612	403	66.17
6-10	70	50	71.42
11-15	52	30	57.69
16-20	24	20	83.33
Above 20	10	6	60

Table 4: Peripheral neuropathy versus caloric intake

Calories	T2DM	Peripheral neuropathy	%
1500	298	285	90.63
1501-2000	500	204	40.80
2001-2500	38	20	52.63
2500 and above	2	0	-

T2DM: Type 2 diabetes mellitus

Table 5: Peripheral neuropathy versus fasting blood sugar level

Fasting blood sugar (mg%)	Number of cases	T2DM with peripheral neuropathy	%
120	312	169	45.16
120-140	168	100	59.52
141-160	76	70	92.10
161-180	60	60	100
181-200	64	60	93.75
Above 200	158	150	94.93

T2DM: Type 2 diabetes mellitus

Table 8 shows a close and significant correlation between serum triglyceride and peripheral neuropathy.

Table 9 shows that values of high-density lipoprotein (HDL) cholesterol have a significant correlation with frequency of peripheral neuropathy. It is inversely proportional to the incidence of peripheral neuropathy. Probably lower HDL

Table 6: Peripheral neuropathy with post-prandial blood sugar

Post-prandial blood sugar (mg%)	T2DM	T2DM peripheral neuropathy	%
150	86	20	23.25
151-200	230	80	34.78
201-240	194	100	51.54
241-280	108	104	96.29
281-320	92	85	92.39
231 and above	128	120	93.75

T2DM: Type 2 diabetes mellitus

Table 7: Peripheral neuropathy versus serum cholesterol

Serum cholesterol (mg%)	T2DM	Peripheral neuropathy	%
150-200	176	109	61.93
201-250	316	208	65.32
251-300	260	130	50.00
301-350	58	52	89.65
350 and above	28	10	37.51

T2DM: Type 2 diabetes mellitus

Table 8: Peripheral neuropathy and serum triglyceride level

Serum triglyceride (mg%)	T2DM	Peripheral neuropathy	%
100	318	109	34.27
101-150	402	300	74.62
151-200	92	81	88.04
201-250	18	15	83.33
251-300	3	3	100
301 and above	1	1	100

T2DM: Type 2 diabetes mellitus

Table 9: Peripheral neuropathy and HDL cholesterol

HDL (mg%)	T2DM	Peripheral neuropathy	%
36-45	318	139	43.71
46-55	402	310	77.11
56-64	102	56	54.60
65 and above	12	4	33.33

T2DM: Type 2 diabetes mellitus, HDL: High-density lipoprotein

values enhance the micro-angiopathy and thereby lead to increase in the incidence of peripheral neuropathy.

The Table 10 shows that DPN frequently presents as pain syndrome and paresthesic. Vibration sense was more diminished in lower extremities than in the upper limbs. Motor disorders were found in only 2% cases. In 95% of patients with DPN, the tendon reflexes were diminished. Abnormal ankle jerk was encountered most frequently, and diminution was often asymmetric. Symmetric polyneuropathy was encountered in 488 out of 509.

Table 10: Symptomatology of distal polyneuropathy in 509 cases

Symptoms	Literature	Present series %
Subjective disturbances	86.2	82
Pain	76.1	70.3
Paresthesis	47.70	60
Cramps	47.70	60
Sensation of weakness and heaviness in lower extremities	37.70	10
Objective disturbances	85	78
Sensory disorders	83.80	62
Tactile hypoesthesia	35.40	18
Diminished sense of vibration	80	76
Impaired musculo-articular sense	9.20	1.80
Impaired discriminative sensation	35	1.20
Motor disorders		
Atrophy of muscles of extremities	16.10	2.00
Fasciculations	00	00
Paresis	00	00
Diminished reflexes	85.30	97
Biceps	11.50	10
Triceps	10	6
Radial	10	6
Knee jerk	50.80	48.00
Ankle jerk	98	95
Trophic disorders	51.60	21.20
Ulcer	0.80	1.20
Osteoarthropathy	1.80	6.20

Table 11: Asymmetric neuropathy

Asymmetric polyneuropathy	Cases (%)
Total	21 (4.01)
Acute/sub-acute motor	2 (0.40)
Cranial mono-neuropathy	7 (1.10)
Truncal neuropathy	12 (2.11)
Entrapment neuropathy	0

Table 12: Features of autonomic neuropathy

Symptoms	%
Diabetic impotence	60.00
Cardiac neuropathy	19.10
Neurogenic bladder	11.00
Seating disturbance	9.00
Neuropathic ulcer	0.60
Nocturnal diarrhea	0.30

The Table 11 reveals that asymmetric polyneuropathy is less common among the diabetics.

Impotence is probably the most frequent manifestation of autonomic neuropathy (Table 12).

It includes cases of impaired glucose tolerance and T2DM with mild hyperglycemia. It appears from the Table 13 that the incidence of peripheral neuropathy is lowest in the insulin-treated group as compared to those on oral hypoglycemic agents/or combinations. The

Table 13: Correlation of peripheral neuropathy with management

Group	Cases	Peripheral neuropathy	%
Diet	296	180	60.80
OHA+diet	480	350	72.90
Insulin	40	04	10
OHA+insulin	22	20	90

Table 14: Correlation of peripheral neuropathy with glycemic control

HbA1C%	T2DM cases	Peripheral neuropathy	%
Less than 8%	202	109	53.90
8% and above	638	400	62.89

Z=2.55. (*P*<0.01). T2DM: Type 2 diabetes mellitus, HbA1C: Glycosylated hemoglobin

oral hypoglycemic agent might probably contribute to peripheral neuropathy.

The Table 14 shows that in uncontrolled diabetes frequency of polyneuropathy is higher, which is statistically significant ($P < 0.01$). It seems to be an important exacerbating factor of subclinical polyneuropathy.

DISCUSSION

Analysis of our material reveals a significant increase in the frequency of DPN with an increase in patient age (Table 11) ($P = 0.001$). This is corroborated by the finding of Jordan (1936), Rundles (1945), Martin (1953), and Gelman (1967).[17,18] The factor of age in the development of DPN could be:

1. The increase in duration of diabetes as the age advanced.
2. Higher incidence of concomitant atherosclerosis leading to DPN.
3. Wittingham *et al.* (1971) have postulated that diabetics may acquire senile neuropathy at middle age.[19]

We observed that incidence of polyneuropathy in the obese diabetic was by about the same as in normal weight (Table 2). This is corroborated by the finding of Richardson (1953). Higher incidence of peripheral neuropathy in diabetes and its decompensation leading to a development of angiopathy in the middle-aged patient. Table 3 shows no linear correlation though highest incidence was noted in disease of 16-20 years. However, this rising trend of incidence was not maintained in disease of more than two decades.

We found that low caloric intake (Table 4) correlated favorably with the frequency of polyneuropathy. Martin (1953), Gelman (1967),[17,18] believe that long-term hyperglycemia is direct or an indirect cause of peripheral neuropathy. We found that the incidence of DPN shows no linear correlation with the fasting of post-prandial hyperglycemia (Tables 5 and 6). Moreover, DPN was also encountered in IGI group. This too shows that glycemia is probably not intimately related to polyneuropathy.

Jorden *et al.* 1935[19,20] showed that in diabetes content of cholesterol, phospholipid in peripheral nerve was reduced, Adams (1954)[21] found that activity of acetic-thiokinase in peripheral nerve of alloxan-diabetic animals was sharply reduced. And considered it as manifestation of the syndrome of abnormal fat metabolism which may lead to earlier development atherosclerosis in vessels of the extremities. However, Table 7 shows no consistent correlation though Table 8 shows significant correlation with serum triglycerides. Table 9 shows that HDL cholesterol is inversely proportional to the incidence of polyneuropathy. Probably lower HDL values enhance the micro-angiopathy and thereby lead to increase the incidence of peripheral neuropathy.

Vibration sense was more diminished in lower extremities than in upper limbs. The disparity between manifestations in upper and lower limb can be explained on the anatomical basis. The cranial mono-neuropathy involving the 7th and 3rd cranial nerves may be due to compression of the nerve in a bony canal.[12]

The prolonged administration of large doses of sulfonamides may produce polyneuritis Govseev and Mints (1948), Stepin (1956),[3,14,19] have reported DPN in diabetes due to sulfonylurea. Our observation contained in Table 13 corroborates these reports.

There are several theories have been postulated for pathogenesis of polyneuropathy viz:[5]

1. Accumulation of sugar, alcohol, leading to swelling and tissue damage.
2. Deficiency of intracellular inositol leading to impairment of membrane phospholipid function.
3. Deficiency of myelin synthesis due to hypoinsulinemia, leading to the segmental myelin loss.
4. Glycosylation of neural membrane proteins with impairment of neural function.
5. Accelerated death and turnover of Schwann cell either secondary to cell injury from of the above or directly due to diabetes independent of metabolic abnormality leading to thickening and accumulation of abnormal basal lamina and impaired nerve function.
6. Immunoreactive mechanism with lipoid acting as hapten and glycolipid as antigen.

Locke and Tarsy[19] have defined complication as "Any pathological process occur in antecedent but not

compulsory to the main disease, and the causes for that not connected with the cause of principal disease." Thus contrary to the consensus regarding polyneuropathy as a complication of diabetes, we believe that it is an accompaniment.

CONCLUSION

1. Mode of therapy and glycemic control can only lessen the severity.
2. Metabolic decompensation of diabetes has a detrimental effect.
3. No single mechanism appears to explain polyneuropathy, a combination of factors appear to be responsible.
4. Diabetic polyneuropathy is a component rather than a complication of diabetes.

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How to cite this article: Patel HS, Jain SK. Distal Polyneuropathy in Type 2 Diabetes Mellitus in and Around Jabalpur, Madhya Pradesh, India. Int J Sci Stud 2016;3(11):218-222.

Source of Support: Nil, **Conflict of Interest:** None declared.