To study the prevalence of Diabetic Peripheral Neuropathy in Newly Diagnosed Patients of Type 2 Diabetes Mellitus (T2DM) in a tertiary care hospital.

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Running Title: diabetic peripheral neuropathy in new diagnosed type 2 diabetes mellitus

Figures: 3

Table: 3

Jaspreet Kaur

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Abstract:

Background: The prevalence of type 2 diabetes mellitus (T2DM) is growing worldwide, and these patients may be asymptomatic and present with complications at the time of diagnosis. Diabetic neuropathy is the most common complication affecting the patients who may present with distal polyneuropathy at the time of diagnosis and also poor glycaemic control. The Diabetic peripheral polyneuropathy affects approximately 1 in every 10 newly diagnosed patients, whereas two third of patients with diabetes mellitus have clinical or subclinical neuropathy. So we designed this study to find prevalence of diabetic peripheral neuropathy in Newly Diagnosed Patients of T2DM in a tertiary care hospital.

Methodology: This observational study was carried out in patients diagnosed with T2DM as per ADA criteria. A thorough clinical examination; Nerve conduction velocity testing; evaluation of plasma glucose and glycosylated hemoglobin and assessment of neuropathy by using the Diabetic neuropathy index and diabetic neuropathy score was performed on all patients.

Result: 18% of patients had signs of peripheral neuropathy as shown by NCV testing at the time of diagnosis. These patients had elevated levels of glycosylated hemoglobin, fasting plasma glucose and 2-hour plasma glucose and lower scores of DNI and DNS which were statistically significant. The most common type of neuropathy seen in these patients was sensorimotor involvement with demyelinating type of neuropathy with more involvement of lower limbs. The NCV studies showed reduced distal latency and prolonged amplitude as well as conduction velocity in patients with diabetic neuropathy.

Conclusion: Our study showed that approximately 1 in 5 newly diagnosed patients with type 2 diabetes mellitus are at risk of developing diabetic peripheral neuropathy.

Keywords: Diabetes mellitus, Nerve Conduction Velocity, Diabetic Neuropathy Index, Diabetic Neuropathy Score

Introduction:

Diabetes mellitus is a common endocrine disorder characterized by hyperglycemia and (1, 2, 3) is categorized into type 1 diabetes mellitus (T1DM) which is a result of complete or near total deficiency of insulin, and type 2 diabetes mellitus (T2DM), which is a heterogeneous group of disease with variable insulin resistance, impaired insulin secretion and increased production of glucose (1). Many factors contribute to resistance to insulin including obesity, aging, and a sedentary lifestyle; it also has a strong genetic factor and is frequently found in certain families and ethnic minority groups (3).

The prevalence of diabetes continues to grow worldwide and is fast emerging as largest global public health emergencies of the 21st century (3, 4). Approximately 415 million adults have diabetes mellitus (DM) and is set to rise to 642 million by the year 2040 (4). Twenty-three million Americans have diabetes, and there is an increase in the incidence of disease by 5% per year (5). India has a higher prevalence of DM (4.3%) as compared with the West (1%–2%), as Asian Indians are more prone for insulin resistance and cardiovascular mortality(6).

Consistently elevated blood glucose levels lead to protein glycation and overproduction of reactive oxygen species resulting in vascular damage and responsive activation of tissue specific growth/ repair system (4). Patients suffering from T2DM might be asymptomatic and present with complications when diagnosed (3), approximately 8% of patient have cardiovascular disease at time of presentation, 37% have microanuerysm/retinopathy in one eye, 18% have microalbuminuria and 2.3-15.2% have polyneuropathy as per clinical signs and electrophysiological properties respectively (7). 193 million people are estimated to be suffering from diabetes, undiagnosed and at greater risk of developing complications (4). Macrovascular complications are associated with coronary artery disease, peripheral arterial disease and

cerebrovascular disease which tend to substantially reduce the life expectancy in all age groups (1, 7). The frequency of microvascular diabetic complication is clearly correlated to the duration of diabetes, quality of metabolic control (HbA1c), systolic blood pressure, obesity, hyperlipidemia and insulin resistance have a considerable impact on the development and progression of microvascular diabetic complications (7) leading to retinopathy, nephropathy and neuropathy which increase the cost for health care resources (1, 7).

The incidence of diabetic neuropathy in India is not known, as per a study done in South India 19.1% type II diabetic patients had peripheral neuropathy (6). Diabetic peripheral polyneuropathy affects approximately 8% of newly diagnosed patients and >50% of patients with long term DM (1, 2). Patients with type 2 diabetes mellitus may present with distal polyneuropathy at the time of diagnosis or even after few years of known poor glycaemic control (1). Symptoms of diabetic neuropathy are symmetrical paresthesia and burning pain that predominantly occurs distally in the legs according to length dependency with severe complications can result in foot ulceration and non traumatic amputation (2). Chronic sensorimotor distal symmetric polyneuropthy is the common form leading to substantial sensory loss, muscle weakness, and pain which is gradual in onset and may go undiagnosed for years (8).

A significant association between cholesterol and fasting triglycerides with diabetic neuropathy has been established by the EURODIAB study (5, 9, 10) Steinmetz in a review from the U.K. Prospective Diabetes Study Group and Fenofibrate Intervention and Event Lowering in Diabetes Study reported lower incidence of macrovascular and microvascular complications with lipid-lowering therapy (5, 11). As there is no treatment for diabetic peripheral neuropathy available, its prevention and early detection assume utmost importance (2) The severity of diabetic neuropathy is dependent on the duration of diabetes and degree of glycaemic control, diabetes mellitus

affects peripheral nerves in somatosensory, auditory system, psychomotor responses and cognitive effect in uncontrolled patient thereby affecting reaction times (2, 5, 8). Nerve conduction velocities are one of the sensitive indices for the severity of neuropathy and localize lesion (1, 12). In many patients with normal clinical examination, a decrease in nerve conduction velocity is observed (13). Nerve conduction velocity (NCV), has been one of the gold standards for diagnosing diabetic peripheral polyneuropathy with nerve dysfunctions, a composite score has been introduced for quantitative analysis of the results of NCV (2, 14).

A thorough literature search has shown that many patients diagnosed with diabetes mellitus might present with neuropathy at the time of diagnosis (1, 2, 5) as two third of patients with diabetes mellitus have clinical or subclinical neuropathy (6), hence, it was considered apt to study prevalence of Diabetic Peripheral Neuropathy in Newly Diagnosed Patients of Type II Diabetes Mellitus (T2DM) in a tertiary care hospital.

Materials and Method:

This observational study was carried out in Department of Physiology, with the collaboration of General Medicine and Neurology Department in a tertiary care hospital of western Uttar Pradesh after approval from the Institutional Ethics Committee. All patients visiting the outpatient department of medicine and neurology diagnosed to be suffering from type II diabetes mellitus as per ADA guidelines (15) were enrolled in the study after obtaining written informed consent from 1st March, 2017 to 31st May, 2018.

All patients in the age group of 30-70 years, of both sexes willing to give written informed consent were enrolled in the study. All patients who were known to be suffering from alternative cause of peripheral neuropathy, alcoholics, renal failure, thyroid disease, autoimmune disease, cancer were excluded from the study. All patients with a positive family history of non diabetic

neuropathy in first-degree relatives, on drugs that could cause neuropathy or were unable to understand or cooperate with the procedure of the study were also excluded from the study. Pregnant and lactating females were also excluded from the study.

Procedure: After approval from the institutional ethics committee and written informed consent, patients diagnosed to be suffering from type II diabetes mellitus fulfilling the inclusion and exclusion criteria were enrolled in the study. Patients diagnosed with type II diabetes mellitus as per ADA guidelines (15)

A thorough clinical examination (including neurological examination); Nerve conduction velocity testing; evaluation of plasma glucose and glycosylated hemoglobin; and assessment of neuropathy by using the Diabetic neuropathy index and diabetic neuropathy score was performed on patients. Data was entered in excel sheet and analyzed.

Primary Outcome Measures:

- Nerve Conduction Velocity was assessed in median, ulnar, peroneal, sural and posterior tibial nerves, motor nerve conduction velocity was measured on the left forearm segment of the median nerve and the left peroneal nerve. A composite score was used for quantitative analysis of result of NCV (2, 14).
- Plasma glucose level and glycosylated haemoglobin level

Secondary Outcome Measures:

- Neuropathy was assessed by using the Michigan Neuropathy program which includes two steps; the Diabetic Neuropathy Index (DNI) and the Diabetic Neuropathy Score (DNS). Patients who score less than 2 on routine clinical examination and are asymptomatic are referred to be assessed by complete neurological examination done by nerve conduction studies (16).

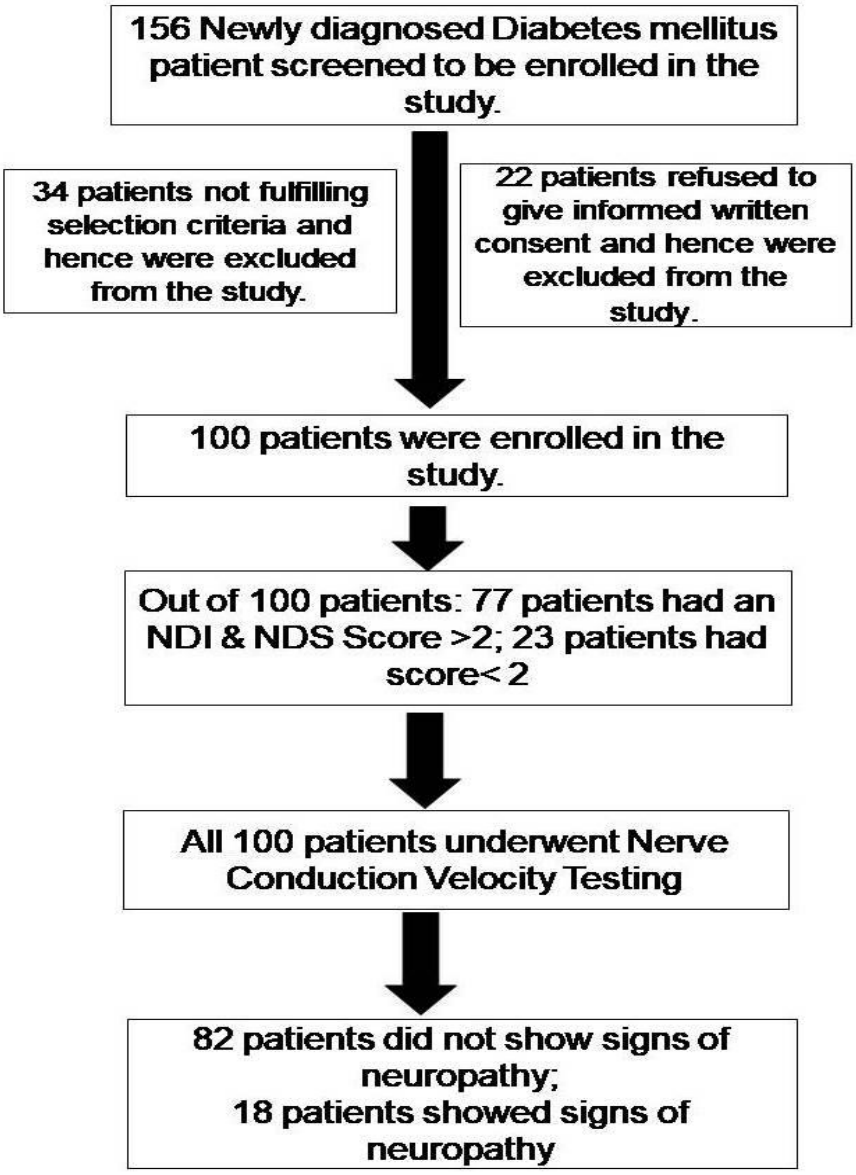
Statistical Analysis:

The data was presented as mean ± standard deviation (Mean ± SD). The result was analyzed using appropriate parametric (two tailed student‘t’ test) and non parametric test (chi-square test,). Nominal variable were compared using Chi-square test. The student‘t’ test was used to compare group means for normally distributed data and Mann-Whitney U test/ Wilcoxon Sign rank test was used for non-normally distributed data. Correlations between the variables were examined using the Pearson correlation coefficients. A $p<0.05$ was considered statistically significant.

Results:

A total of 156 patients with newly diagnosed diabetes mellitus were screened for the study from March, 2017 to May, 2018. Thirty four (34) patients did not fulfil the inclusion and exclusion criteria and were excluded from the study; another 22 patients did not give written informed consent to participate in the study and hence were also excluded from the study. One hundred (100) patients who fulfilled the inclusion and exclusion were enrolled in the study after they give written informed consent (Figure 1). All the patients underwent a thorough clinical examination, all these patients were subjected to diabetic neuropathy index (DNI) and diabetic neuropathy score (DNS). Seventy seven (77) patients had DNS and DNI score more than 2, whereas 23 patients had a score less than 2. All the 100 patients were subjected to nerve conduction velocity (NCV) testing, 82 of these 100 newly diagnosed patients did not have neuropathy, whereas 18 of these patients had neuropathy.

Figure 1. CONSORT diagram



The baseline parameters of all the patients are shown in Table1. The mean age of patients enrolled in the study was 55.31±11.38 years, a total of 45 males and 55 females were enrolled in the study. The average glycosylated haemoglobin (HbA1c) levels in these patients were 7.45±1.90 %. All these patients had elevated levels of fasting plasma glucose (FPG) and 2-hours plasma glucose (2h - PG). Any patient with DNI or DNS score less than 2 should be subjected to NCV, 23 patients in our study had a DNI or/and DNS score less than 2.

Table 1. Baseline parameters of patients enrolled in the study.

Parameter	**Patient enrolled (n=100)**
Age (years) (Mean±SD)	55.31±11.38
Weight (kilograms) (Mean±SD)	71.32±8.46
Glycosylated Hemoglobin (HbA1c) (%)(Mean±SD)	7.45±1.90
Fasting Plasma Glucose (FPG) (mg/dL) (Mean±SD)	149.55±42.21
2-hours Plasma Glucose (2h-PG) (mg/dL) (Mean±SD)	215.77±26.89
Diabetic Neuropathy Index (DNI) (Mean±SD)	3.11±1.37
Diabetic Neuropathy Score (DNS) (Mean±SD)	3.81±1.79

23 patients in our study had a DNI or/and DNS score less than 2. These patients were categorized in group A (n=23), whereas patients with patients with a DNI or/and DNS score more than 2 were placed in group B (n=77). The demographic and baseline characteristic of patients in both group is shown in Table 2. The patients with abnormal scores (Group A) had statistically significant ($p<0.05$) higher fasting plasma glucose levels, 2-hours plasma glucose levels and glycosylated haemoglobin levels as compared to group B. All the other baselines parameters were higher in group A but it was not statistically significant.

Table 2: **Demographic and Biochemical Parameters in both groups**

Parameter	Group A (n=23)	Group B (n=77)
Age (Years) (Mean±SD)	59.09±10.4	54.18±11.5[#]
Sex (M:F)	11:12	34:43[$]
Weight (Kg) (Mean±SD)	72.96±8.1	70.83±8.6[#]

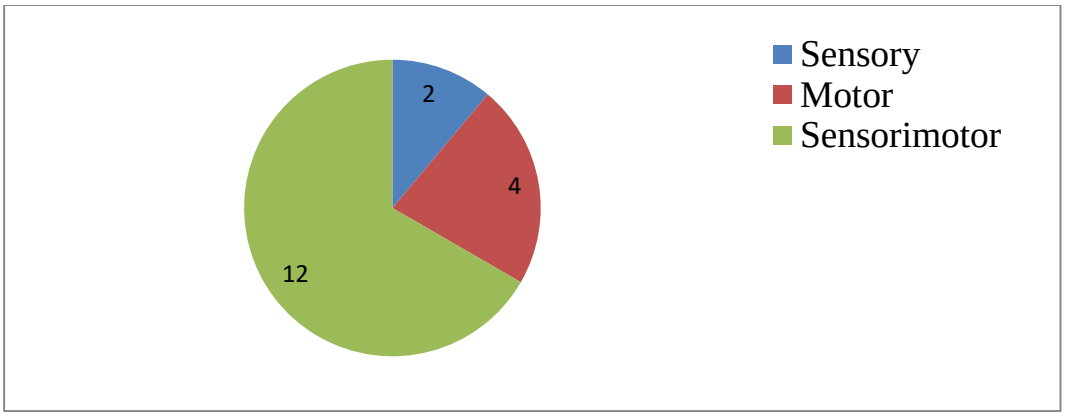
Fasting Blood Glucose (mg/dl) (Mean±SD)	216.61±43.3	96.36±3.8#*
2-hours Plasma Glucose (2h-PG) (mg/dL) (Mean±SD)	246.74±43.4	121.46±7.6#*
Glycosylated Hemoglobin (HbA_{1c}) (%)(Mean±SD)	10.64±1.5	6.51±0.3#*
Diabetic Neuropathic Index (Mean±SD)	3.30±1.9	3.55±1.2#
Diabetic neuropathy Score (Mean±SD)	3.52±2.3	4.42±1.6#
# Using Student T test; $ Using Chi Square test		
*p<0.05 as compared to other group		

All patients underwent nerve conduction velocity and the results showed that 18 patients enrolled in the study had neuropathy associated with diabetes mellitus and all these patients belonged to the group with persistently low DNI and/or DNS Score (Group A).

Neuropathy – Type:

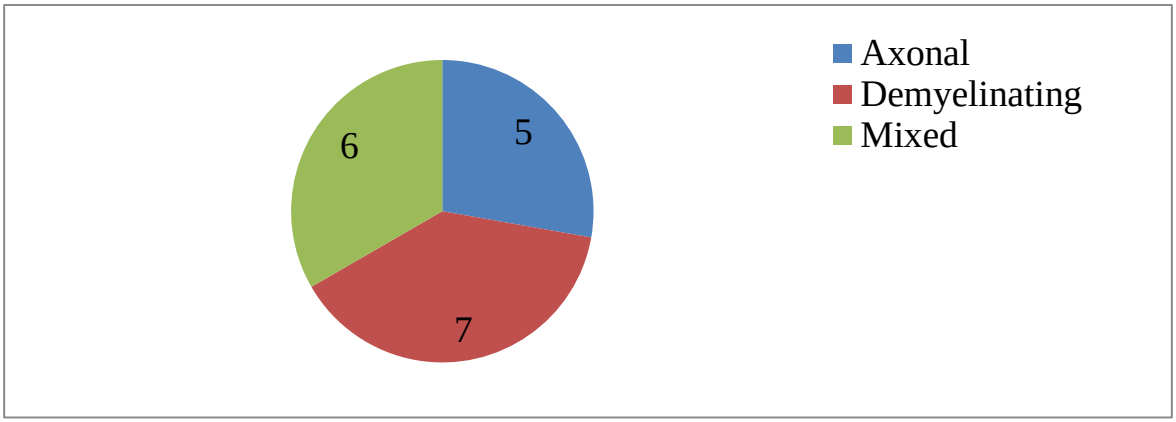
The neuropathy diagnosed in new onset diabetes mellitus could be further classified into either motor, sensory or mixed. In our study as shown in Figure 2, most of the patients had presentation of sensorimotor neuropathy, and least patients had presentation of sensory neuropathy. As per the NCV testing, 2 patients were having sensory neuropathy, 4 patients had motor neuropathy and 12 patients had sensorimotor neuropathy.

Figure 2. Neuropathy type as per NCV testing



The neuropathy diagnosed in new onset diabetes mellitus could be further classified into either axonal, demyelinating or mixed type based on the results of NCV testing mainly conduction velocity, amplitude and Distal latency. In our study as shown in Figure 3, most of the patients had presentation of demyelinating neuropathy, and least patients had presentation of axonal neuropathy. As per the NCV testing, 5 patients were having axonal neuropathy, 7 patients had demyelinating neuropathy and 6 patients had mixed neuropathy.

Figure 3. Neuropathy type as per NCV testing



Correlation (Table 3)

Glycosylated hemoglobin was correlated with fasting plasma glucose, 2-hours plasma glucose, diabetes neuropathy index and diabetes neuropathy scores for all the patients. No correlation of HBA_{1C} with FBS, 2-hPG, DNI and DNS was seen in patients of Group B (n=77), whereas there

was a statistically significant correlation of HBA_{1C} with FBS, PPBS, DNI and DNS in patients of Groups A (n=23).

Table 3: **Correlation of HBA_{1C} in both groups**

Parameter	**Group A (n=23)**		**Group B (n=77)**	
	r	**p**	**r**	**p**
Fasting Plasma Glucose (FPG) (mg/dL)	**0.93**	**<0.05***	**-0.20**	**>0.05**
2-hours Plasma Glucose (2h-PG) (mg/dL)	**0.92**	**<0.05***	**0.07**	**>0.05**
Diabetic Neuropathy Index (DNI)	**-0.68**	**<0.05***	**-0.04**	**>0.05**
Diabetic Neuropathy Score (DNS)	**-0.70**	**<0.05***	**0.09**	**>0.05**
*p<0.05 as compared to other group				

Discussion:

Diabetic neuropathies are one of most common cause of neuropathies (17) affecting different parts of nervous system and presenting with diverse clinical manifestation (18). Diabetic neuropathy is a disease of exclusion (18) and up to 50% of patients with type 2 diabetes mellitus develop some degree of peripheral neuropathy (17). Peripheral neuropathy in diabetes mellitus is due to metabolic and microvessel alterations manifesting as a symmetric, length-dependent sensorimotor polyneuropathy pattern and associated cardiovascular risk factors (19). Though peripheral neuropathy is association with the duration of disease as well as poor glycemic control, but evidences suggest an estimated prevalence of neuropathy varying from 11.5 to 48% in new onset patients of diabetes mellitus in various population based studies (20, 21). There have been contradictory studies on the prevalence of peripheral neuropathy, as shown in recent British and German database with 2.4-5.7% newly diagnosed diabetic patients suffering from

peripheral neuropathy (22). In an effort to find out neuropathy in patients diagnosed with diabetes mellitus as these patients might have clinical or subclinical neuropathy we conducted this study to find prevalence of diabetic peripheral neuropathy in newly diagnosed patients of type 2 diabetes mellitus (T2DM) in a tertiary care hospital.

The results of our study showed that 18% of patients had signs of peripheral neuropathy as shown by NCV testing at the time of diagnosis of type 2 diabetes mellitus, though, 23% patients had low scores in Diabetes Neuropathy Index and Diabetes Neuropathy Score with females being more effected as compared to males. The patients with diabetes neuropathy as compared to the subset of patients without neuropathy had elevated levels of glycosylated hemoglobin, fasting plasma glucose and 2-hour plasma glucose which were statistically significant. These patients also had lower scores on DNI and DNS which was statistically significant. The NCV studies showed reduced distal latency and prolonged amplitude as well as conduction velocity in patients with diabetic neuropathy. There was a positive correlation between glycosylated hemoglobin and fasting plasma glucose, 2-hour plasma glucose, DNI as well as DNS in patients with diabetic neuropathy, whereas in patients without diabetic neuropathy no correlation with glycosylated hemoglobin was found.

One study done in Western India, studied the association of duration of diabetes with auditory and visual reaction time, the patients were divided into two groups based on the duration of disease as more/less than 5 years demonstrated that patients with longer duration of disease had delayed reaction time. The study also demonstrated delayed reaction time could serve as an indicator for early nerve damage and could serve as a routine clinical screening procedure for neuropathy. Our study also used DNI and DNS are parameter to assess all the patients diagnosed with diabetes mellitus. The results of our study showed that higher number of patients had

abnormal scores for both DNI and DNS which when subjected to NCV testing showed that 18 out of 23 patients had neuropathies. Though, our study limited itself to newly diagnosed patients of type 2 diabetes mellitus (8).

One more study done in Romania which evaluated the role of diabetic neuropathy with balance impairment and risk of fall in patients showed the prevalence of diabetic neuropathy of 28.8% which was associated with increased age, body mass index and increased depression severity. These patients had higher levels of glycosylated hemoglobin associated with impaired balance with increased risks of falls. Our study is somewhat similar to this study as in our study also the patients with diabetic neuropathy belonged to higher age groups and had statistically significant levels of glycosylated hemoglobin levels as compared to patients without diabetic neuropathy. The results of our study are different from this study as only 18% patients enrolled in our study had diabetic neuropathy and all the patients enrolled in the study were newly diagnosed patients. Moreover, we wanted to find out presence of diabetic peripheral neuropathy in newly diagnosed patients whereas in this study, they also wanted to evaluated the risk of fall in these patients (4).

Another study done in Korea to look into the risk factors for neuropathy as well as to study the correlation with severity and glycosylated hemoglobin level demonstrated that patients with diabetic neuropathy had higher levels of glycosylated hemoglobin as well as belonged to higher age group. The study also demonstrated the positive correlation of age and glycosylated hemoglobin levels with higher propensity of motor and sensory nerve involvement of nerves of lower limbs. The study also highlighted that duration of the disease was also one factor that had to be taken into consideration. The results of our study are also in similar lines as in our study also the patients with diabetic neuropathy had higher levels of glycosylated hemoglobin levels and plasma glucose levels. Our study differs from this study as in our study we laid emphasis on

finding out the number of newly diagnosed patients of type 2 diabetes mellitus afflicted with neuropathy (2).

A study done by Mojaddidi, et.al. for early detection of impaired nerve functions, along with risk factors associated with diabetic neuropathy found that the mean duration of patients with diabetes of 14 years was associated with development of neuropathy. Along with the duration of disease, higher age group, abnormal levels of glycosylated hemoglobin levels as well as abnormal plasma glucose level were associated with diabetes neuropathy. The study also showed a slight higher prevalence of neuropathy in females as compared to males. The results of our study are similar to this study as more number of females was affected, a higher age group was affected and the patients also had abnormal plasma glucose levels. Our study only studied the newly diagnosed patients and this study showed a positive correlation of duration of disease with neuropathic changes (12).

A study done by Lee, et.al. – The PROMISE cohort for prevalence of peripheral neuropathy and nerve dysfunction for patients with high risk for type 2 diabetes mellitus with the aid of Michigan Neuropathy Screening Instrument and vibration perception threshold showed that prevalence of diabetic neuropathy in newly diagnosed patients with diabetes mellitus was 50%. The average age of the study population was 53 years with patients having neuropathy were older and had higher level of fasting plasma glucose as well as 2-hour plasma glucose. The results of our study are quite similar to this study as in our study also we found that the presenting mean age of patients in our study was 54 years almost similar to that in the PROMISE cohort. Our study also showed that patients with neuropathy were having a higher mean age and elevated fasting plasma glucose and 2-hour plasma glucose, which is similar to this study. Our study differed from this study, as in our study we only included patient who were newly

diagnosed diabetic patients with 18% cases of diabetic neuropathy, and we did not include the patients who were having normal glycemia or prediabetics. In our study we conducted NCV testing for all the patients as compared to PROMISE cohort where Vibration Perception Threshold was used (23).

There are certain limitations in our study; firstly the sample size of the study was small – as this was a time based study so we could not enroll higher number of patients which could have shown a different result. Secondly, we did not have any intervention in our study, as keeping an intervention for patients with diabetic neuropathy would not have solved the aim of our study. The aim of our study was to find the prevalence of peripheral neuropathy in patients who are newly diagnosed. Thirdly, we did not have a control group in our study, the patients who did not have diabetic neuropathy served as a control for the other group of patients and the purpose of our study was to evaluate diabetic neuropathy in patients with new onset diabetes mellitus.

To conclude our study showed that all patients with type 2 diabetes mellitus should be thoroughly examined for signs of diabetic neuropathy irrespective of the duration of the disease. As many patients with type 2 diabetes mellitus are often asymptomatic and are diagnosed with the disease after several years of illness. Our study showed that 23% of newly diagnosed patients had abnormal clinical examination and when subjected to NCV testing 18% of patients were diagnosed with neuropathy at the time of diagnosis of disease. Approximately 1 in 5 newly diagnosed patients with type 2 diabetes mellitus is at risk of developing diabetic neuropathy. The females had slightly higher preponderance, and patients with abnormally high levels of glycosylated hemoglobin, plasma glucose levels and lower score on neuropathic scales had higher chance of developing neuropathy. These patients had a positive correlation of glycosylated hemoglobin levels with plasma glucose levels. The NCV findings of these patients

showed prolonged latencies, reduced amplitudes and reduced conduction velocity suggestive of neuropathy. The most common presentation of patients with diabetic neuropathy was sensorimotor involvement with demyelinating type of neuropathy.

References:

1. Kakrani AL, Gokhale VS, Vohra KV, Chaudhary N. Clinical and Nerve Conduction Study Correlation in Patients of Diabetic Neuropathy. Journal of the Association of Physician of India 2014; 62: 24-7.
2. Lee WJ, Jang S, Lee SH, Lee HS. Correlation between the Severity of Diabetic Peripheral Polyneuropathy and Glycosylated Hemoglobin Levels: A Quantitative Study Ann Rehabil Med 2016; 40: 263-70.
3. Kumar S, Aneja GK, Trivedi A, Atam V, Shankhwar SN, Panwar A, et.al. Correlation of Diabetic Nephropathy and HbA1C in Newly Diagnosed Type 2 Diabetic Patients of Western UP. International Journal of Scientific and Research Publications 2014; 4 (12): 1-4.
4. Timar B, Timar R, Gaiță L, Oancea C, Levai C, Lungeanu D. The Impact of Diabetic Neuropathy on Balance and on the risk of falls in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study. PLoS ONE 2016; 11(4): e0154654. doi:10.1371/journal.pone.0154654
5. Wiggin TD, Sullivan KA, Pop-Busui R, Amato A, Sima AAF, Feldman EL. Elevated Triglycerides Correlate With Progression ofDiabetic Neuropathy. Diabetes 2009; 58: 1634–40.
6. Bansal V, Kalita J, Misra UK. Diabetic neuropathy. Postgrad Med J 2006; 82: 95–100. doi: 10.1136/pgmj.2005.036137

7. Tomić M, Poljičanin T, Pavlić-Renar I, Metelko Ž. Obesity – A risk factor for Microvascular and Neuropathic Complication in Diabetes? DiabetologiaCroatica 2003; 32: 73-8.
8. Gupta S, Jain P, Vij V. Correlation of Auditory and Visual Reaction Tiem with duration of Diabetes. World Journal of Pharmaceutical Research 2014; 3: 877-85.
9. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, et.al. Vascular risk factors and diabetic neuropathy.N Engl J Med 2005;352:341–50.
10. Kempler P, Tesfaye S, Chaturvedi N, Stevens LK, Webb DJ, Eaton S, et.al. Autonomic neuropathy is associated with increased cardiovascular risk factors: the EURODIAB IDDM Complications Study. Diabet Med 2002; 19: 900–09.
11. Steinmetz A. Lipid-lowering therapy in patients with type 2 diabetes: thecase for early intervention. Diabetes Metab Res Rev 2008;24:286–93.
12. Mojaddidi MA, Aboonq M, AL Nozha OM, Allam A, El-Bab MF. Early Diagnosis of Diabetic Neuropathyin AlmadinahAlmunawwarah. Journal of Taibah University Medical Sciences 2011; 6: 121-31.
13. Dolu H, Ulas UH, Bolu E, Ozkardes A, Odabasi Z, Ozata M, et.al. Evaluation of central neuropathy in type II diabetes mellitus by multimodal evoked potentials. ActaNeurolBelg 2003; 103: 206-11.
14. Dyck PJ, Davies JL, Litchy WJ, O'Brien PC. Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. Neurology 1997; 49: 229-39.
15. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014; 37(Suppl. 1): S81–90.

16. Meijer JWG, Sonderen EV , Blaauwwiekel EE, et al. Diabetic Neuropathy Examination, A Hierarchical Scoring System To Diagnose Distal Polyneuropathy In Diabetes, Diabetes Care 2000; 23: 750-3.
17. Assessing diabetic peripheral neuropathy in primary care. Available at url: https://bpac.org.nz/bpj/2014/june/diabetic-peripheral-neuropathy.aspx. (Last Accessed 15th October, 2018)
18. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et.al. Diabetic neuropathy: A position statement by the American Diabetes Association. Diabetes Care 2017; 40: 136-54.
19. Petropoulos IN, Javed S, Azmi S, Khan A, Ponirakis G, Malik RA. Diabetic neuropathy and painful diabetic neuropathy in the Middle East and North Africa (MENA) region: Much work needs to be done. J Taibah Univ Med Sc 2016; 11 (4): 284-94.
20. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53
21. Spijkerman AM, Dekker JM, Nijpels G, Adriaanse MC, Kostense PJ, Ruwaard D, et.al. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: the Hoorn screening study. Diabetes Care 2003;26: 2604–8.
22. Kostev K, Jockwig A, Hallwachs A, Rathmann W. Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: a retrospective database analysis in Germany and U.K. Prim Care Diabetes 2014; 8: 250–5.

23. Lee CC, Perkins BA, Kayaniyil S, Harris SB, Rethakaran R, Gerstein HC, et.al. Peripheral neuropathy and nerve dysfunction in individual at high risk for type 2 diabetes: The PROMISE cohort. Diabetes Care 2015; 38: 793-800.

"Evaluation of Diabetic Neuropathy Changes in Newly Diagnosed Patients of Type 2 Diabetes Mellitus (T2DM)"

Submitted By

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Submitted

In partial fulfillment of the requirement of the degree of
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(2019)

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Submitted

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INTRODUCTION

Diabetes mellitus is a common endocrine disorder characterized by hyperglycemia with lack of insulin, insulin action or both and associated with disturbance of carbohydrate, protein and fat metabolism (1, 2, 3). Diabetes mellitus is categorized into type 1 diabetes mellitus (T1DM) which - a result of total or near complete deficiency of insulin, and type 2 diabetes mellitus (T2DM), which is a diverse group of disease with changeable insulin resistance, impaired secretion of insulin and higher production of glucose (1).The lack of insulin action/resistance results in subnormal response for given concentration of insulin with greater levels of insulin corresponding to greater degrees of insulin resistance. Resistance is due to many factors to insulin mainly a sedentary lifestyle, obesity, and aging. T2DM also has a strong genetic element and more frequently found in certain families and ethnic minority groups, such as Hispanícs, Afrícan Amerícans, Pacífic Islanders, and Amerícan Indians (3).

Diabetes continues to grow world aide with a higher prevalence, higher disease-related morbidity and mortality, it is unfolding as biggest public health emergencies of the 21st century (3, 4). As per estimates approximately 0.415 billion adults have DM and this number is set to rise to 0.642 billion by the year 2040 (4). Approximately 2 crore Americans have diabetes, and with an increase in the incidence of disease by 5% per year (5). The prevalence of diabetes in Romania is 11.6% with 1.5-1.9 million diabetic patients (4). A study done in Kingdom of Saudi Arabia has shown a significant rise in prevalence of diabetes in 2011 to 30% as compared to 23.7% in 2004(6).India has a higher prevalence of DM(4.3%) in comparison to the Western Countries (1%–2%), in all likelihood Asian Indíans are more prone for resistance to insulin and mortality due to cardiovascular diseases (7).

Consistently raised blood sugar level causes high production of reactive oxygen species along with protein glycation leading to damage to the vascular system and stimulation of tissue specific

growth/ repair system(4). Patients suffering from T2DM can remain without symptoms and present with complications when first diagnosed to be suffering from the disease (3), approximately 8% of patient have cardiovascular disease at time of presentation, 37% have microanuerysm/retinopathy in one eye, microalbuminuris is found in 18% and polyneuropathy based on the signs is 2.3 and diagnosed on the basis of electrophysiology is 15.2% (8). According to estimates 193 million people are suffering from diabetes, without diagnosis for the disease and have higher chances to develop complications (4).

The chronic complications of DM can be further subdivided to microvascular and macrovascular complications, and non vascular complications (1, 8). Macrovascular complications are associated with disease affecting the coronary arteries, peripheral arteries and cerebrovascular system which tend to considerably decrease the life expectancy in all ages (1, 8). The frequentness of complications affecting the microvascular system is associated with duration of disease(Diabetes mellitus), amount of metabolic control(HbA1c), blood pressure(mainly systolic), higher BMI(obesity), deviated serum lipid levels and resistance to insulin. All these factor tend to have a high impact on the development and progress of microvascular diabetic complications(8). Microvascular complications lead to retinopathy, nephropathy and neuropathy which increase the cost for health care resources (1, 8).

The most common cause for hospital admission related to diabetes and amputation(non-traumatic) in the U.S. is diabetic nephropathy occurring as the most common complication in 60% of all diabetic patients (4, 5). The occurrence of diabetic neuropathy in India is unknown, as per data available from South India, the patients with diabetes (type 2) having peripheral neuropathy was 19.1%(7). Diabetic peripheral polyneuropathy affects nearly eight percent of newly diagnosed and more than half of patients with long term DM and is “the presence of

symptoms and/or signs of peripheral nerve dysfunction in DM patients after exclusion of other possible causes where the symptoms of polyneuropathy may vary from painful sensory changes to motor weakness" (1, 2). Distal polyneuropathy may be the presenting complaint of patients with type 2 diabetes mellitus at the time of diagnosis and the presentation may also be seen in other patients within few years of known deranged glycaemic control (1). Patients affected with diabetic neuropathy are significantly less stable during quiet and perturbed standing (9).

Some of the common symptoms of diabetic neuropathy are paresthesia(usually symmetrical) and pain described as burning sensation that predominantly occurs in the extreme end of the lower limbs as per dependency on length with foot ulcerations as well as amputation(non-traumatic) as some of the severe complications (2).One of the most common types of neuropathy is the distal symmetric polyneuropathy(Chronic sensorimotor) causing substantial sensory loss, pain and weakness in muscles which is gradual in onset and may go undiagnosed for years (10)

The pathophysiology of abnormalities in DM is not known but may factors have been implicated as a cause for damage to the neurons which includes chronic elevated levels of plasma glucose, hypoglycemic episodes, and dysfunction of the blood - brain barrier, angiopathy, and many more (11). A significant association between serum cholesterol and fasting serum triglycerides with diabetic neuropathy has been established by the EURODIAB study (5, 12, 13) Steinmetz in a review from the U.K. Prospective Diabetes Study Group (UKPDS) and Fenofibrte Intervention and Event Lowering in Diabetes Study reported lower incidence of macrovascular and microvascular complications with lipid-lowering therapy (5, 14). Aparameterto measure average glycemic control over the last 2-3 months is glycosylated hemoglobin indicating a poor diabetic control and a level of less than 6.5% (<6.5%) is important to lower the occurrence of diabetic

complications (2).Evidences suggest association of gylcosylated hemoglobin and hyperglycemia with diabetic nephropathy (2, 5).

As diabetic peripheral neuropathy is not amenable to treatment, its prevention and early identification assume significant importance (2) The severity of diabetic neuropathy is dependent on the duration of disease(diabetes) and glycaemic control, the peripheral nerves are affected diabetes mellitus mainly the psychomotor response, cognitive effect, the somatosensory, and auditory system, effect in uncontrolled patient thereby affecting reaction times (2, 5, 10). Nerve conduction velocities(NCV)is a sensitive indexto assess for the severity of neuropathy as well as to localize the site of lesion (1, 6). In many patients with normal clinical examination, a decrease in nerve conduction velocity is observed (11). Nerve conduction velocity(NCV), has been one of the gold standards for diagnosis of peripheral polyneuropathy(diabetes) with nerve dysfunctions, with composite score for quantitative analysis of the results of NCV (2, 15).

A thorough literature search has shown that many patients diagnosed with diabetes mellitus might present with neuropathy at the time of diagnosis (1, 2, 5) as two third of patients with diabetes mellitus have clinical or subclinical neuropathy (7), hence, it was considered apt to study Evaluation of Diabetic Neuropathy Changes in Newly Diagnosed Patients of Type II Diabetes Mellitus (T2DM).

NEED FOR STUDY

Need for study:

- Prevalence of diabetes mellitus continues to grow worldwide
- Patients suffering from T2DM are without symptoms and present with complicationsat the time of diagnosis. Patients with type 2 diabetes mellitus may present with distal polyneuropathy at the time of diagnosis and also after only a few years of known poor glycaemic control.
- One of the most common complications is diabetic nephropathy affecting 60%of all diabetic patients in U.S. Diabetic peripheral polyneuropathy affects approximately 8% of newly diagnosed patients and >50% of patients with long term DM. A study done in South India showed that 19.1% type II diabetic patients had peripheral neuropathy.
- Two third of patients with diabetes mellitus have clinical or subclinical neuropathy
- As diabetic peripheral neuropathy is not treatable, its prevention and early identification assume significant importance

AIMS AND OBJECTIVES

Aim of the study :

- “Evaluation of Diabetic Neuropathy Changes in Newly Diagnosed Patients of Type II Diabetes Mellitus (T2DM)”

Objective of the study :

- Study the correlation of diabeticneuropathy changes in newlydiagnosed patients with T2DM with demographic profile (age, sex, body mass index)
- Study the correlation of diabeticneuropathy changes in newlydiagnosed patients with T2DM with systemic hypertension and other risk factors
- Study the correlation of diabeticneuropathy changes in newlydiagnosed patients with T2DM with glycosylated haemoglobin levels, and plasma glucose levels.

“REVIEW OF LITERATURE”

Diabetes mellitus (DM) refers to a group of common metabolic disorders that is characterized by hyperglycemia with disturbance of carbohydrate, fat and protein metabolism due to absolute or relative deficiency of insulin (16, 17, 18). A complex interaction of genetics and environmental factors can cause several distinct types of DM; along with decreased insulin secretion, elevated glucose production and reduced utilization of glucose leading to hyperglycemia (16). DM is broadly categorized into type1 and type2, where T1DM is due to total or bear complete deficiency of insulin. T2DM is a diverse group of disorders with shifting degrees of resistance to insulin, defective insulin secretion, and elevated glucose production (1). The metabolic derangement with DM leads to a huge burden on patients with diabetes mellitus as well as health care system due to involvement of multiple organ system with secondary pathophysiologic changes. A prolonged derangement characteristically affects the eye, kidney and nervous system (16, 17).

Epidemiology:

Diabetes mellitus (DM) is a major public health problem occurring worldwide (19) a large public health emergency worldwide of the twenty-first century (20). As per estimates of World Health Organization(WHO), the adult population suffering from diabetes mellitus would rise from 0.135 billion to 0.3 billion (from year 1995 to 2025) worldwide (19). Another estimates show that the prevalence of diabetes is rising with 0.366billion people with diabetes in 2011, which is anticipated to reach 0.552 billion by 2030, thereby having a major burden upon health-care facilities in all countries (17). Recent trends have shown that approximately 415 million adults have diabetes which will rise to 642 million by the year 2040 (20).

In United States, the occurrence of diabetes is rising by 5% per year with an estimated 29.1 million (9.3%) have diabetes mellitus (21, 22, 23). Only approximately 12.5 lakh Americans

have T1DM and majority of other patients have T2DM (24). The prevalence of diabetes in Romania is 11.6 % with 1.5–1.9 million patients (25). Another study done in the Kingdom of Saudia Arabia showed a prevalence of 23.7% in 2004 (26) which significantly increased to 30% in 2011with 34.1% males and 27.6% females were suffering from DM (27). India has witnessed a rapidly exploding epidemic of diabetes mellitus in the recent decades; (18) as a greater prevalence of DM is seen in Indian population as compared to the population of the Western countries (28, 29). The population of India are probably more likely to develop resistance to insulin and mortality associated with cardiovascular diseases (30) as India has the second largest number of people with diabetes in the world today (18). The report of the International Diabetes Federation(IDF) in 2017, showed that 7.29 crore people had diabetes in India and this is estimated to reach to 13.43 crore by the year 2045 (18). The prevalence of diabetes mellitus in much higher in the urban areas as compared to rural areas (Overall prevalence of 2.1% vs. 1.5) (28). The frequentness of diabetes in India in urban population, has risen from 2% in the 1970s to 20% at present especially in large metropolitan cities (18). Community Study done by the Indian Council of Medical Research(ICMR) reported a leer number of patients affected with diabetes in Northern Indian States (Chandigarh 1.2 lakh, Jharkhand 9.6 lakh) in comparison to the Central (Maharashtra92 lakhs) and Southern (TamilNaidu 48 lakhs) part of the country (28). Similar trends were noted across the metropolitan cities of India done by the NationalUrban Survey with 11.7% - Kolkata, 6.1% - Kashmir Valley, (31) 11.6% - New Delhi, compared to 13.5% in Chennai, 16.6% in Hyderabad, and 12.4% in Bangalore were affected with diabetes (32). The prevalence of diabetes in the rural areas is also fast catching up (18), lifestyle and environmental changes are mainly responsible for this epidemic (28). The rural population is more likely to suffer from diabetes complication mainly due to a disparity in the allocation

between urban and rural areas of the various health resources, disparity in disease management and in addition poverty in rural areas is multi-faceted (28, 33).

A consistently elevated blood glucose level leads to biochemical abnormalities affecting the eyes, kidney, nerves, heart and blood vessels (34, 35).The altered blood glucose level causes increased production of reactive oxygen species and protein glycation leading to the damage of the vascular system and stimulation of the growth/repair systems(tissue specific) (35). Around 0.193 billion people at present are not aware about the diagnosis of the disease and have high risk of developing complications related to diabetes (20). When the patients is confirmed to be suffering from diabetes mellitus 8% have disease afflicting the cardiovascular system, 37% patients have involvement of one eye(diabetic retinopathy) whereas 18% have involvement of both eyes(retinopathy), microalbuminuria is seen in around 18% patients(36), 2.3-15.2% have polyneuropathy (37). Patients with type 2 DM (T2DM) may already have neuropathy at the time of diagnosis or could come with symptoms of neuropathy within few years of abnormal glycemic control (4). Another study revealed that diabetic neuropathy affects approximately 8% of newly diagnosed patients and more than 50% patients with long-term diabetes (38).

One of the common complication of diabetes mellitus is peripheral neuropathy, seen in around 60% of all patients suffering from diabetes (35, 39). Diabetic peripheral neuropathy leads to considerable morbidity, discomfort and is associated with raised mortality is seen in up to 50% of affected patients with T1DM and T2DM (40, 41). The common cause of diabetes related hospital admission and non-traumatic amputation in the United States is diabetic neuropathy (21, 22). The exact occurrence of Diabetic neuropathy in India is unknown, study done in Southern Indian patients found that 19.1% of patients with T2DM had peripheral neuropathy (42).

Classification & Pathogenesis:

Diabetes can be classified into four types as per ADA and the WHO. Out of this T2DMis seen in 90-95% of all people suffering from the disease and is characterized by insulin resistance and/ or abnormal insulin secretion. Type 1 diabetes the other most important form is due to primarily autoimmune-mediated destruction of pancreatic beta cells leading to absolute insulin deficiency (18, 43).

"The new classification of diabetes based on etiology is shown below (ADA)" (16,43)

TABLE 417-1 ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

1. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)
   - A. Immune-mediated
   - B. Idiopathic
2. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
3. Other specific types of diabetes
   - A. Genetic defects of beta cell development or function characterized by mutations in:
     1. Hepatocyte nuclear transcription factor (HNF)-4α (MODY 1)
     2. Glucokinase (MODY 2)
     3. HNF-1α (MODY 3)
     4. Insulin promoter factor-1 (IPF-1; MODY 4)
     5. HNF-1β (MODY 5)
     6. NeuroD1 (MODY 6)
     7. Mitochondrial DNA
     8. Subunits of ATP-sensitive potassium channel
     9. Proinsulin or insulin
     10. Other pancreatic islet regulatory proteins such as *KLF11*, *PAX4*, *BLK*, *GAD14*, *GAD46*, *SLC2A2* (GLUT2), *IPX6*, *GLIS3*
   - B. Genetic defects in insulin action
     1. Type A insulin resistance
     2. Leprechaunism
     3. Rabson-Mendenhall syndrome
     4. Lipodystrophy syndromes
   - C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase
   - D. Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
   - E. Drug- or chemical-induced—glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, β-adrenergic agonists, thiazides, calcineurin and mTOR inhibitors, hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine
   - F. Infections—congenital rubella, cytomegalovirus, coxsackievirus
   - G. Uncommon forms of immune-mediated diabetes—"stiff-person" syndrome, anti-insulin receptor antibodies
   - H. Other genetic syndromes sometimes associated with diabetes—Wolfram's syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome
4. Gestational diabetes mellitus (GDM)

Abbreviation: MODY, maturity-onset diabetes of the young.

Pathogenesis

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus is caused by destruction of B cells of islet of pancreas mainly by autoimmune process(in approximately more than ninety-five percent of patients) known as

type1A and rarely due to idiopathic causes (in less than five percent patients) known as type 1B. T1DMcan occur at any age, though it is mostly seen in adolescents, young adults and children with a peak occurrence in less than 5years of age(just before school age) and again at around puberty, with a variable rate of destruction of B cells of islet of pancreas which is acutein some individuals and gradual in others. The disease is a disorder of catabolism with elevated levels of glucagon, insulin is virtually absent and usually associated with ketosis in untreated patients (16, 24).

Type 1A Diabetes mellitus (Immune-mediated): The susceptibility of the disease is due to environment and genetic factor withapproximately one-third is due to genetic factor and two-third is because of environmental factors. HLA-DR3 or HLA-DR4 is found in about 95% of patients with type 1 diabetes with *HLA-Dq*genes is a more specific markers for susceptibility of T1DM and *HLA-DqB1*0302* is seen in the DR4 patients with type 1 diabetes mellitus. Another gene present in the 5′ polymorphic region of the insulin gene contributes about Ten(10%) of the genetic risk (17, 24). 20% of patients with homozygote mutation in autoimmune regulatory gene (*AIRE)* develop type 1 diabetes mellitus along with other autoimmune disorders (like autoimmune polyglandular syndrome 1). Circulating antibodies to islet cells (ICA), glutamic acid decarboxylase 65 (GAD65), insulin (IAA), tyrosine phosphatase IA2 (ICA-512), and zinc transporter 8 (ZnT8) are seen in patients with T1DMduring diagnosis (24).

Sibling of a women suffering from T1DM have three percent risk of developing the disease and this doubles to 6% in case father of the sibling is suffering T1DM. The risk of developing T1DMis related to diabetic proband of HLA haplotypes which is shared by the siblings with the risk being 6% if single haplotype is shared. Where there is sharing of two haplotypes the risk is

increased to more than double at 12-25%. The concordance rate of type 1 diabetes mellitus is 25-50% which is the highest risk to develop the disease is seen in identical twins (16, 24).

Environmental factors also has a key role in the development of T1DM, evidences suggest that the people in Scandinavian countries are more likely to suffer and less frequently seen in countries near the equator. The frequency tends to decrease in countries nearer and nearer to the equator. Migrations of individuals from countries with low risk to Scandinavian countries increases the risks for type 1 diabetes mellitus, with the exact factor responsible not known. Other factors that play a role are improvement in public health and decrease in infections causes dysregulation of the immune system and leads to autoimmune disease, breastfeeding the infant for the first 6 months of life appears to be protective (17, 18).

Patients receiving treatment for advanced malignancies with check point inhibitor immunotherapies: like nivolumab, pembrolizumab, and ipilimumab, should be monitored for development of diabetes as they tend to precipitate autoimmune disorders (16).

Type 1B diabetes mellitus (Idiopathic): Approximately 5% of patients who do not have any evidence of pancreatic B cell autoimmunity come inthis group and are mostly from Asian or African origin. Patients homozygous for mutation in *PAX-4* (*Arg133Trp*) which is important for development of pancreatic islets have ketosis-prone diabetes and account for about 4% of the West African patients (16, 24).

B. Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is a heterogeneous group of conditions commonly seen in adults, though now it is frequently seen in children and adolescents. Ketoacidosis is rarely seen as circulating endogenous insulin is present in sufficient quantities to prevent it, though patients have hyperglycemia due to increased need and tissue insensitivity (insulin resistance) (17).

The loss of beta cells of islet of Langerhan's and insulin resistance is because of combination of environmental and genetic factors. Concordance rate of developing type 2 diabetes mellitus in monozygotíc twíns over 40 years of age is more than seventy percent within a year. More than30 genetic locia have been connected with increased risk of type 2 diabetes, mostly with code for proteins that are assumed to play a role in beta cell development or function with largest risk effect of *TCF7L2*. *TCF7L2* codes for WNT signaling pathway. Initially in the disease there is hyperplasia of pancreatic beta cells with fasting hyperinsulinism and exaggerated response to insulin and proinsulin. As the disease progresses there is deposition of amyloid in islets of langerhans along with inherited genetic defect leading to impaired beta cell function (18, 24).

Environmental factors:

Obesity: There is a variable frequentness of T2DM with obesity among different racial groups. T2DM is found with obesity in 60-70% of North Amerícans, Europeans, or Afrícans and it reaches 100% among Píma Indians or Pacífic Islanders (of Nauru/Samoa), on the other hand it accounts for 30% in Chinese and Japanese patients. Insulin sensitivity tends to correlate with visceral obesity which is because of accumulation of fat in the mesenteric and omental regions (24). The Japanese wrestlers have a daily intake of 5000-7000 kcal are euglycemic and have normal serum lipids due to daily vigorous exercise leading to development of massive subcutaneous obesity (16).

C. Other Types of Diabetes Mellitus

1. Maturity-onset diabetes of the young (MODY) : This type of diabetes manifests at an age of 25 years or less and is a rare monogenic disorder. It is non-insulin-dependent diabetes and has an autosomal dominant inheritance. Patients with MODY have impaired glucose-induced secretion of insulin leading to hyperglycemia and are non obese. MODY has been categorized

into six types and all of them involve mutation of a nuclear transcription factor regulating islet gene expression except MODY type 2 where the glucokinase gene is defective (17, 24).

2. Mitochondrial DNA mutation associated Diabetes mellitus: mitochondrial genes are transmitted from the mother to her offspring and accounts for <2% of patients with diabetes.Patient with this type of diabetes usually present in their late 30s and have accompanying loss of hearing. This type of maternally inherited diabetesand deafness(MIDD) is commonly due to mutation of the gene coding (A3243G) for the tRNA (Leu, UUR) (16, 24).

3. Wolfram syndrome : It is autosomal recessive neurodegenerative disorders consisting of diabetesinsipidus, diabetesmellitus, opticatrophy, and deafness (DIDMOAD) first evident in childhood. 60-75% of patients develop diabetes insipidus(cranial) and deafness(sensorineural) in the 2nddecade of life; many people develop cerebellar ataxia, neurogenic bladder, peripheral neuropathy, psychiatric illness and ureterohydronephrosis in later life. The gene encoding for transmembrane protein in endoplasmic reticulum, *WFS1* develops the mutation (16).

4. Autosomal recessive syndromes:

- Neonatal or childhood diabetes is seen in homozygous mutations in *NEUROG3, PTF1A*, *RFX6*, and *GLI-similar 3 (GLIS3).*
- Absent pancreas and cerebellar atrophy in seem in homozygous *PTF1A,* whereas severe malabsorption anddiabetes before puberty is with mutation in*NEUROG3* gene.
- Mitchell-Riley Syndrome is associated with absence of all islet cells (except pancreatic polypeptide), hypoplasia of pancreas and gall bladder; and intestinal atresia is due to homozygous mutations in *RFX6* gene.
- Neonatal diabetes and congenital hypothyroidism is associated with homozygous mutation in *GLIS3* gene that plays a role in transcription of insulin gene (24).

5. Secondary Causes of Diabetes mellitus: Glucose intolerance can occur due to tumors of the endocrine gland secretinggrowth hormones, glucocorticoid, catecholamine, glucagon, or somatostatin. Excessive glucocorticoid, catecholamine, or glucagon cause a raised hepatic-output of glucose as well as impaired peripheral responsiveness to insulin, whereas catecholamines cause a decreased insulin release with additional carbohydrate intolerance (18, 24).

Some patient have other autoimmune disease where there are raised titers anti-insulin receptor antibody which tend to block insulin binding resulting in very severe insulin-resistance, glucose-intolerance, and acanthosis nigricans (24).

Use of medication can lead to carbohydrate intolerance and development of frank diabetes which might be due to either decreased insulin secretion or increased insulin resistance or both.

- Drugs that tend to impair insulin secretion are cyclosporine and tacrolimus, whereas sirolimus causes increased insulin resistance leading to new-onset diabetes in patients who have had porgan transplantation.
- Patients on corticosteroids therapy can develop diabetes mellitus due to increased insulin-resistance and effect on functions of beta cell.
- Moderate increase in risk of DM in seen in patient on therapy of either diuretics (thiazide diuretics) or beta-blockers (16-18, 24).

Glucose Homeostasis:

The plasma blood glucose is controlled in individual in the range of 80 to 140 mg/dL depending on either the fasting state or fed state (i.e. first hour or so after a meal) with the plasma glucose back to the control level within 2 hours of the last meal. But in the state of starvation the plasma glucose level is maintained with the help of multiple functions performed by the liver (16, 44).

The liver serves as a glucose buffer system with various functions performed during fed and fasting state. The post prandial rise in plasma glucose increases the secretion of insulin with more than two third glucose converted to glycogen in the liver. With preceding time and fall in plasma glucose the glycogen stored in the liver is released as glucose in the plasma by glycogenolysis. Other pathways that are activated in the liver during fasting state include gluconeogenesis to maintain the plasma glucose level. Liver tends to decrease the fluctuation in plasma glucose level by about one third (17, 44).

The plasma glucose level is also maintained by another feedback control system which involves the role of both insulin and glucagon. An increase in plasma glucose level causes a rise in insulin secretion leading to fall in plasma glucose level and reverse is under the control of glucagon. That is level of glucagon rises on fall of plasma glucose level which tends to increase plasma glucose level towards normalcy. By far the mechanism of insulin feedback is very important and mechanism of glucagon has role in starvations or raised utilization of glucose in stress (44).

The hypothalamus also seems to be stimulated in cases of severe hypoglycemia which leads to stimulation of sympathetic nervous system and increase in secretion of adrenaline from the adrenal medulla of the gland. The consequence of rise in epinephrine in the blood leads to increase release of glucose from the liver (24).

In case the starvation period extends over hours to days, the prolonged hypoglycemia leads to secretion of growth hormone and cortisol as both these hormones decrease the utilization rate of glucose by most of the cells of the body. These two hormones convert the cell metabolism towards greater amounts of fat utilization (44).

The importance of regulation of plasma glucose

It is important to maintain a constant plasma glucose as it's the only nutrient used by the retina,brainand germinal epithelium of gonad, to supply them with energy for optimal requirements. Compared to many other tissues in the body that shifts their utilization of fat and protein, when the plasma glucose level is decreased. During fasting state and starvation the secretion of insulin from the pancreas is minimal as the glucose formed by gluconeogenesis is used for the metabolism in the brain. Equally, important is the fact the blood glucose concentration should not be very high as high plasma glucose increases the osmotic pressure of the extracellular fluid which can lead to variable cellular dehydration, the renal threshold of plasma glucose could be reached leading to excessive loss of glucose in urine, excessive glucose in urine could lead to depletion of fluid and electrolytes by the phenomenon of osmotic dieresis, and persistently elevated plasma glucose level could lead to damage to many tissues. Hence, uncontrolled diabetes mellitus increases the chances for heart attack, retinopathy, end stage renal disease and stroke (16, 24, 44).

Diagnosis

There are three broad categories of glucose tolerance: impaired glucose homeostasis(IGT), diabetes mellitus(DM) and normal (N). This glucose tolerance is evaluated by measuring the fasting plasma glucose (FPG), the plasma glucose levels on the response to OGTT, or the glycosylated hemoglobinA1c(HbA1c). Normal tolerance of glucose is defined by measuring the level of plasma glucose(PG) and HbA1c, a fasting plasma glucose(FPG) level < 100 mg/dL, a glucosylated hemoglobin <5.7% and a plasma glucose level of <140 mg/dL after an oral glucose tolerance test is considered normal. The diagnostic criterion for diabetes mellitus has been laid by The International Expert Committee (ADA), IDF, and European Association for the Study of Diabetes. Diabetes mellitus is diagnosed on the basis of the fasting plasma glucose levels,

glycosylated hemoglobin and response of individuals to oral glucose tolerance test (OGTT). The level of glycemia at which complications specific to diabetes occur is labeled as diabetes mellitus. Diabetes mellitus is diagnosed if fasting plasma glucose is > 126mg/dL, glycosylated hemoglobin ≥ 6.5% or plasma glucose level > 200 mg/dL seen two hours after oral glucose tolerance test or patients reposting with complaints of classical symptoms of diabetes mellitus namely polyuria, polydipsia and weight loss with a random plasma glucose level ≥ 200 mg/dL(24, 43).

Impaired fasting glucose (IFG) is when the level of FPG is between 100-125 mg/dL.

Impaired glucose tolerance (IGT) is when following an oral glucose tolerance test when the plasma glucose level lies between 140 to 199 mg/dL.

Differing from the IGT and IFG if the glycosylated hemoglobin level is between 5.7 to 6.4% these group of individuals do differ from the above two categories but have greater chance of progression to T2DM.

The categories of individuals are labeled according to World Health Organization as *prediabetics*, *increased risk of diabetesmellitus*, or *intermediate hyperglycemia.*

The most reliable and convenient test to identify asymptomatic patients suffering from DM is based on the values of FPG and HbA1c. Though another valid means of diagnosing diabetes mellitus is oral glucose tolerance test, but this is not routinely done (16, 43).

Screening

Screening for asymptomatic individuals is recommended for T2DM with aid of fasting plasma glucose and glycosylated hemoglobin. The routine screening of individual is recommended as many individuals may be asymptomatic and unaware of the disease though they may fall in the criteria of diabetes mellitus, individuals may be asymptomatic for more than a decade before

they are confirmed to be suffering from diabetes mellitus, or individuals may present with complications when are diagnosed with diabetes mellitus. Screening of individual with no symptoms of DM for diagnosing T2DM also assume importance as treatment of the disease not only favorably alter the natural history, the diagnosis of prediabetes also spurs the effort for diabetes prevention. As per the recommendations by the American Diabetes Association (ADA): individuals >45 years should be screened every 3 years and at an earlier age if the BMI is more than 25 kg/m^2 (overweight) or have one additional risk factor for diabetes mellitus (24, 45).

Clinical features:

Presenting problem in diabetes: In a patient reporting with hyperglycemia, it is important to establish whether the patients is having diabetes mellitus and also the type of diabetes the patient is coming with so as to formulate a treatment plan. A patient having diabetes is at a very high risk of micovascular complications which include diabetic retinopathy, diabetic nephropathy and diabetic neuropathy. Any patient who falls under the category of pre-diabetes has a greater risk of conversion to DM. Elevated plasma glucose in patients is found to have a high continuous risk for macrovascular disease. These patients are at greater risk of atheroma of large blood vessels and increased risk of cardiovascular disease. These groups of patients stand a high chance to develop myocardial infarction, stroke or peripheral vascular disease. Patients who fall under the category of pre-diabetes and have associated risk factors (like hypertension and dyslipidemia) should be aggressively managed. They are also advised for lifestyle modification so as to decrease it to the progression of diabetes mellitus (17, 24).

Another situation where hyperglycemia is commonly encountered is stress which tends to impose burden on the pancreatic beta cells like pregnancy, infection, or treatment with

corticosteroids. The hyperglycemia so encountered is temporary and tends to resolve once the acute phase of illness is over, regular monitoring of plasma glucose is required (18).

The clinical features of patients with diabetes mellitus vary from patient to patient and may include all /or few of the following: polyuria, polydipsia , pruritus vulvae/ balanitis, polyphagia, irritability, headache, decreased concentration, blurred vision and nocturia. The patients may also complaint of symptoms of weight loss, weakness, frequent superficial infections especially fungal infections and there could also be complaint of slow healing of skin lesions following trauma which could even be a minor trauma. A complete medical history of patients must be taken and various aspects like weight, life style (which include exercise, smoking and ethanol use) should be thoroughly sought for risk factors of cardiovascular disease. Patient may complaint of excessive urination which is due to hyperglycemia as a result of osmotic diuresis (17, 24).

Patients having T1DM is seen in <40 years of age with patient complaining of symptoms from the past few weeks. These patients may have normal/ low body weight, occasionally may present with ketonuria, have autoantibodies present in 80-90% of individuals and often associated with other autoimmune diseases also. The treatment in this group of patients is insulin and it can prove fatal if treatment is delayed (24, 45).

Type 2 diabetes is often seen in individual who are invariably more than 50 years of age and patient may be asymptomatic for months to years before the disease is diagnosed. Invariably this group of individuals is obese and has a positive family history. Chronic fatigue or malaise may sometime be the only presentation of patients suffering from type 2 diabetes mellitus. Elevated hyperglycemia in patients with uncontrolled diabetes mellitus increases the susceptibility of infection and these patients can come with complaints of skin infections (17).

The physical examination of individuals with diabetes mellitus should be done completely and thoroughly with special attention to aspects like weight, body mass index (BMI), retinal examination, blood pressure (sitting and standing), detailed foot examination, all the peripheral pulses and the site of insulin injection. The oral cavity should be carefully examined to rule out periodontal disease. It is recommended that foot should be annually examined in patients with diabetes mellitus for blood flow, sensation and ability to sense touch with a monofilament, pin prick sensation, ankle reflexes and nail care. Any deformity in the foot should be carefully observed (hammer or claw toe, Charcot joint), and the potential sites of ulceration in foot should be carefully observed. As per the recommendations of American Diabetes Association (ADA) screening for distal symmetric neuropathy should be done annually beginning from the initial diagnosis of diabetes, the patients should also be screening for autonomic neuropathy annually in cases of type 2 DM and after 5 years of diagnosis of T1DM (18, 45).

In individuals with already established diagnosis of diabetes mellitus the initial monitoring should focus on the therapy of the patients along with appropriate diabetes care, the earlier levels of glycosylated hemoglobin, monitoring of plasma glucose levels, and frequeny of hypoglycemia. It is also important to evaluate the patient's knowledge about DM, and any complication associated with diabetes mellitus. Patients should be specifically assessed for diabetes mellitus related complications, it may affects several organ systems and patients should also be assessed for co morbidities associated with DM like disease of the cardiovascular system, hypertension and dyslipidemia (24, 45).

Type 1 diabetes is characterized by accumulation of circulating fatty acids and glucose leading to a formation of complex of hyperosmolality and hyperketonemia which leads to increased urination and thirst. The polyuria and polydipsia are due to osmotic diuresis following persistent

elevated plasma glucose causing glucose loss and loss of free water and electrolytes. The hyperosmolar fluids due to hperosmolality seen in diabetes mellitus results in blurred vision due to exposure of the lenses. The patients with T1DM have an raised or normal appetite but develop weight loss subacutely which is initially due to loss of water, glycogen and triglyceride. Later there is reduced muscle mass due to gluconeogenesis as ketones and glucose are formed from amino acids. Postural hypotension is produeces due to lowered plasma volume. In case of sub acute onset of diabetes patients may present with paresthesia which is due to involvement of peripheral sensory nerves though temporarily. This nerve dysfunction tends to clear with insulin replacement. In individuals with absolute insulin deficiency the onset of symptoms is acute and abrupt, accumulation of ketone bodies leads to ketoacidosis causing anorexia, nausea and vomiting which tends to interfere with oral fluid replacement. There is exacerbation of dehydration and hyperosmolality and this determines the level of consciousness of the patient. Relative deficiency of insulin when slow allows sufficient time for patients to maintain water intake and thus patient remains relatively alert and there are minimal physical findings. In the other scenario where there is absolute deficiency of insulin there is worsening of ketoacidosis, as the compensatory mechanism is inadequate due to vomiting leading to dehydration and have stupor or coma, patients have fruity breath odour of acetone suggestive of diabetic-ketoacidosis (DKA), recumbent position hypotension is associated with grave prognosis. In individuals were the insulin deficiency develops slowly there are changes suggestive of loss of subcutaneous fat and muscle wasting (17, 18, 45).

Type 2 diabetes individuals may be asymptomatic with an insidious onset hyperglycemia in the initial few years or they may present with symptoms of polyuria and polydipsia. Most of the patients with diabetes are diagnosed during routine laboratory studies esp in cases of obese

individuals coming with glycosuria or hyperglycemia on routine investigations. Many patients with T2DM may present with neuropathy or complications of cardiovascular apparatus. Few individuals may present with chronic skin infection, female mayay present with complaints of generalized pruritis and symptoms of vaginitis.Any female individual coming with complaints of chronic candidal vulvovaginitis or has delivered large babies (larger than 4.1 kilograms)/ has complaints of poly hydramnios, preecplampsia or unexplained fetal loss should be suspected to have diabetes mellitus. There might be significant obesity with features if localization of lipid deposition on the upper portion of the body(mainly abdomen, chest, neck, and face) and relatively less fat on the appendages and hence quite muscular. This centripetal fat distribution results in the characterization of high waist circumference; waist circumference larger than 40″(102 cm) in men and 35″(88 cm) in women has an increased risk of diabetes mellitus. Few patients might have an associated increased insulin-resistance leading to acanthosis nigricans, where the skin in the axilla, groin, and back of neck is involved which becomes hyper pigmented and hyper keratotic. Diabetes patients with obesity often have mild hypertension. The flexor surface of the both limbs and the buttocks might have the manifestation of eruptive xanthomas as well as lipemia retinalis because of hyperchylomicronemia can be seen in patients with uncontrolled T2DM, there also might be manifestation of hypertriglyceridemia which is of the familial type. Hyperglycemic hyperosmolar coma(HHS) can also be present; where the patient are significantly dehydrated, have hypotension are lethargic or comatose but do not have Kussmaul respirations (16, 17, 24, 45).

Monitoring in Diabetes Mellitus:

1. Urine Glucose: to screen diabetes mellitus, urine dipsticks are a convenient method to detect glucosuria as these are strips which have a chromogen system and are containing glucose

oxidase. The sensitivity of these paper strips are for as low as 100 mg/dL glucose present in urine, the testing with these strips should be done on urine passed 1-2 hours after a meal. The application of paper strips when directly applied to the passing urine can give a differing colouring response that is indicative of different glucose concentrations. For effective interpretation of the result the patient should have a normal renal threshold and reliable bladder emptying, glycosuria could be due to lowered renal threshold for glucose. Glycosuria warrants further assessment of the patient, which may be the consequence of excessive glucose load being presented to the tubules as seen in case of pregnancies. Approximately 50% of pregnancies have demonstrable glucose during the third and fourth month of pregnancy, sometimes lactose is present in the late weeks of pregnancy. Other non diabetic causes for glycosuria can be from mutation in the *SGLT2*gene coding for sodium-glucose transporter2 or dysfunction of the proximal tubules as seen in the case of chronic kidney disease (17, 24).

2. Ketones in urine and blood: Ketonesdetected in urine with glycosuria is suggestive of diabetes mellitus though it is not confirmative as ketone bodies can be found in people who are fasting, exercising, have repeated vomiting of are on low carbohydrate and high fat diet. The detection of ketone bodies in urine is done by nitroprusside tests which cannot pickup beta-hydroxybutyric acid as it does not have ketone group. Monitoring whole blood ketone can measure beta-hydroxybutyric acid which are useful for guiding insulin adjustment during the time of intercurrent illness, a level greater than 0.6mmol/L require further investiagtion. The levels more than 3 mmol/L is suggestive of a very large quantity of ketones in urine and therefore requiring hospitalization (16, 24).

3. Proteins in Urine: An albumin level of less than 300mg/L are not detected by the standard dipsticks and require specific laboratory urinalysis, a level greater than 300 mg/L is detected by

dipsticks. Proteinuria (micoralbuminuria) without urinary tract infection is highly suggestive of increased risk of macorvascular disease and/ or indicator of diabetic nephropathy (16, 17).

4. Blood Glucose: A cheap and reliable method of assessing patient with diabetes mellitus is measure of the blood glucose level where capillary blood glucose level can be measured with the help of portable electronic meter. The whole blood glucose concentration is ten to fifteen percent more in plasma or serum due to absence of structural component of blood cells. A plasma glucose concentration of more than or equal to 126mg/dL on one or more than one occasions following fasting for 8 hours is diagnostic for diabetes mellitus. Those subset of patients who have impaired fasting glucose tolerance i.e. FPG level between 100-125mg/dL, are associated with greater risk of diabetes mellitus (17, 43, 45).

5. Oral glucose tolerance test (OGTT): An oral glucose tolerance test is done in cases of impaired tolerance of fasting glucose and where the FPG level is <126mg/dL. Three days prior to the test patients should have 150-200 g of carbohydrates per day so that the insulin secretion is optimized and effective. On the day when OGTT is to be performed patient should not take anything orally after midnight, during the test an adult is given 75gram of glucose with 300mL of water, in case of a child the dose is 1.75gram/kg body weight of glucose of the ideal body weight. OGTT is performed in the morning and a patient is required to rest during the test and should neither smoke (24, 45).

Blood samples are taken at 0 and 2 hours after ingestion of glucose for plasma glucose estimation. A patient is said to be normoglycemic if the FPG is <100mg/dL and 2-hours serum value is <140mg/dL. A patient is said to be suffering from diabetes mellitus if the FPG level is more than 126mg/dL and level at 2-hours is >200 mg/dL. Patient is said to have impaired plasma glucose level if the 2 hour level of plasma glucose is between 140-199 mg/dL (17).

6. Glycosylated Hemoglobin (HbA1c): HbA1c is an immunoassay that gives the glycemic status of the past 2-3months and gives an improved method of assessment of control of diabetes mellitus. The level of glycosylated hemoglobin are monitored every 3-4 months for diabetes mellitus, it serves as a valuable cross check/it also accurately monitor the patients who routinely monitor their plasma glucose levels. The levels of glycosylated hemoglobin are also helpful for monitoring the drug-therapy of diabetics as well as also are a useful guide for patient who cannot monitor their blood glucose levels. The relation between the average blood glucose level and glycosylated hemoglobin as reported by the A1c Derived Average Glucose Study was (28.7 × HbA1c) – 46.7. It is advisable to exercise caution when the average glucose level is estimated form the levels of HbA1c, the variability is substantial in individuals i.e. when values of glycosylated hemoglobin is between 6.9-7.1% the average glucose level ranges between 125-205 mg/dL. Similarly when the glycosylated hemoglobin levels were 6% the average glucose level varied between 100-152 mg/dL and for the level of 8% the average glucose level varied between 147-217 mg/dL (24).

The hemoglobin variant or trait of an individual can also affect the accuracy of HbA1c and further information can be obtained from the National Glycohemoglobin Standardization Program website (24, 46, 47).

A falsely low value of HbA1c is seen in patients with high level of hemoglobin F and any condition that tends to decrease the survival of erythrocytes or the mean erythrocyte age (as seen in recovery from acute blood loss , hemolytic value). Low levels of HbA1c are also seen in patients of chronic kidney disease who are on treatment of anemia with intravenous iron therapy and erythropoietin therapy. Intake of Vitamin C and E inhibit glycation of hemoglobin and can also result in false low values (17).

On the contrary any condition which would increase the erythrocyte survival as is seen in patient with hereditary spherocytosis who undergo splenectomy would have falsely high levels of glycosylated hemoglobin. Raised HbA1c is also seen in patient with iron deficiency anemia. The ADA has endorsed glycosylated hemogloin as a diagnostic test for diabetes mellitus with cut off value of 6.5%. Level of HbA1c greater than 6.5% substantially increases the risk of retinopathy. Estimation of HbA1c for diabetes mellitus has many advantages: it gives a good estimate of control of plasma glucose over the past 8-12 weeks, there is minimal intraindividual variability, and there is no need to be in fasting state. Glycosylated hemoglobin levels between 5.7-6.4% are seen as a marker for high risk for diabetes mellitus (17, 24, 47).

7. Serum fructosamine: Serum proteins (mainly albumin) undergo non enzymatic glycosylation leading to formation of serum fructosamine which helps to determine the glycemic control of the past 1-2 weeks as serum-albumin has a short life. Decreased plasma fructosamine levels are seen in patients with reduced plasma albumin levels (e.g., nephrotic syndrome, protein-losing enteropathy, or liver disease). Plasma fructosamine are helpful where glycemic control is required over a narrower time frame like determining levels at time of conception in diabetic women. The levels of serum fructosamine are between 200-285mcmol/L where as the serum albumin level is 5g/dL. The serum fructosamine levels of 300, 367, and 430mcmol/L correspond with the glycosylated hemoglobin values of 7%,8%, and9%, respectively (24, 45, 47).

8. Self-monitoring of blood glucose: Measure of capillary blood glucose levels in outpatients setting / patients themselves are quite useful in DM, especially in patients with T1DM where tight metabolic controls are required. Many glucose meters to assess the plasma glucose are available, which are quite accurate, and variable in speed of testing, convenience of the patients, size of sample required, reporting capability, and cost of device. These blood glucose meters are

relatively inexpensive; contain a lancet device and disposable lancets with a storage memory of 100-1000 glucose values. The blood glucose values measured with glucose meters can vary with the hematocrit, as these strips are calibrated to measure blood glucose level between 60-160 mg/dL a level higher or lower than these values can have a difference between meter and laboratory value of 20% (24, 47).

9. Lipoprotein abnormalities: Patient's with diabetes mellitus have variable circulating lipoproteins along with the plasma glucose levels. A slight rise of low density lipoprotein(LDL) Cholesterol and triglyceride levels are seen with impaired control of hyperglycemia in patients with T1DM. The levels come back to its normal values if the glycemic control is taken care of. Patients with type 2 diabetes mellitus have characteristic feature of insulin resistance syndrome with a distinct "diabetic dyslipidemia". This dyslipidemia is characterized by features of elevated serum triglycerides level (300–400mg/dL), and low high density lipoprotein(HDL) cholesterol (less than 30mg/dL). Diabetic dyslipidemia is also associated with a qualitative change in LDL particles where they tend to produce smaller dense particles with their membranes carrying supranormal amounts of free cholesterols. The smaller dense low density lipoprotein(LDL) particles undergo oxidation and are having higher chances of atherogenesis. Treatments of patients with diabetic dyslipidemia are correction of obesity and hyperglycemia with the help of exercise, diet and hypoglycemic drugs. These measures when followed like achieving a normal weight tends to clear all the features of lipoprotein abnormalities. There is all possibility of co existence of primary disorder with diabetes mellitus even after adequate control of blood glucose level and weight. This subset of patients are candidates for pharmacotherapy of lipid disorder also (24, 47).

Complications associated with diabetes mellitus:

As per reports published when compared to people suffering from diabetes mellitus in European countries, in India there is occurrence of diabetes mellitus around a decade earlier. Along with this late diagnosis of diabetes mellitus affects the most productive years of youth in our part of the world. Many of the people suffering from diabetes mellitus when diagnosed often present with micro- and macrovascular complications (48, 49).

The health related cost of diabetes mellitus is particularly greater in India as phenotype associated with diabetes appears different. Patients diagnosed with DM in India have the onset of the disease at a lower BMI (Body Mass Index), younger age group, a greater visceral adiposity and decreased insulin secretion as compared to patients in developed countries (45).

As per landmark study of UKPDS for type 2 diabetes mellitus patients and DCCT for type 1 diabetes mellitus patients have demonstrated that a tight glycemic control results in decreased vascular complications in these patients. In India as there has been a steep increase in patients diagnosed with diabetes, there is also a rise in complications associated with the disease so the primary and secondary prevention assumes importance. The complications in patients suffering from diabetes mellitus can be categorized to acute and chronic complications (49).

Acute Complications:

Patients diagnosed with diabetes mellitus and having a plasma glucose level more than 300 mg/dL should also be evaluated for mental stability and hydration status. The evaluation helps in deciding the further course of therapy to lower plasma glucose levels. The patients with severe hyperglycemia might present with diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state (HHS). The demarcation between DKA and HHS is only presence or absence of ketosis as these two exist in a continuum of hyperglycemia. The earlier demarcation that diabetic-ketoacidosis is found in patients with T1DM has blurred as its also noted in obese individual

suffering from T2DM of the African-Amerícan or Hispanic descents, and this group is treated with drugs given by the oral route (Hypoglycemic/Euglycemic Drugs). The basic abnormality in both these conditions is an absolute/relative insulin deficiency, water and electrolytes imbalance as well as acid-base abnormality (49, 50).

Diabetic-Ketoacidosis(DKA): Mostly seen with patients diagnosed with T1DM and tends to develop over 24 hours. Diabetic patients complaining of nausea and vomiting should undergo further evaluation of various laboratory parameters to rule out DKA. These patients have elevated plasma glucose level leading to gylcosuria which further aggravates volume depletion and tachycardia, patients may also present with severe abdominal pain that might resemble either acute pancreatitis or ruptured viscus. Volume depletion associated with peripheral vasodilatation leads to hypotension. As a result of increased acetone and secondary to metabolic acidosis patient breath has a fruity odor and Kussmaul respiration. Patients with severe diabetic ketoacidosis may be comatose which precedes lethargy and depression of the central nervous system. Any deviation of altered mental status demands prompt evaluation for other causes like infection and hypoxemia, cerebral edema may be one of the presenting symptoms in children which are a serious complication of ketoacidosis. Diabetic ketoacidosis may also be seen in patients of a mental health disorder or unstable psychosocial environment associated with avoidance of insulin (24, 50).

The pathophysiology for diabetic ketoacidosis involves an imbalance between insulin and other counter regulatory hormones; there is a relative or absolute deficiency of insulin along with excess of glucagon, corticosteroids, catecholamines and growth hormones. The excess secretion of glucagon induces formation of ketone bodies along with gluconeogenesis and glycogenolysis, it also increases the delivery of free fatty acids(FFA) and amino acids(AA) to liver. There is

altered activity fructose -1,6-bisphosphatase, phosphofructokinase, pyruvate kinase and phosphoenolpyruvate carboxykinase which tend to shift the pyruvate handling away from glycolysis. Relative or absolute deficiency of insulin reduces the GLUT4(glucose transporter) glucose transporter levels and hence impaired glucose metabolism in fat and skeletal muscles. There is increased lipolysis in absence of insulin with release of free fatty acids, which under the excess glucagon level favours activation of enzyme carnitine palmitoyltransferase I increasing formation of ketone bodies. These ketone bodies are neutralized by bicarbonates, the stores of which get depleted leading to metabolic acidosis, there is also increased production of lactic acid. The reduced activity of insulin sensitive lipoprotein lipase decreases the clearance of VLDL in muscle and fats resulting in hypertriglyceridemia which can cause pancreatitis if it's very high. One of the factors that is responsible for precipitation of diabetic ketoacidosis is increased insulin requirement which is not supplemented/ inadequately supplemented as seen in concurrent illness. Laboratory parameters: The characteristic laboratory findings in DKA are elevated Plasma glucose levels(hyperglycemia), ketosis and decreased pH(metabolic acidosis) with riased anion gap. The serum bicarbonate levels are less than 10 mmol/L, arterial pH is in between the range of 6.8-7.3. The serum potassium levels may be mildly elevated and decreased total body levels of sodium, chloride, phosphorus and magnesium. There are elevated levels of blood urea nitrogen (BUN) and serum creatinine due to hypovolemia. There are findings of leukocytosis, hypertriglyceridemia and hyperlipoproteinemia, in case of suspected pancreatitis – serum lipase levels should be determined (49, 50).

" Annexure 1: **Management of Diabetic Ketoacidosis (49, 50)**:

1. Confirm diagnosis (↑ plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive care setting may be necessary for frequent monitoring or if pH <7.00 or unconscious.
3. Assess:

   Serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate)

   Acid-base status—pH, HCO_3^-, P_{CO_2}, β-hydroxybutyrate

   Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 h (10–20 mL/kg per hour); subsequently, 0.45% saline at 250–500 mL/h; change to 5% glucose and 0.45% saline at 150–250 mL/h when plasma glucose reaches 250 mg/dL (13.9 mmol/L).
5. Administer short-acting insulin: IV (0.1 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase two- to threefold if no response by 2–4 h. If the initial serum potassium is <3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is corrected.
6. Assess patient: What precipitated the episode (noncompliance, infection, trauma, pregnancy, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, CXR, ECG).
7. Measure capillary glucose every 1–2 h; measure electrolytes (especially K^+, bicarbonate, phosphate) and anion gap every 4 h for first 24 h.
8. Monitor blood pressure, pulse, respirations, mental status, fluid intake and output every 1–4 h.
9. Replace K^+: 10 meq/h when plasma K^+ <5.0–5.2 meq/L (or 20–30 meq/L of infusion fluid), ECG normal, urine flow and normal creatinine documented; administer 40–80 meq/h when plasma K^+ <3.5 meq/L or if bicarbonate is given. If initial serum potassium is >5.2 mmol/L (5.2 meq/L), do not supplement K^+ until the potassium is corrected.
10. See text about bicarbonate or phosphate supplementation.
11. Continue above until patient is stable, glucose goal is 8.3–13.9 mmol/L (150–250 mg/dL), and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.
12. Administer long-acting insulin as soon as patient is eating. Allow for a 2–4 hour overlap in insulin infusion and SC insulin injection.

Hyperglycemic-hyperosmolar state (HHS): HHS is commonly seen in elderly patients with long complaint of polyuria, loss of weight, and reduced intake by oral route that results in lethargy,mental confusion,or coma in patients suffering from type 2 diabetes mellitus. On examination of these patients they have hypotension, tachycardia and altered mental status due to dehydration and hyperosmality. The characteristic findings of ketoacidosis namely nausea, vomiting, abdominal pain and Kussmaul respiration is missing. HHS often develops in patients with serious or concurrent illness like myocardial infarction, stroke, sepsis, pneumonia or others with a compromised water intake. The underlying pathophysiology for HHS is decreased fluid intake along with insulin deficiency leading to increased hepatic glucose production and impaired utilization of glucose in the muscles. The patient has hyperglycemia which leads to osmotic diuresis causing volume depletion which is not supplanted by adequate fluid intake. In comparison to diabetic ketoacidosis there are lower levels of counter regulatory hormones in HHS. The laboratory finding are plasma glucose levels more than 1000 mg/dL, hyperosmolarity (more than 350mosm/L) and pre renal azotemia. A small anion-gap acidosis is due to high lactic acid (24, 49).

The management involves careful evaluation of patient's fluid status and laboratory parameters along with intra venous insulin infusion. The patient is started on fluid replacement 1-3L of 0.9% normal saline over the initial first 2-3 hours to stabilize the hemodynamic status. In patients where the Sodium is more than 150mEq/L, normal saline of half the concentration (0.45%) is used. During the next few hours following hemodynamic stability the free water deficit is reversed with hypotonic fluids i.e. initially 0.45%saline is used followed by 5%dextrose in water(D5W). The calculated free water deficit which on an average is 9-10L is to be reversed over the next few days with hypotonic solutions. The serum potassium level should be monitored

and potassium repletion be done accordingly, Potassium phosphate (KPO4) can be used to improve the hypophasphatemia. The blood glucose also needs to be lowered so initially an Insulin bolus dose is given of 0.1Units/kg which is followed by constant insulin infusion at a rate of 0.1Unit/Kg/ Hour. Continuous monitoring of plasma glucose is done and when the plasma glucose levels fall to less than 250mg/dL, the rate of infusion of insulin is reduced to a rate of 0.05-0.1Unit/Kg/ Hour. The insulin is given till patient starts eating per orally (48, 49).

Chronic complications:

"Annexure 2: Chronic complications of diabetes mellitus (17, 48):

Microvascular complications	**Macrovascular complications:**
Eye: Proliferative /non proliferative retinopathy Macula edema	Coronary Heart Disease Peripheral arterial disease Cerebrovascular disease
Neuropathy: Sensory and motor (mono or polyneuropathy) Autonomic neuropathy	**Other Diseases:** Gastrointestinal (Gastroparesis, Diarrhea)
Neuropathy	Genitourinary, Cataract, glaucoma, hearing loss, infections and dermatologic"

Annexure 3: Long Term Complications of diabetes mellitus (48):

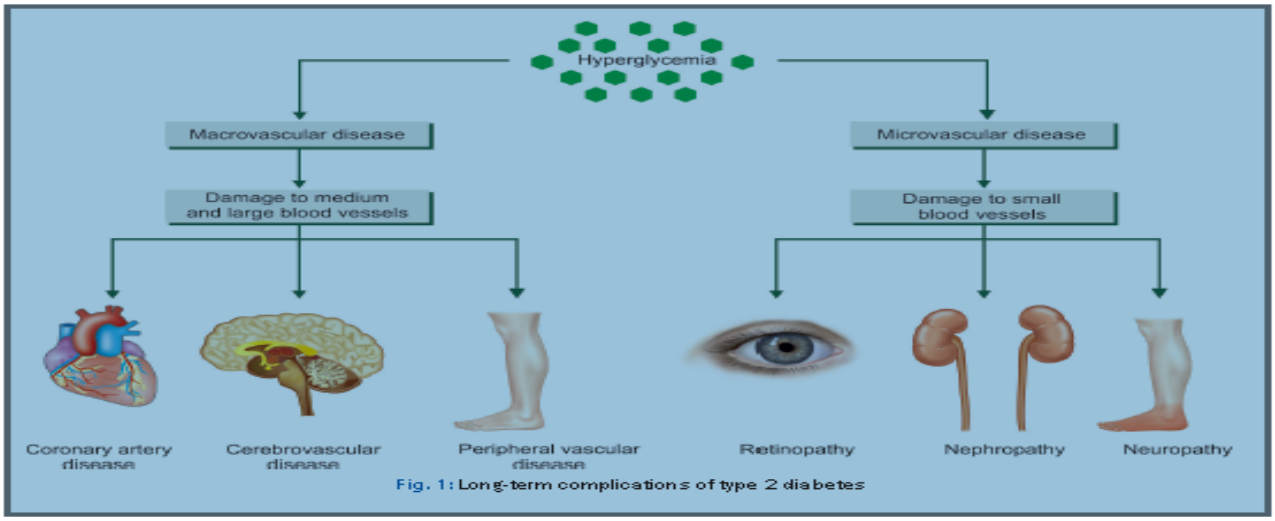


Fig. 1: Long-term complications of type 2 diabetes

Macrovascular complications:

Coronary Heart Disease: Irrespective of the race, ethnicity, gender or geography diabetes mellitus has excessive predilection for coronary arteries with a more severe presentation of CAD and associated with greater complication rates as compared to a non diabetic. Patients with diabetes mellitus can present with a myocardial infarction or sudden cardiac death with no prior history. The occurrence of CAD is two to three decade earlier and females are more prone as compared to males with diabetes (51). A study done in a tertiary care hospital in Eastern India showed that patients with diabetes mellitus with CAD had more extensive involvement and a higher frequentness of multi vessels disease in comparison to a non diabetic cohort (52). The pathogenesis of CAD in diabetes mellitus is multifactorial and involves risk factors like gender, increased total or LDL-c, decrease HDL-c, smoking and diabetes mellitus. Some other risk factors that are likely to be involved in higher occurrence of CAD in diabetes mellitus include Apolipoproteins A1 and B, microalbuminuria, plasminogen-activator inhibitor-1(PAI-1), prothrombin fragments 1 & 2, tissue plasminogen activator, adhesion molecules, lipoprotein (a) and insulin resistance (IR) (48). A study done in South India on Urban population showed a significant finding of increased platelet activation in patients with coronary artery disease and

diabetes mellitus. There was a significantly higher binding of collagen induced GpIIb/IIIa among diabetic subjects with/ without coronary artery disease and non diabetics with coronary artery disease ad compared to non diabetic subjects without CAD. Collagen induced GPIIb/IIIa binding was having significant association with CAD and diabetes mellitus as depicted by regression analysis (53).

A study done on patients with diabetes mellitus with macrovascular disease in New Delhi showed significant post-prandial hypertriglyceridemia and delay in post-prandial trigluceride clearance after challenge of standardized fat meal in patients. The proatherogenic environment in patient with type 2 diabetes mellitus could be due to persistent postprandial hypertriglyceridemia leading to atherosclerosis and macrovascular disease (54). Many studies have been done to find out prevalence of coronary artery disease, a study done on the Urban population of Chennai (CUPS NO5) showed the prevalence of CAD to be 11% in total population and prevalence in diabetic subject to be 21.4%, 9.1% of this population had normal glucose tolerance test whereas 14.9% had impaired glucose tolerance test. A study done in Bikaner and New Delhi found the prevalence of CAD in diabetic subjects to be 25.8% and 7% respectively (55, 56). Another multicentric study demonstrated that the prevalence of CAD in newly diagnosed subjects with T2DM was 6%. In another 11-year follow up study done in south India incidence of cardiovascular disease among diabetic patients was 5-6 cases/1000 person years (57, 58). A study done in North Delhi regarding the prevalence of cardiovascular risk factors in type 2 diabetes mellitus found that 28.9% patients had silent CAD. The study also found that parameter that could predict the risk of silent ischemia in patients with T2DM were high LDL-C level and greater carotid intima-media thickness (CIMT) (59).

Cerebrovascular disease: Patients with diabetes mellitus are more prone to stroke, diabetes being an risk factor which is independent of any other associated comorbidity for it, recurrent stroke encountered in diabetics is associated with a higher mortality and has a female preponderance. The UKPDS study found that patients with diagnosed DM have approximately 8-20% chance of developing stroke as compared to undiagnosed patients where the chance of developing stroke was estimated between 6-42%. Overall 2.6% patients with a follow-up period of 7.9 years developed stroke (60). Studies done in India over 1970-80s demonstrated that the incidence of stroke in diabetic subjects varied between 0.5-9%, though the prevalence is more than doubled in patients suffering from diabetes mellitus as compared to general population. A study done in Cuttack in 2011 showed a prevalence of diabetes mellitus to be 38.75% in stroke patients. The study also showed association of carotid plaque Intima-Media Thickness(IMT) and Resistivity-Index(RI), Pulsatility-Index(PI) in patients suffering from stroke because of acute ischemic with/without diabetes mellitus in Asian –Indians (61). The CUPS study revealed that patients with diabetes mellitus had a higher frequentness of carotid atherosclerosis as compare to control (20 vs. 15) with a significantly higher mean CIMT. The diabetic population had greater arterial stiffness and endothelial dysfunction as compared to control (62, 63). It has been demonstrated that about 1.12% of patients suffering from diabetes mellitus present with cerebrovascular disease. In India patients with diabetes mellitus are more likely to suffer from cerebral infarction (22.1%) as compared to cerebral hemorrhage (6.35%) (64, 65).

Peripheral Vascular Disease (PVD): Other Risk Factors of major importance for lower limb amputation is patients with DM and suffering from peripheral vascular disease. These subset of patients invariably have associated symptomatic cardiovascular and cerebrovascular disease. Peripheral vascular disease in one of the undertreated disease conditions in several developing

countries, and is associated with a fourfold increase in incidence in diabetes mellitus patients. Arteries below the knee are generally involved due to atherosclerotic changes observed in patients with diabetes mellitus showing stenosis as well as occlusion. The anteriortibial artery, posteriortibial artery and peronealartery are commonly involved. The patients with DM have added risk factors like smoking, hypertension and hyperlipidemia thereby increasing the prevalence of PVD. As per estimates revealed by Framingham Heart Study(FHS) approximately twenty percent of patients with diabetes mellitus have symptomatic peripheral vascular disease (48). The prevalence of peripheral vascular disease is between 3-6% in Asians, a population based study in South India showed that 6.3% of patients with diabetes in comparison of 2.7% in the group acting as control had peripheral vascular disease (66). Studies done in Bikaner and North Delhi reported a prevalence rate of 28% and 7.4% respectively of peripheral vascular disease (55, 56). A study done is South India demonstrated an incidence of 17 per 1000 patients year with a progression seen in 16.5% patients to PVD. The prevalence of PVD was found in 5.1% males and 11.8% females with an overall prevalence of 7.6% (67).

Microvascular Complications in Diabetes Mellitus: The microvascular complications encountered in diabetes mellitus include retinopathy, neuropathy and nephropathy, also contributing to diabetic cardiomyopathy and exacerbation of limb ischemia in diabetic foot. Microangiopathy seen in diabetes mellitus is due to hyperglycemia, hypertension and lipid abnormalities leading to triggering of multiple pathways causing pathogenic sequences. There is formation of advanced glycation end product(AGE), the protein kinase C(PKC) is activated and riased flux via sorbitol(polyol) and hexosamine pathway causing oxidative stress. This oxidative stress causes vascular remodeling, altered tone of the vessels, permeability and changes in basement membrane at the target tissue. Accumulation of extracellular matrix (ECM) in the

mesangium leads to diabetic nephropathy, neovascularization in the retina under the influence of vascular endothelial growth factor (VGEF) leads to diabetic retinopathy (68). A study done to determine the coagulation profile and its association with microvascular complications in New Delhi showed that and raised levels of VWF and reduced levels of Protein S were associated with retinopathy of DM. Nephropathy because of DM was also relatedted with an increased PAI-1, hence a hypercoagulable state could be responsible for microvascualr complications of diabetes mellitus (69). A patient presenting with diabetic retinopathy is at risk of developing diabetic nephropathy as well as neuropathy. Age, elevated glycosylated hemoglobin , duration of diabetes and elevated serum trigylcerides are risk factors for development of micovascular complication in patient suffering from diabetes mellitus with a more stronger association with development of retinopathy and nephropathy (70).

Diabetic Retinopathy: Retinopathy because of DM is a complication of microvascular system seen in DM that is an important preventable cause of blindness. The two forms of retinopathy seen in patients suffering from diabetes mellitus are proliferative and non-proliferative diabetic retinopathy, while blindness is related with macular edema and proliferative diabetic retinopathy. One of the complications seen in patients with DM is diabetic retinopathy determined by duration of illness, glycemic status of the patients and blood pressure control. Patients with history of diabetes mellitus for more than 15years have 60% chance for being affected by diabetic retinopathy, and a patient suffering from diabetes mellitus for more than 25 years the chance of developing diabetic retinopathy is up to 90% (71).

The prevalence of diabetic retinopathy at the time of diagnosis varies between 5-7.3% in Indian sub-continent as compared to Western population where the prevalence varies between 20-50% at the time of diagnosis. The difference seen in the Indian sub-continent is due to difference in

reporting in clinic-based and population-based studies. The reported prevalence is much lower in Indian sub continent where reports available from populations based studies which have reported that 1 out of 5 patients suffering from diabetes mellitus has diabetic retinopathy (48). A study done in Chennai (Chennai Urban Rural Epidemiological Study (CURES)) was the first population-based study for diabetic retinopathy, the study showed that the overall frequentness of diabetic retinopathy was17.6%, where the frequentness of retinopathy among known diabetics were 20.8% and 5.1% of newly diagnosed patients with diabetes mellitus had presentation of diabetic retinopathy. Other findings in the study were that with every 5 year increase with the disease the risk of diabetic retinopathy increased by 1.89 times, and a rise of 2% in glycosylated hemoglobin increased the risk of diabetic retinopathy by 1.75 times (70). A family aggregation study demonstrated that diabetic retinopathy showed familial clustering with diabetic retinopathy being three times higher in siblings of patients suffering from diabetes mellitus with diabetic retinopathy (72). Another study done in Tamil Naidu to study the association of diabetic retinopathy with duration of the disease showed a significantly increased prevalence with duration of the disease. A prevalence of 6.6% of diabetic retinopathy was seen in patients who were diagnosed with diabetes mellitus less than one year (71).

Diabetic Nephropathy: An epidemiological study done by the Indian Chronic Kidney Disease (CKD) Registry demonstrated that diabetes mellitus was associated with chronic kidney diseas in 31.2% of patients. An association was also demonstrated between chronic kidney disease and cardiovascular disease which progressed with the severity of chronic kidney disease. Patients suffering from stage 1 chronic kidney disease lead to cardiovascular disease in 0.7% patients which progressed to 48.5% patients with stage 5 chronic kidney disease (73). Another study done for prevalence of chronic kidney disease, the Screening and Early Evaluation of Kidney Disease

(SEEK Study) demonstrated a prevalence of 17.4% with higher prevalence in urban areas as compared to rural areas (25.5 vs. 9.4%). The study also highlighted that diabetes mellitus and hypertension were the main causes of chronic kidney disease (74). A study done in Jhansi to demonstrate the development of nephropathy in patients with diabetes mellitus demonstrated 20.4% of development of diabetic nephropathy in patients with diabetes mellitus over years. In patients with newly diagnosed diabetes mellitus the most important factor contributing to nephropathy was hypertension and the incidence of diabetic nephropathy in newly diagnosed patients was 17.34% (75). A number of studies conducted across Chennai, Bikaner and North Delhi have demonstrated microalbuminuria in a range between 26.9 to 41% with overt proteinuria seen in 2.2% of patient with diabetes mellitus (55, 56, 76). Familial clustering of diabetic nephropathy has been observed in population-based studies. In one study done in Cuttack, patients with diabetes had a greater degree of atherosclerosis and beta-cell dysfunction as compared to control with microalbuminuria as a markerfor generalized vascular endothelial dysfunction (74).

Other complications: Several other complications can occur in patients with diabetes mellitus which include:

Noncoronary Cardiac Complications: Some of the other cardiac disorders encountered in patients with diabetes mellitus are diabetic cardiomypathy, heart failure, sudden cardiac death and autonomic neuropathy with cardiomyopathy seen in a third of all the patients. Heart block in diabetics is due to degenerative changes in the conducting system. A rise in glycosylated hemoglobin by 1% increases the risk of getting congestive heart failure by 15%. Other risk factor related with development of heart failure in patients with DM is inadequate glycemic control and

duration of diabetes mellitus. In people diagnosed with congestive heart failure it is estimated that around 20% are diabetics as compared to only 4-6% controls (77).

Hypertension: Hypertension and diabetes mellitus are seen in together in around 40-60% of patient's worldwide. As per Hypertension in Diabetes Study (HDS-1) in patients with recently diagnosed diabetes mellitus, hypertension was associated at a prevalence rate of 39%. Reports from India suggest that both hypertension and diabetes mellitus co-exist in around 20.6% of patients (78).

Chronic Liver Disease: Amarpurkar, et.al. in 2001 conducted a study on etiology of chronic liver disease in patients with/ without diabetes mellitus in India, they showed that as compared to control patient with diabetes mellitus had greater chances of non alcoholic steatohepatitis (NASH). Patients with diabetes mellitus had higher evidence of NASH with cirrhosis of liver and cryptogenic cirrhosis (79). The determinant factors which demonstrated positive correlation with histopathological grades of NASH had insulin resistance and dyslipidemia (80).

Infections: Patients with diabetes mellitus have higher morbidity and mortality as they are at an increased susceptibility of acute as well as chronic infection. There is a threefold higher risk of developing tuberculosis in patients suffering from diabetes mellitus. As per data available, 15% of patients with tuberculosis have diabetes mellitus and 21% of patients with diabetes mellitus have smear-positive tuberculosis (81). A study done in India demonstrated that diabetes mellitus is found in 18.4% of patients with pulmonary tuberculosis with a greater prevalence (23.4%) of diabetes mellitus in patients with smear positive patients. The study also highlighted that prevalence of diabetes mellitus was more in urban population as compared to rural population in smear positive patients of tuberculosis (82). Another study done in South India on prevalence of diabetes mellitus on a cohort of patients of tuberculosis registered under RNTCP showed the

occurence of diabetes mellitus in 25.3% patients & 24.5% of patients were prediabetic (83). Patients with diabetes mellitus commonly reported with urinary tract infection, which was also the most common cause of hospital admission. Around 9-14% of patients with diabetes mellitus reported with symptomatic urinary tract infection, which was most commonly seen in postmenopausal women (84, 85). Patients with diabetes mellitus have greater mortality associated with pneumonia and urinary tract infection as compared to controls (48).

Diabetic Neuropathy: One of main causes of morbidity associated with DM is neuropathy affecting half of all patients of diabetes mellitus which is governed by the severity and duration of hyperglycemia. The prevalence of diabetic neuropathy in patients with diabetes mellitus is almost equivalently reported in clinical based studies (19-33%) as well as population based studies (13-31%) (86). An observational study done at a tertiary care centre in Cuttack to demonstrate the clinical presentation of patients with diabetic neuropathy showed that the most frequent presentation was distal symmetrical sensorimotor neuropathy. The other presentations of patients with diabetic neuropathy in decreasing frequency were cranial mononeuropathy, mononeuropathy multiplex, and autonomic neuropathy (87). Peripheral neuropathy was commonly seen in patients with diabetes mellitus falling in the low body weight group (88). Another population based study done to determine the age-standardized prevalence of diabetic neuropathy showed that 11.2% of patients with recently diagnosed diabetes mellitus and 13.6% patient who were already diagnosed with diabetes mellitus presented with neuropathy. When crude prevalence was determined it was seen that patients already diagnosed with DM had a higher frequency of neuropathy in compariosn to newly diagnosed patients with diabetes mellitus (89).

A study was done in Croatia to evaluate if obesity alone or in combination with few more risk factors could increase the chance for microvascular and neuropathic complications in cases suffering from T2DM. The study recruited 156 patients of DM and based on body mass index this group of patients were further divided into three groups, which were categorized for age, duration of the disease, therapy received & estimation of serum lipid profile (cholesterol, HDL-cholesterol and triglycerides). A rise in body mass index was significantly associated with aberrant values of glycosylated hemoglobin and rise in LDL-cholesterol and blood pressure(both systolic and diastolic). There was significant increase in prevalence of microvascular complications and neuropathic complications with obesity (8).

A study was done in Greece to evaluate whether diabetic peripheral neuropathy could be related with myocardial infarction in patients with T2DM with no prior history of cardiovascular events showed a strong association. The study demonstrated that patients with diabetic peripheral neuropathy had significantly higher number of patients had abnormal summed stress score (which represents the extent and severity of perfusion abnormalities). The study recommended that diabetic peripheral neuropathy assessment could be helpful in identifying patients who are at risk for cardiovascular diseases (90).

One more study done to study that elevated triglyceride levels associated with progression of diabetic neuropathy using sural nerve morphometry indexes obtained from prior clinical trials analyzed the myelinated fibre density (MFD) of sural nerve, NCV, VPT, clinical symptom score and visual analogue score for pain in participants with diabetic neuropathy. The study demonstrated that elevated triglyceride levels correlated MFD loss in participants with mild to moderate diabetic neuropathy. This correlation was independent from other variables like age, duration of disease, and diabetes control (5).

A study done in China to evaluate the asymptomatic polyneuropathy(distal symmetric) in patient suffering from T2DM used sudomotor function test so as to give more attention asymptomatic patient. The rational for using sudomotor function test (Sudoscan) was to evaluate the function of sweat gland as this gives us a early reflection of sympathetic nerve impairment. This study recruited 394 patients suffering from T2DM, the results of sudoscan depicted that patients who were asymptomatic had higher abnormal results than those without neuropathy, the study concluded the Sudoscan could be one of the tools for screening of patients for neuropathy (91).

A retrospective analysis done in South Korea toinvestigate risk factors in patients with diabetes mellitus for peripheral polyneuropathy and to correlate the findings of nerve dysfunction with the severity recruited 187 cases of suspected polyneuropathy clinically. These patients were classified into two group based on the electrophysiological abnormality with or without polyneuropathy. The study demonstrated that patient with polyneuropathy had significantly higher levels of glycosylated hemoglobin and composite score as compare to the other group. Higher values of glycosylated hemoglobin and older age group were factors predictive of polyneuropathy and HbA1c was having significant association with composite score. The study concluded that increased glycosylated hemoglobin levels were independent risk factor for polyneuropathy in DM patients (2).

Another study done in Pune, India to examine the types of neuropathy and associate clinical features of peripheral neuropathy with the help of NCV studies was done on patients suffering from T2DM and have features predictive of peripheral neuropathy. The study recruited 50 patients and all these patients undertook a thorough clinical examination and nerve conduction study. The patients were examined for symptoms of paraesthesia, hyperesthesia, foot ulcers and any history of weakness and gait abnormality. The results of the study showed that more than

half of all the patients enrolled had abnormal clinical presentations which included tingling sensation and burning feet; diminished ankle jerk,; diminished/loss of vibration sensation and around 40% of patients also had complaints of diminished light touch and loos of joint position sensations. All the patients had neuropathic involvement of lower limb as shown by nerve conduction studies with involvement of tibial and sural nerve most commonly. Half of the patients had involvement of the upper limb also, so the study concluded that the most common form of diabetic neuropathy seen in patients is distal symmetric polyneuropathy (1).

A study done was done in Taiwan to investigate excitability properties of sensory and motor nerve using clinical assessments, nerve conduction studies and nerve excitability test for determining development of neuropathy in patients with T2DM recruited 106 patients. These patients were sub-divided into three groups based on the total neuropathy score-reduced(TNS-r) and were compared with values of healthy controls. The study revealed that there was a significant increased stimulus for nerve action potential, a shortened strength –duration time constant, increased super excitability, and decreased sub excitability in the patients with diabetic neuropathy in comparison to healthy controls. The cases with diabetes mellitus also had a significant decreased accommodation to depolarizing current and hyperpolarizing current as compared to healthy controls. These changes progressed in different groups of diabetes mellitus. The motor changes seen in patients with diabetes mellitus also showed a significant raised stimulus for action potential of compound motor nerve in comparison to healthy controls. The study showed axonal dysfunction development was different in diabetic patients; the sensory dysfunction occurred prior to motor dysfunction. Both of them followed a different pattern and early detection of sensory axonal abnormalities could help provide neuroprotection (92).

The PROMISE Study i.e. (Prospective Metabolism and Islet Cell Evaluation), a prospective observational study with the aim to study the frequentness of peripheral neuropathy and nerve-dysfunction and to investigate the role of glucose tolerance status and metabolic syndrome associated with these neurological changes of individuals who are at high risk for type 2 diabetes mellitus. The cohort of well characterized individual at greater risk for T2DM explored the longitudinal relationship of insulin-resistance and beta cell dysfunction of islets of pancreas was conducted for more than 2 year and had a recruitment 712 participants of Toronto and London, Ontario and Canada. The participant's recruitment was based on the risk factor for T2DM which included obese individuals, positive family history of diabetes mellitus, diabetes mellitus during pregnancy(Gestational diabetes mellitus), birth of Macrosomicinfant or hypertension. The Michigan Neuropathy Screening Instrument(MNSI) was used in define the peripheral neuropathy and vibration perception thresholds (VPT) was utilized to find the severity of nerve dysfunction. This study demonstrated that patients with prediabetes or new onset diabetes mellitus had almost similar trends for prevalence of peripheral neuropathy. The severity of nerve dysfunction was similar in prediabetes and diabetes mellitus and further course of glucose dysfunction for a period of 3years predicted a greater risk for nerve dysfunction and peripheral neuropathy. The study also showed that the risk for developing peripheral neuropathy and severity of nerve dysfunction were similar in prediabetes and new-onset diabetes mellitus (93).

A prospective descriptive study done in Saudi Arabia to evaluate the risk factors that are associated with the development of diabetic neuropathy and early detection of impaired nerve factor recruited 263 age-matched patients with diabetes mellitus. All patients recruited underwent thorough clinical examination and neuropathy was assessed by DNI and DNS. All patients who had a score of less than 2 underwent nerve conduction studies. The study

demonstrated that old age group, abnormal glycemic control, prolongs duration of disease, hyperlipidemia and higher body mass index were risk factors for the development of neuropathy. A strong correlation was found in asymptomatic patients with duration of disease, age, body mass index and glycosylated hemoglobin levels. This study concluded that early diagnosis of sub-clinical nerve conduction could lead to higher intensive supervision of these diabetic patients (6).

An exhaustive literature search has shown that patients diagnosed with diabetes mellitus might have manifestation of neuropathy due to DM when first diagnosed with the disease (1, 2, 5) as two-third of cases of diabetes mellitus have clinical or subclinical neuropathy (7), hence, it was considered apt to study Evaluation of Diabetic Neuropathy Changes in Newly Diagnosed Patients of Type II Diabetes Mellitus (T2DM).

MATERIALS & METHODS

Study Design: This observational study was done in Department of Physiology, with the association of General Medicine and Neurology Department in Teerthanker Mahaveer Medical College and Research Centre after obtaining approval from the Institutional Ethics Committee(IEC).

Study Population: All patients visiting the outpatient department of medicine and neurology of Teerthanker Mahaveer Medical College and Research Centre and diagnosed to be suffering from type II diabetes mellitus as per ADA guidelines (43) were recruited in the study after obtaining consent(Written informed consent) from 1st March, 2017 to 31st May, 2018.

Inclusion Criteria:

- Patients diagnosed to be suffering from type II diabetes mellitus
- Patients between the age of 30-70 years
- Patients of both sexes
- Patients those who were willing to give consent

Exclusion Criteria:

- Pregnancy and lactation
- Any alternative cause for peripheral neuropathy
- Alcoholics
- Renal failure
- Thyroid disease
- On drugs that cause neuropathy (Isoniazid)
- Previous history of autoimmune disease
- Previous history of cancer
- Family history of a non-diabetic neuropathy in a first-degree relative

- An inability to understand or cooperate with the procedures of the study

Procedure: After approval from IEC and consent(written informed consent), patients diagnosed to be suffering from type II diabetes mellitus fulfilling the seelction criteria were enrolled in study. Patients with diagnosis of type II diabetes mellitus as per ADA guidelines (43)

"Annexure 4 - Criteria for the diagnosis of diabetes as per the ADA Guidelines (43)"

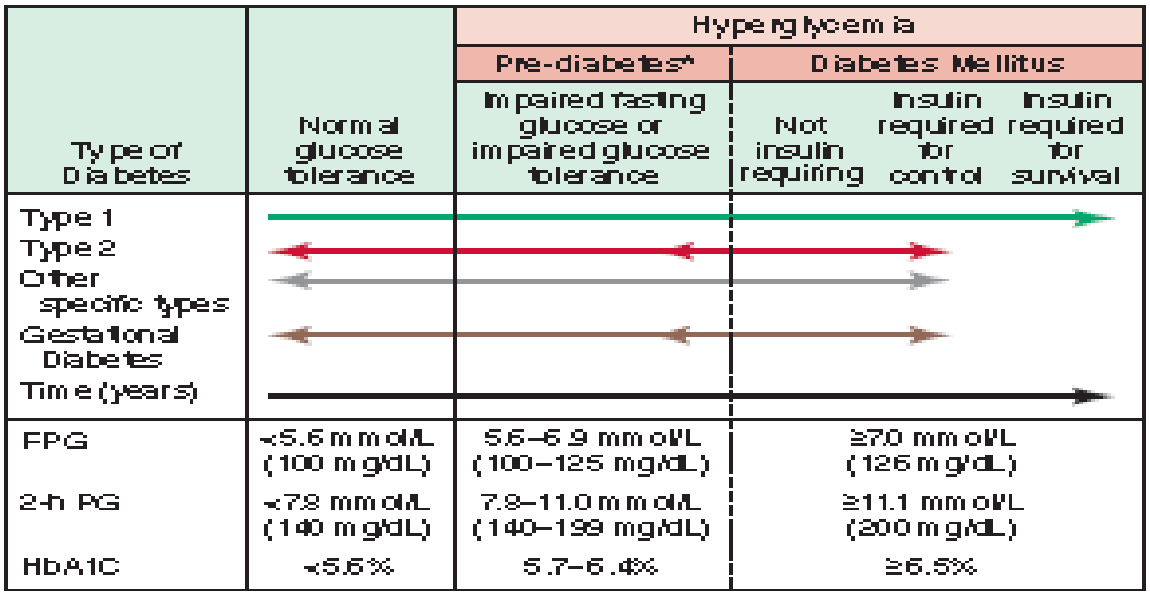


FIGURE 417-1 Spectrum of glucose homeostasis and diabetes mellitus (DM). The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2 DM, other specific types of diabetes, and gestational DM is shown from left to right. In most types of DM, the individual traverses from normal glucose tolerance to impaired glucose tolerance to overt diabetes (these should be viewed not as abrupt categories but as a spectrum). *Arrows* indicate that changes in glucose tolerance may be bidirectional in some types of diabetes. For example, individuals with type 2 DM may return to the impaired glucose tolerance category with weight loss; in gestational DM, diabetes may revert to impaired glucose tolerance or even normal glucose tolerance after delivery. The fasting plasma glucose (FPG), the 2-h plasma glucose (PG) after a glucose challenge, and the hemoglobin A_{1c} (HbA_{1c}) for the different categories of glucose tolerance are shown at the lower part of the figure. These values do not apply to the diagnosis of gestational DM. Some types of DM may or may not require insulin for survival. ^Some use the term *increased risk for diabetes* or *intermediate hyperglycemia* (World Health Organization) rather than *prediabetes*. (*Adapted from the American Diabetes Association, 2014.*)

A thorough clinical examination (including neurological examination); Nerve conduction velocity testing; evaluation of plasma glucose and glycosylated haemoglobin;and aassessment of neuropathy by using the DNI and DNS was performed on participants. Data was entered in excel sheet and analyzed.

Annexure 5. Schedule of Events:

Clinical Visit No.	**1**
Observation/procedure	
Medical History	X
Informed Consent	X
Inclusion/Exclusion Criteria	X
Physical Examination (Including Neurological Examination)	X
Biochemical Test	X
Nerve Conduction Velocity testing	X
(Diabetic Neuropathy Index)	X
(Diabetic Neuropathy Score)	X

Primary Outcome Measures:

- Nerve Conduction Velocity was assessed in median, ulnar, peroneal, sural and posterior tibial nerves, motor nerve conduction velocity was measured on the left forearm segment of the median nerve and the left peroneal nerve. A composite score was used for quantitative analysis of result of NCV (2, 15).
- “Auditory and visual reaction time is considered as an ideal tool for measuring sensory motor association (94, 95). Reaction time (RT) is the elapsed time between the presentation of a stimulus which can be of any modalities of sensory input like visual,

auditory, pain, touch or temperature and the subsequent behavioural response to occur. It is considered an index of speed of processing. The behavioural response is typically a button press but can also be an eye movement, a vocal response, or some other observable behaviour"(10, 96).

- Plasma glucose level and glycosylated haemoglobin level

Secondary Outcome Measures:

- Neuropathy was assessed by using the Michigan Neuropathy program which includes two steps; the Diabetic Neuropathy Index (DNI) and the Diabetic Neuropathy Score (DNS). Patients who score less than 2 on routine clinical examination and are asymptomatic are referred to be assessedby complete neurological examinationdone by nerve conduction studies (97).

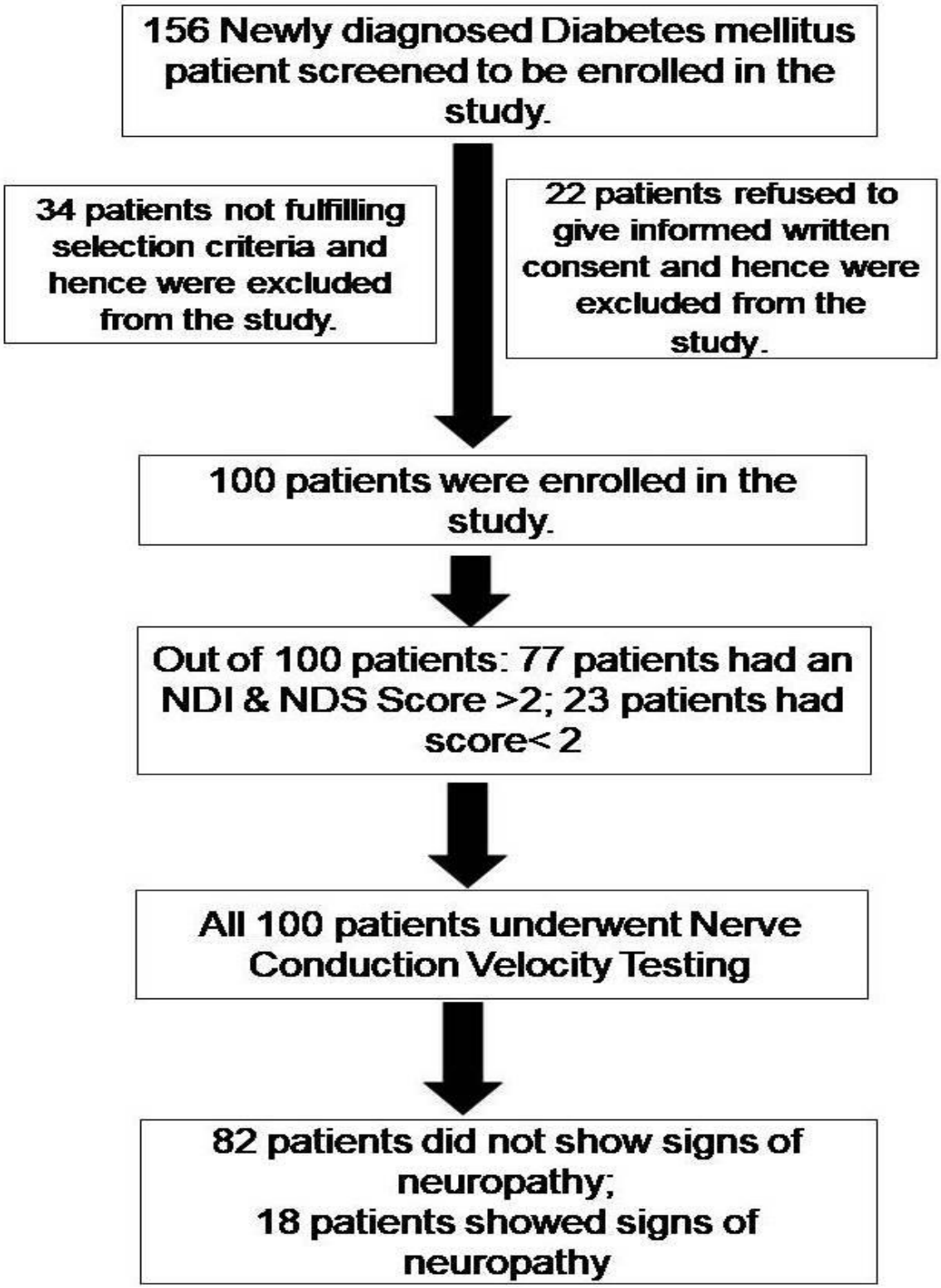
Statistical Analysis:

The data was presented as mean ± standard deviation (Mean ± Sd). SPSS software (version 16) was used for data analysis. The result were analyzed using appropriate parametric (two tailed student 't' test) and non parametric test (chi-square test,). Nominal variable were compared using Chi-square test. The student't' test was used to compare group means for normally distributed data and Mann-Whitney U test/ Wilcoxon Sign rank test was used for non-normally distributed data. Correlations between the variables were examined using the Pearson correlation coefficients. A $p<0.05$ was considered statistically significant.

“OBSERVATION AND RESULT”

156 patients with newly diagnosed diabetes mellitus were screened for the study from March, 2017 to May, 2018. Thirty four (34) patients who didn't fulfil the inclusion as well as the exclusion criteria and were not recruited for the study; another 22 patients did not give written informed consent to participate in the study and hence were also not recruited for the study. One hundred (100) patients who fulfilled the inclusion and exclusion were enrolled in the study after they give written informed consent (Figure 1). All the patients underwent a thorough clinical examination, all these patients were subjected to "diabetic neuropathy index (DNI)" and "diabetic neuropathy score (DNS)". Seventy seven (77) participants had DNS and DNI score more than 2, whereas 23 patients had a score less than 2. All the 100 patients were subjected to nerve conduction velocity (NCV) testing, 82 of these 100 newly diagnosed patients did not have neuropathy, whereas 18 of these patients had neuropathy.

Figure 1. CONSORT diagram

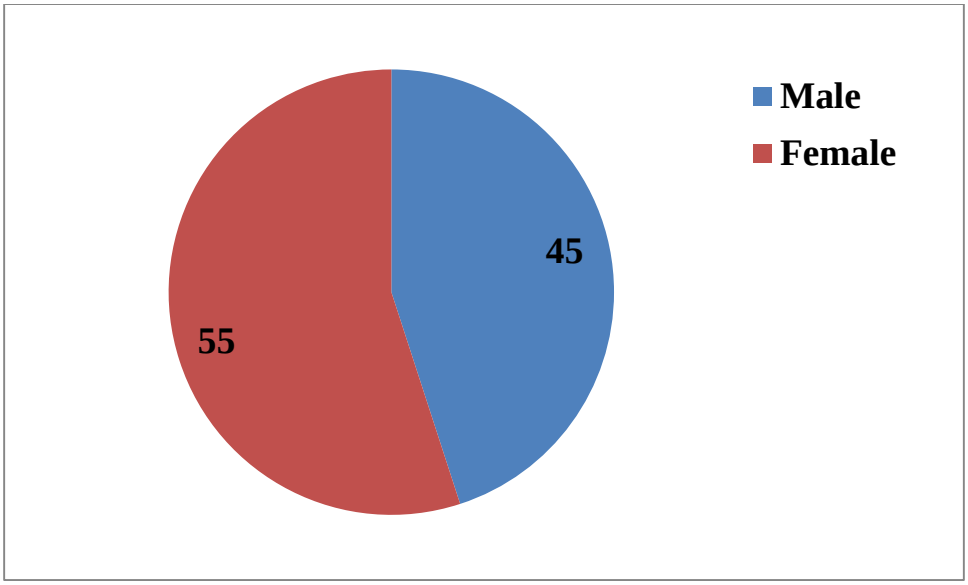


The baseline parameters of all the patients are shown in Table1. The mean age of patients enrolled in the study was 55.31±11.38 years, there were 45 men and 55 women (Figure 2) enrolled in the study with a mean weight of all patient enrolled being 71.32±8.46 kgs and the average glycosylated haemoglobin (HbA1c) levels in these patients were 7.45±1.90 %. All these patients had elevated levels of fasting plasma glucose (FPG) and 2-hours plasma glucose (2h - PG) – the mean FPG was 149.55±42.21 mg/dL and mean 2h-PG was 215.77±26.89 mg/dL. All patients recruited in the study underwent thorough clinical examination and were subjected to DNI and DNS, the mean DNI was 3.11±1.37 and the mean DNS was 3.81±1.79. Though all patients enrolled in the study underwent nerve conduction velocity (NCV) testing. Any patient with DNI or DNS score less than 2 should be subjected to NCV, 23 patients in our study had a DNI or/and DNS score less than 2.

“Table 1. Baseline parameters of patients enrolled in the study.”

Parameter	**Patient enrolled (n=100)**
Age (years) (Mean±SD)	55.31±11.38
Weight (kilograms) (Mean±SD)	71.32±8.46
Glycosylated Hemoglobin (HbA1c) (%)(Mean±SD)	7.45±1.90
Fasting Plasma Glucose (FPG) (mg/dL) (Mean±SD)	149.55±42.21
2-hours Plasma Glucose (2h-PG) (mg/dL) (Mean±SD)	215.77±26.89
Diabetic Neuropathy Index (DNI) (Mean±SD)	3.11±1.37
Diabetic Neuropathy Score (DNS) (Mean±SD)	3.81±1.79

Figure 2. Sex distribution of patients in the study



All patients underwent nerve conduction velocity and the results showed that 18% of all participants recruited in the study had neuropathy associated with diabetes mellitus (Figure 3). Based on the results of nerve conduction velocity these partiicpants were divided into two groups. Group A (n=82) were those patients who did not have neuropathy as suggested by NCV testing, whereas Group B (n=18) were those participants who had signs of neuropathy as suggested by NCV testing. The parameters of both the groups are depicted in Table 2. The participants with neuropathy (Group B) belonged to a higher age group (58.06 vs. 54.71 years) and had a slightly more weight (71.89 vs. 71.20 kgs) then patients who did not have neuropathy (Group A) though it was not significant ($p>0.05$). The participants with neuropathy (Group B) had a significantly ($p<0.05$) higher glycosylated haemoglobin (10.58 vs. 6.71 %), fasting plasma glucose (220.28 vs. 134.02 mg/dL) and 2-hour plasma glucose (247.50 vs. 208.81 mg/dL) as compared to patients who did not have neuropathy (Group A). All the patients were also subjected to DNI and DNS, patients in Group A has higher DNI (3.40 vs. 1.78) and DNS (4.22 vs. 1.94) as compared to Group B and this was significant ($p<0.05$).

Figure 3. Results for Nerve Conduction Velocity Testing in the study

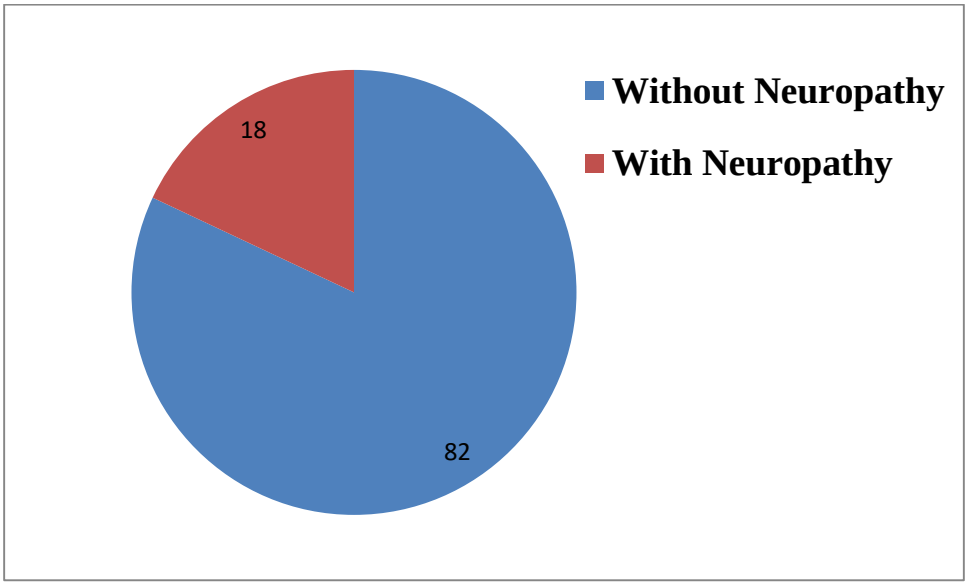


Table 2. Parameter of patients with and without neuropathy

Parameter	**Group A (n=82) – without neuropathy**	**Group B (n=18) – with Neuropathy**	**p value**
Age (years) (Mean±SD)	54.71±11.35	58.06±11.39	>0.05*
Sex (M:F)	37:45	8:10	>0.05#
Weight (kilograms) (Mean±SD)	71.20±8.49	71.89±8.59	>0.05*
Glycosylated Hemoglobin (HbA1c) (%)(Mean±SD)	6.76±1.12	10.58±1.55	<0.05$^{\phi}$*
Fasting Plasma Glucose (FPG) (mg/dL) (Mean±SD)	134.02±19.86	247.50±45.47	<0.05$^{\phi}$*
2-hours Plasma Glucose (2h-PG) (mg/dL) (Mean±SD)	208.81±13.31	247.50±45.47	<0.05$^{\phi}$*
Diabetic Neuropathy Index (DNI) (Mean±SD)	3.40±1.32	1.78±0.55	<0.05$^{\phi}$*
Diabetic Neuropathy Score (DNS) (Mean±SD)	4.22±1.70	1.94±0.54	<0.05$^{\phi}$*

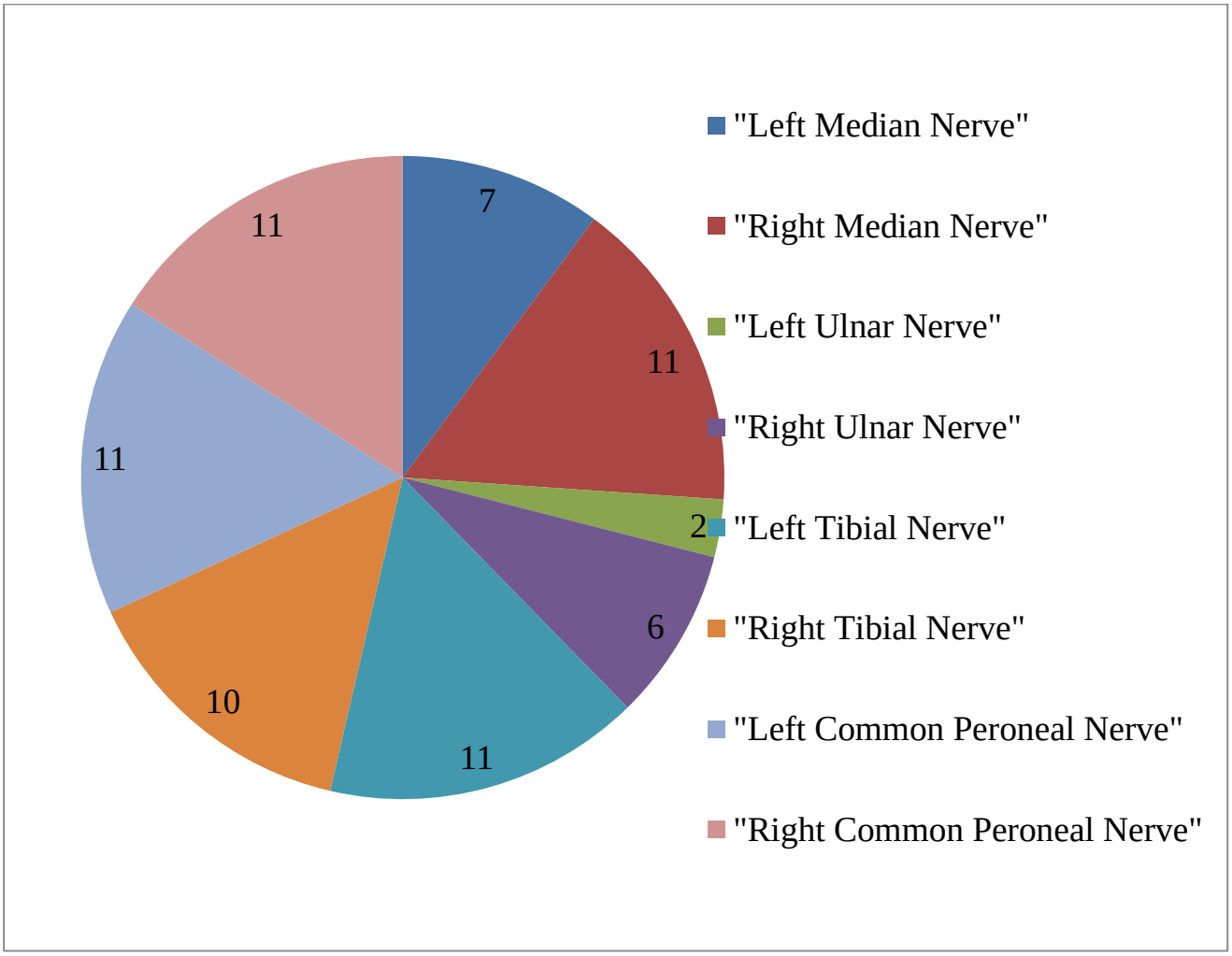
$^{\phi}$statistically significant as compared to the other group

*using student ‘t’ test and Mann-Whitney U Tes

#using Chi-Square Test

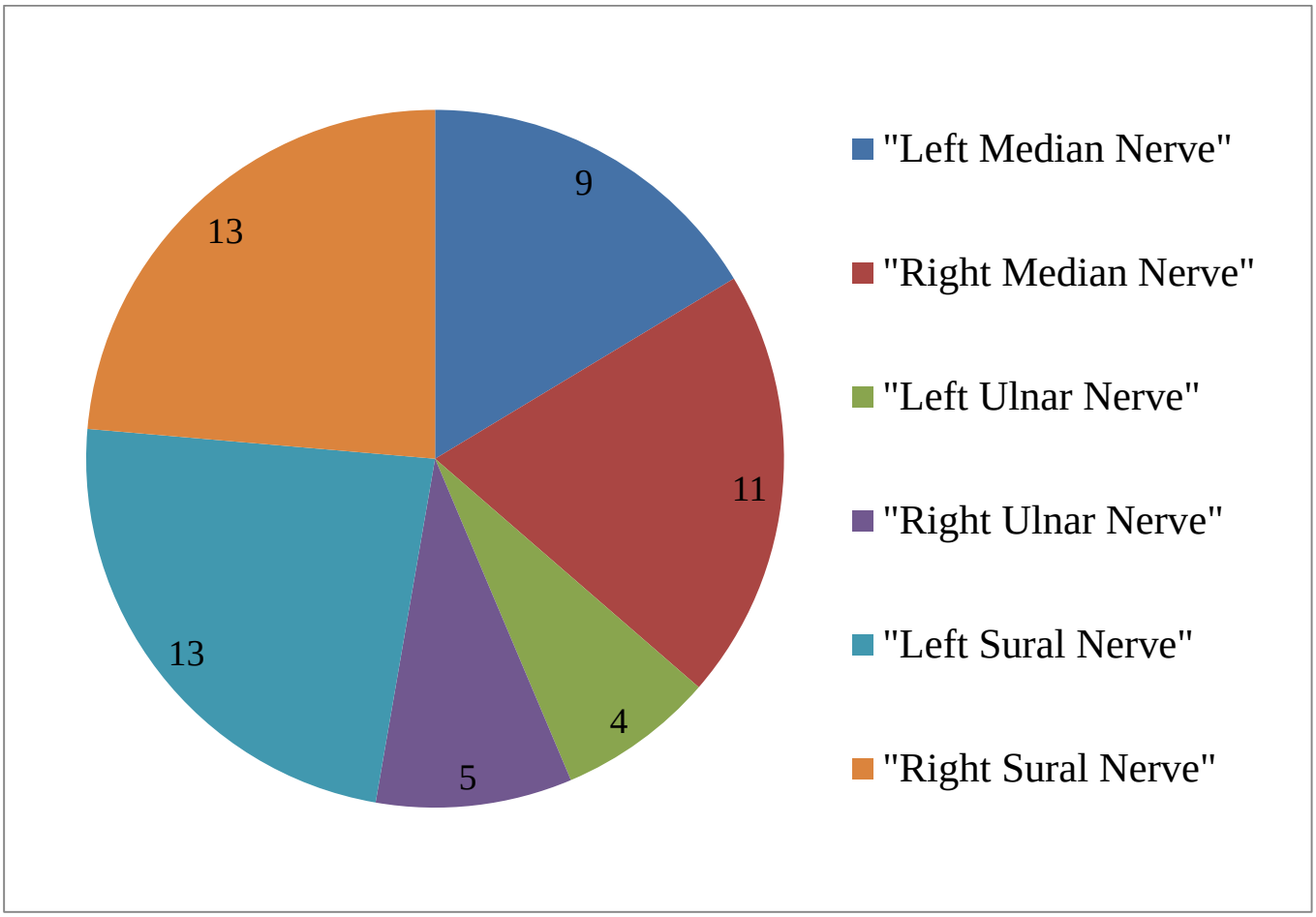
The motor component involvement in patients suffering from diabetic neuropathy, as per the nerve conduction velocity testing is shown in Figure 4. The most common nerve involved was the tibial nerve and least involvement was seen in ulnar nerve, right limbs were more commonly involved then the left limbs. Median Nerve of the left side was involved in 7 patients and right side was involved in 11 patients, whereas in case of ulnar nerve, 2 patients had abnormal findings in Left ulnar nerve and 6 patients had abnormal findings in right ulnar nerve. The tibial nerve of the left side as involved in 11 patients and right side was involved in 10 patients. The Common peroneal nerve was involved bilaterally in 11 patients.

Figure 4. Motor Component Invlovement as per NCV testing



The sensory component involvement in patients suffering from diabetic neuropathy, as per the nerve conduction velocity testing is shown in Figure 4. The most common nerve involved was the sural nerve and least involvement was seen in ulnar nerve, right limbs were more commonly involved then the left limbs. Median Nerve of the left side was involved in 9 patients and right side was involved in 11 patients, whereas in case of ulnar nerve, 4 patients had abnormal findings in Left ulnar nerve and 5 patients had abnormal findings in right ulnar nerve. The sural nerve was involved bilaterally in 13 patients.

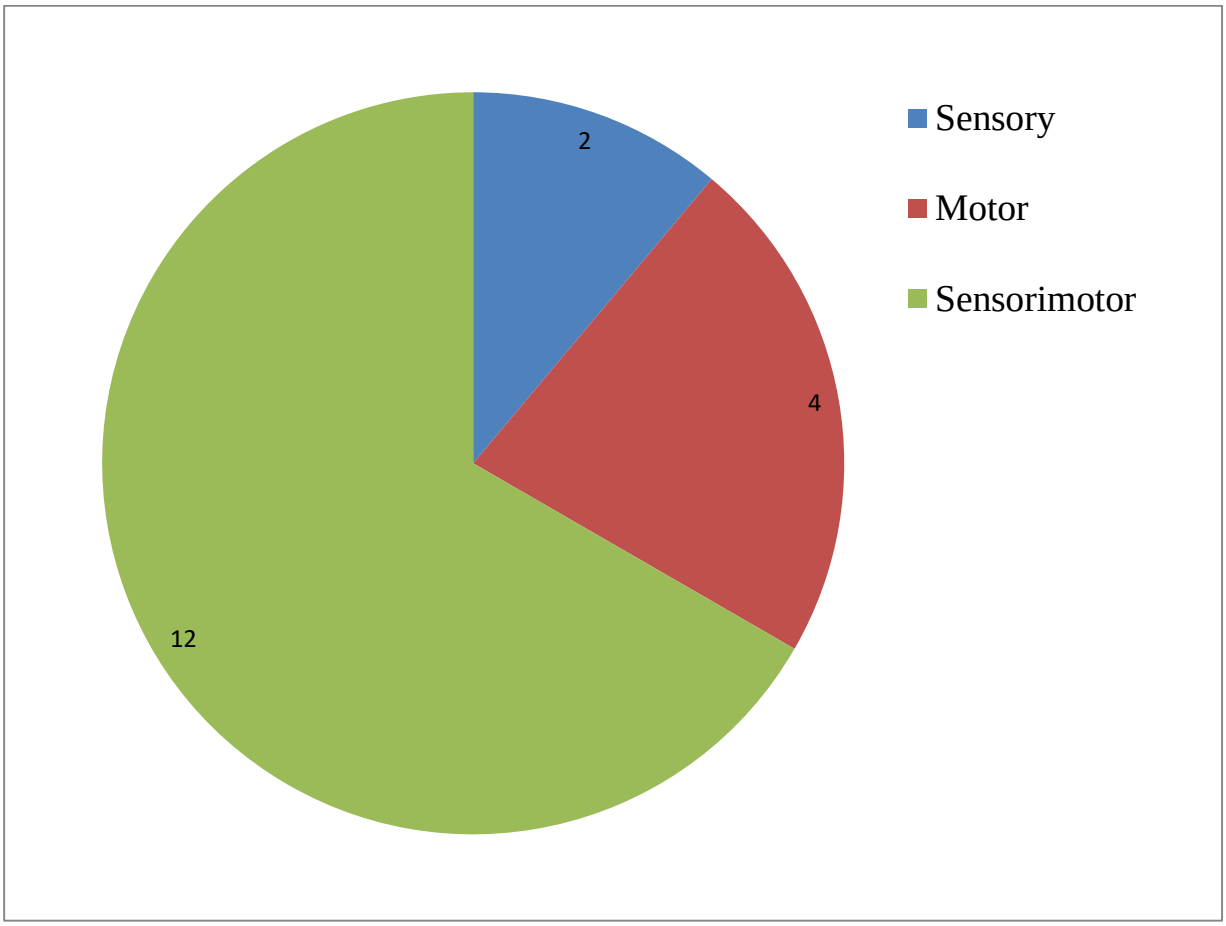
Figure 5. Sensory Component Involvement as per NCV testing



Neuropathy – Type:

Neuropathy diagnosed in new onset diabetes mellitus could be further classified into either motor, sensory or mixed. In our study as shown in Figure 6, most of the patients had presentation of sensorimotor neuropathy, and least patients had presentation of sensory neuropathy. As per the NCV testing, 2 patients were having neuropathy-sensory pattern, 4 patients had neuropathy-motor pattern and 12 patients had neuropathy-sensorimotor pattern.

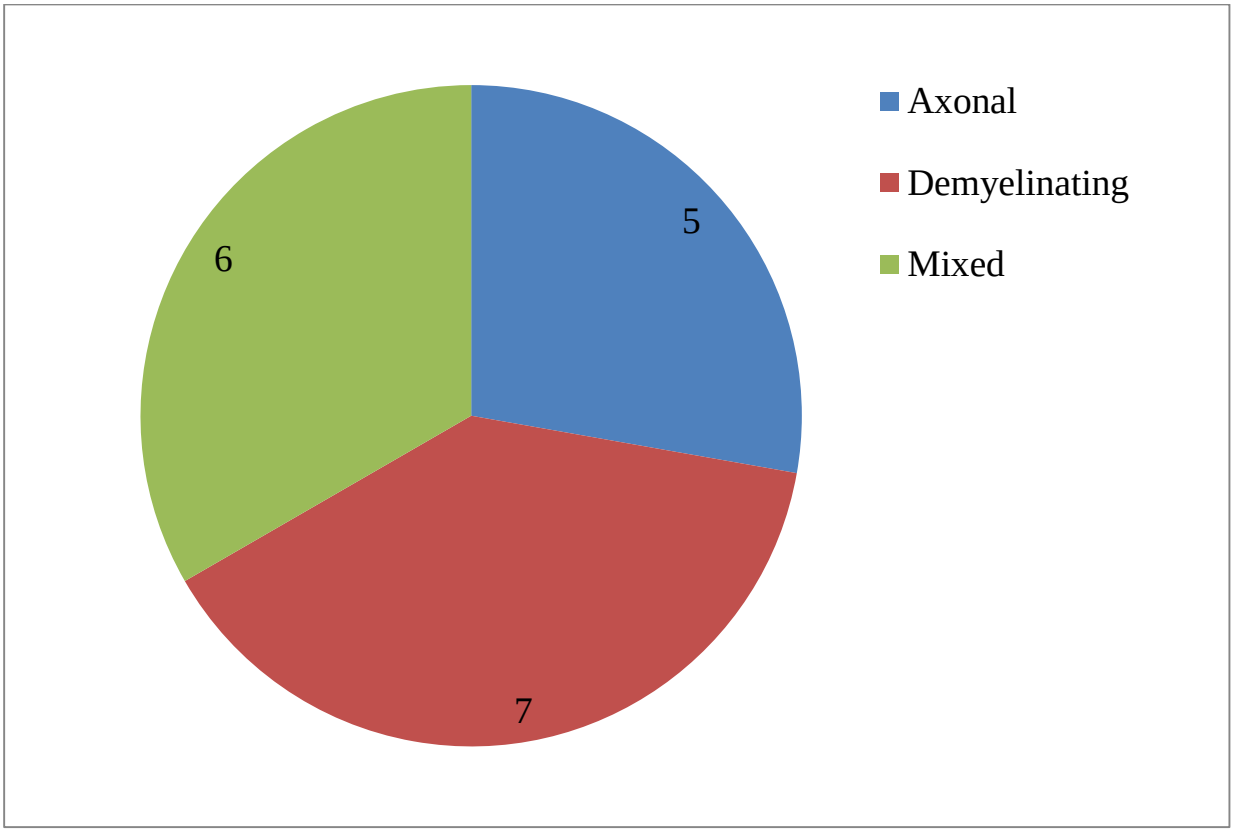
Figure 6. Neuropathy type as per NCV testing



Neuropathy – Type:

The neuropathy diagnosed in new onset diabetes mellitus could be further classified into either axonal, demyelinating or mixed type based on the results of NCV testing mainly conduction velocity, amplitude and Distal latency. In our study as shown in Figure 7, most of the patients had presentation of demyelinating neuropathy, and least patients had presentation of axonal neuropathy. As per the NCV testing, 5 patients were having axonal neuropathy, 7 patients had demyelinating neuropathy and 6 patients had mixed neuropathy.

Figure 7 Neuropathy type as per NCV testing



Nerve Conduction Velocity Testing:

All 100 patients under went NCV testing, out of which 82 patients had normal findings, the results are shown in Table 3. MNC studies were done for Median Nerve, Ulnar Nerve, Common Peroneal Nerve, Tibial Nerve of both the limbs, whereas SNC was done for Median Nerve, Ulnar Nerve and Sural Nerve bilaterally. In the MNC finding the conduction velocity of Median Nerve, Ulnar Nerve, Common Peorneal Nerve and Tibial Nerve was more than or equal to 49m/s, 49m/s, 44m/s, and 41 m/s respectively, whereas the amplitude of Median Nerve, Ulnar Nerve, Common Peorneal Nerve and Tibial Nerve was more than or equal to 4 mV, 6 mV, 2 mV, and 4 mV respectively. The distal latency of Median Nerve, Ulnar Nerve, Common Peorneal Nerve and Tibial Nerve was less than or equal to 4.4ms, 6ms, 6.5ms, and 5.8 ms respectively. The SNC finding the conduction velocity of Median Nerve, Ulnar Nerve, and Sural Nerve was more than or equal to 50m/s, 50m/s, and 40m/s respectively, whereas the amplitude of Median Nerve, Ulnar Nerve, and Sural Nerve was more than or equal to 20 µV, 17 µV, and 6 µV, respectively. The distal latency of Median Nerve, Ulnar Nerve, and Sural Nerve was less than or equal to 3.5ms, 3.1ms, and 4.4ms,respectively.

Table 3. NCV finding of patients without diabetic neuropathy

MNCS		**SNCS**	
Nerve	**N=82**	**Nerve**	**N=82**
Median		**Median**	
CMAP amplitude (mv)	≥ 4.0	Amplitude (μV)	≥ 20
Motor Distal Latency (ms)	≤ 4.4	Latency (ms)	≤ 3.5
ConductionVelocity (m/s)	≥ 49	ConductionVelocity (m/s)	≥ 50
Ulnar		**Ulnar**	
CMAP amplitude (mv)	≥ 6	Amplitude (μV)	≥ 17
Motor Distal Latency (ms)	≤ 3.3	Latency (ms)	≤ 3.1
ConductionVelocity (m/s)	≥ 49	ConductionVelocity (m/s)	≥ 50
Common Peroneal		**Sural**	
CMAP amplitude (mv)	≥ 2	Amplitude (μV)	≥ 6
Motor Distal Latency (ms)	≤ 6.5	Latency (ms)	≤ 4.4
ConductionVelocity (m/s)	≥ 44	ConductionVelocity (m/s)	≥ 40
Tibial			
CMAP amplitude (mv)	≥ 4		
Motor Distal-Latency (ms)	≤ 5.8		
ConductionVelocity (m/s)	≥ 41		

Nerve Conduction Velocity Testing of patients with diabetic neuropathy:

The nerve conduction velocity findings of 18 patients with diabetic neuropathy are shown in Table 4 & 5. MNC studies were done for MedianNerve, UlnarNerve, CommonPeroneal Nerve, TibialNerve of both the limbs (Table 4). The mean amplitude, conduction velocity were lower in participants with diabetic neuropathy, whereas mean distal latency was more in participants with diabetic neuropathy as compared to participants without neuropathy. In the MNC findings the mean conduction-velocity of RightMedian Nerve, RightUlnar Nerve, Right CommonPeorneal Nerve and RightTibial Nerve was 43.36±6.27m/s, 46.45±14.80m/s, 39.28±5.37m/s, and 39.84±7.66 m/s respectively, whereas the mean amplitude of RightMedian Nerve, RightUlnar Nerve, Right CommonPeorneal Nerve and RightTibial Nerve was 2.63±1.18 mV, 2.06±2.17 mV, 1.32±0.84 mV, and 2.98±3.37 mV respectively. The distal latency of RightMedian Nerve, RightUlnar Nerve, Right CommonPeorneal Nerve and RightTibial Nerve was 10.48±4.22ms, 8.35±3.29ms, 14.76±3.43ms, and 13.72±0.88ms respectively. The mean conduction-velocity of LeftMedian Nerve, LeftUlnar Nerve, Left CommonPeorneal Nerve and LeftTibial Nerve was 44.75±9.23m/s, 39.41±25.59m/s, 38.52±4.17m/s, and 38.31±5.98 m/s respectively, whereas the mean amplitude of LeftMedian Nerve, LeftUlnar Nerve, Left CommonPeorneal Nerve and LeftTibial Nerve was 3.34±2.14 mV, 3.72±4.38 mV, 1.24±0.39 mV, and 2.11±1.19 mV respectively. The distal latency of LeftMedian Nerve, LeftUlnar Nerve, Left CommonPeorneal Nerve and LeftTibial Nerve was 9.52±5.41ms, 11.68±6.79ms, 13.95±0.53ms, and 16.98±2.88ms respectively.

Table 4. Motor Nerve Conduction findings in Diabetic Neuropathy patients (n=18)

Nerve	**CMAP Amplitude (Mean±SD) (mV)**	**Motor Distal Latency (Mean±SD) (ms)**	**Conduction Velocity (Mean±SD) (m/s)**
Left Median	3.34±2.14	9.52±5.41	44.75±9.23
Right Median	2.63±1.18	10.48±4.22	43.36±6.27
Left Ulnar	3.72±4.38	11.68±6.79	39.41±25.59
Right Ulnar	2.06±2.17	8.35±3.29	46.45±14.80
Left Common Peroneal	1.24±0.39	13.95±0.53	38.52±4.17
Right Common Peroneal	1.32±0.84	14.76±3.43	39.28±5.37
Left Tibial	2.11±1.19	16.98±2.88	38.31±5.98
Right Tibial	2.98±3.37	13.72±0.88	39.84±7.66

SNC studies were done for Median Nerve, Ulnar Nerve, and Sural of both the limbs (Table 5). The mean amplitude, conduction velocities were lower in participants with diabetic neuropathy, whereas mean distal latency was more in participants with diabetic neuropathy as compared to participants without neuropathy. In the SNC finding the mean conduction-velocity of RightMedian Nerve, RightUlnar Nerve, and RightSural Nerve was 33.97±7.66m/s, 43.52±7.87m/s, and 35.55±4.44 m/s respectively, whereas the mean amplitude of RightMedian Nerve, RightUlnar Nerve, and RightSural Nerve was 17.91±3.98 µV, 14.10±8.92 µV, and 4.69±1.38 µV respectively. The distal latency of RightMedian Nerve, RightUlnar Nerve, and RightSural Nerve was 3.70±0.41ms, 4.05±0.62ms, and 7.14±1.98ms respectively. The mean conduction velocity of LeftMedian Nerve, LeftUlnar Nerve, and LeftSural Nerve was 33.12±7.05m/s, 42.40±1.77m/s, and 32.59±3.63 m/s respectively, whereas the mean amplitude of LeftMedian Nerve, LeftUlnar Nerve, and LeftSural Nerve was 17.53±5.14 µV, 12.47±2.89 µV, and 4.77±0.67 µV respectively. The distal latency of LeftMedian Nerve, LeftUlnar Nerve, and LeftSural Nerve was 3.93±1.24ms, 3.70±0.20 ms, and 6.26±1.05ms respectively.

Table 5. Sensory Nerve Conduction findings in Diabetic Neuropathy patients (n=18)

Nerve	**Amplitude (Mean±SD) (µV)**	**Motor Distal Latency (Mean±SD) (ms)**	**Conduction Velocity (Mean±SD) (m/s)**
Left Median	17.53±5.14	3.93±1.24	33.12±7.05
Right Median	17.91±3.98	3.70±0.41	33.97±5.70
Left Ulnar	12.47±2.89	3.70±0.20	42.40±1.77
Right Ulnar	14.10±8.92	4.05±0.62	43.52±7.87
Left Sural	4.77±0.67	6.26±1.05	32.59±3.63
Right Sural	4.69±1.38	7.14±1.98	35.55±4.44

Correlation:

Estimates of correlation using the Pearson correlation coefficients for glycosylated hemoglobin with various parameters were calculated for all patients. Glycosylated hemoglobin was correlated with age, weight, fasting plasma glucose, 2-hours plasma glucose, diabetes neuropathy index and diabetes neuropathy score for all the patients is shown in Tables 6 and 7. The correlation of glycosylated hemoglobin in patients (n=82) without diabetic neuropathy is shown in Table 6. No significant ($p>0.05$) correlation for glycosylated hemoglobin with age as well as weight with the correlation coefficient of 0.23 and 0.20, respectively. Though glycosylated hemoglobin had statistically significant ($p<0.05$) correlation with FPG and 2-hPG with a correlation coefficient of 0.95 and 0.78 respectively. Glycosylated hemoglobin was also statistically significantly correlated with the DNI and DNS with a correlation coefficient of -0.40 and -0.40 respectively

Table 6.Correlation of glycosylated hemoglobin in patients without diabetic neuropathy (n=82)

Parameter	**r value**	**p value**
Age	0.23	0.06
Weight	0.20	0.08
Fasting plasma glucose	0.95	<0.05*
2-hour plasma glucose	0.78	<0.05*
Diabetic neuropathy index	-0.40	<0.05*
Diabetic neuropathy score	-0.40	<0.05*
*p<0.05 hence statistically significant		

The correlation for glycosylated hemoglobin in patients (n=18) with diabetic neuropathy is shown in Table 7. There was no significant ($p>0.05$) correlation for glycosylated hemoglobin with age as well as weight with the correlation coefficient of 0.43 and 0.34, respectively. Though glycosylated hemoglobin had statistically significant ($p<0.05$) correlation with FPG and 2-hPG with a correlation coefficient of 0.96 and 0.93 respectively. Glycosylated hemoglobin was not statistically significantly correlated with the DNI and DNS with a correlation coefficient of 0.12 and -0.26 respectively

Table 7.Correlation of glycosylated hemoglobin in patients with diabetic neuropathy (n=18)

Parameter	**r value**	**p value**
Age	0.43	0.07
Weight	0.34	0.17
Fasting plasma glucose	0.96	<0.05*
2-hour plasma glucose	0.93	<0.05*
Diabetic neuropathy index	0.12	0.16
Diabetic neuropathy score	-0.26	0.30
*p<0.05 hence statistically significant		

The correlation of glycosylated hemoglobin in patients (n=18) with diabetic neuropathy with NCV values is shown in Table 8 and 9. Table 8 demonstrates the correlation of amplitude, conduction velocity and distal latency of glycosylated hemoglobin with motor nerve conduction studies. No significant ($p>0.05$) correlation for glycosylated hemoglobin with amplitude of left median and right median nerve with the correlation coefficient of 0.27 and 0.14, respectively. Similarly, no significant ($p>0.05$) correlation for glycosylated hemoglobin with amplitude of right ulnar nerve with the correlation coefficient of 0.59. There was also no significant ($p>0.05$) correlation for glycosylated hemoglobin with amplitude of left commonperoneal and right commonperoneal nerve with the correlation coefficient of 0.10 and -0.54, respectively. The glycosylated hemoglobin had no statistically significant ($p>0.05$) correlation for amplitude of left tibial and right tibial nerve with the correlation coefficient of -0.25 and 0.58, respectively. Similarly, glycosylated hemoglobin was not statistically significantly correlated with both the conduction velocity and distal latency of all the nerves in the motor nerve conduction studies as shown in table 8. The correlation coefficient of Left Ulnar Nerve was not calculated as there were only 2 patients affected.

Table 8.Correlation of glycosylated hemoglobin in patients - MNCS (n=18)

Nerves	Parameter	r value	p value
Left Median Nerve	Amplitude	0.27	0.57
	Conduction Velocity	-0.58	0.18
	Distal Latency	-0.42	0.35
Right Median Nerve	Amplitude	0.14	0.69
	Conduction Velocity	0.40	0.22
	Distal Latency	-0.40	0.22
Right Ulnar Nerve	Amplitude	0.59	0.22
	Conduction Velocity	0.10	0.86
	Distal Latency	0.23	0.66
Left Common Peroneal Nerve	Amplitude	0.10	0.79
	Conduction Velocity	0.08	0.84
	Distal Latency	0.33	0.35
Right Common Peroneal Nerve	Amplitude	-0.54	0.13
	Conduction Velocity	0.04	0.91
	Distal Latency	0.49	0.18
Left Tibial Nerve	Amplitude	-0.25	0.49
	Conduction Velocity	-0.04	0.92
	Distal Latency	0.20	0.58
Right Tibial Nerve	Amplitude	0.58	0.17
	Conduction Velocity	0.75	0.051
	Distal Latency	-0.69	0.09

Table 9 demonstrates the correlation of amplitude, conduction velocity and distal latency of glycosylated hemoglobin with sensory nerve conduction studies. No significant ($p>0.05$) correlation for glycosylated hemoglobin with amplitude of left median and right median nerve with the correlation coefficient of 0.44 and -0.09, respectively. Similarly, no significant ($p>0.05$) correlation for glycosylated hemoglobin with amplitude of left ulnar and right ulnar nerve with the correlation coefficient of -0.24 and -0.17 respectively. There's also no significant ($p>0.05$) correlation for glycosylated hemoglobin with amplitude of left sural with the correlation coefficient of 0.24. The glycosylated hemoglobin had significant ($p<0.05$) correlation for amplitude of right sural nerve with the correlation coefficient of -0.82. Similarly, glycosylated hemoglobin was not statistically significantly correlated with both the conduction velocity and distal latency of all the nerves in the sensory nerve conduction studies as shown in table 9.

Table 9.Correlation of glycosylated hemoglobin in patients - SNCS (n=18)

Nerves	Parameter	r value	p value
Left Median Nerve	Amplitude	0.44	0.27
	Conduction Velocity	-0.35	0.39
	Distal Latency	0.51	0.20
Right Median Nerve	Amplitude	-0.09	0.82
	Conduction Velocity	0.08	0.83
	Distal Latency	0.47	0.21
Left Ulnar Nerve	Amplitude	-0.25	0.84
	Conduction Velocity	-0.25	0.84
	Distal Latency	-0.97	0.16
Right Ulnar Nerve	Amplitude	-0.17	0.78
	Conduction Velocity	-0.58	0.31
	Distal Latency	0.43	0.46
Left Surall Nerve	Amplitude	0.24	0.65
	Conduction Velocity	0.17	0.75
	Distal Latency	0.57	0.24
Right Sural Nerve	Amplitude	-0.82	<0.05*
	Conduction Velocity	-0.19	0.72
	Distal Latency	-0.24	0.64
*p<0.05 hence statistically significant			

DISCUSSION

Diabetic neuropathies are one of most common cause of neuropathies (98) which affects different parts of nervous system and present with varied clinical manifestation (99). Diabetic neuropathy is a disease of exclusion (99) and up to half of patients with type 2 diabetes mellitus develop some degree of peripheral neuropathy (98) so as to implement foot care to prevent injury to insensitive foot (99). Peripheral neuropathy in diabetes mellitus is due to metabolic and microvessel alterations from chronic hypergylcemia manifesting in a symmetric, length-dependent sensorimotor polyneuropathy pattern and associated cardiovascular risk factors (100). Though peripheral neuropathy is association with the duration of disease as well as poor glycemic control, but evidences suggest an estimated prevalence of neuropathy varying from 11.5 to 48% in new onset patients of diabetes mellitus in various population based studies (101, 102). There have been contradictory studies on the frequentness of peripheral neuropathy, as shown recently in British and German database with 2.4-5.7% newly diagnosed diabetic patients suffering from peripheral neuropathy (103). In an effort to find out neuropathy in patients diagnosed with diabetes mellitus as these patients might have clinical or subclinical neuropathy we conducted this study for evaluation of diabetic neuropathy changes in first time diagnosed patients of T2DM.

Our study showed that 18% of patients had signs of peripheral neuropathy as shown by NCV testing at the time of diagnosis of type 2 diabetes mellitus, though, 23% patients had low scores in Diabetes Neuropathy Index and Diabetes Neuropathy Score with females being more effected as compared to males. The patients with diabetes neuropathy as compared to the subset of patients without neuropathy had elevated levels of glycosylated haemoglobin, fasting plasma glucose and 2-hour plasma glucose which were statistically significant. These patients also had lower scores on DNI and DNS which was statistically significant. In the MNC studies bilateral

common peroneal nerve and left tibial nerve was involved in these patients (11 out of 18), whereas, in SNC studies bilateral sural nerve was effected in 13 patients. The most common pattern of neuropathy seen in these participants was sensorimotor involvement with demyelinating pattern of neuropathy. The NCV studies showed reduced distal latency and prolonged amplitude as well as conduction velocity in patients with diabetic neuropathy. There was a positive correlation between glycosylated haemoglobin and fasting plasma glucose, 2-hour plasma glucose, DNI as well as DNS in participants without neuropathy. Whereas in patients with neuropathy only FPG and 2-hPG showed a correlation for glycosylated haemoglobin. There was no correlation of glycosylated haemoglobin with amplitude, conduction velocity and distal latency in all the patients except for patients with diabetic neuropathy where correlation existed between amplitude of right sural nerve (SNCS) with glycosylated haemoglobin.

A study done by Mao, et.al. to evaluate the asymptomatic patients with neuropathy in patients with T2DM in China, enrolled patients who underwent sudoscan of both hand and feet for electrochemical skin conductance. This study demonstrated the patients who were asymptomatic for neuropathy as well as patients with neuropathy had abnormal rate of sudoscan with age and feet conductance level independently associated with neuropathy. The study also demonstrated that patients with neuropathy belonged to higher age had prolonged duration of disease and higher levels for glycosylated haemoglobin. The results of our study are to an extent similar to this study as in our study also patients with diabetic neuropathy were of higher age and had higher plasma glucose levels as well as higher glycosylated haemoglobin levels. Though at the same time our study differs from this study as the patients included in the study were already known to be suffering from diabetes mellitus and sudoscan was used for evaluation of these

patients for asymptomatic neuropathy, whereas in our study we conducted NCV testing of all the patients diagnosed with diabetes mellitus (91).

One more study done in Western India, studied the association of duration of illness with reaction time of auditory and visual system, the patients were divided into two groups based on the duration of disease as more/less than five years, the study demonstrated that participants with longer duration of disease had delayed reaction time. The study also demonstrated delayed reaction time could serve as a indicator for early nerve damage and could serve as a routine clinical screening procedure for neuropathy. Our study also used DNI and DNS are parameter to assess all the patients diagnosed with DM. Our study showed higher number of participants had abnormal scores for both DNI and DNS which when subjected to NCV testing showed that 18 out of 23 patients had neuropathies. Though, our study limited itself to first-time diagnosed patients of T2DM (10).

One study done by Dolu, et.al. used bimodal evoked potentials for evaluating central neuropathies in type 2 diabetes mellitus where in 51 patients with type 2 diabetes mellitus were enrolled in the study suggested prolonged latencies of median and tibial somatosensory, brainstem auditory evoked potential along with visual evoked potential as well as bilateral cortical latency thereby showing central neuropathies. These findings correlated with duration of disease as well as age of patients. The NCV results in our study were abnormal in patients with diabetic neuropathy with prolonged distal latencies, reduced amplitude and reduced conduction velocity as compared to patients without diabetic neuropathy though they did not correlate with glycosylated haemoglobin levels (11).

Another study done by Sung, et.al. tried to find out the development of diabetic neuropathy by investigating the sensory and motor nerve excitability of asymptomatic participants with type 2

diabetes mellitus. The study showed that axonal dysfunction occurred earlier in sensory axons as compared to motor axons and in a different pattern. The study also showed that even in asymptomatic patients there was abnormality in the sensory nerve excitability, the participants were of mean age group of 62years and had elevated glycosylated haemoglobin levels. The results of our study are different as most of the newly diagnosed patients had sensorimotor pattern of neuropathy and the patients with diabetic neuropathy had elevated levels of glycosylated haemoglobin (92).

One more study done in Romania which evaluated the role of neuropathy with impairment in balance and risk of fall in participants showed the prevalence of diabetic neuropathy of 28.8% which was associated with increased age, body mass index and increased depression severity. These patients had higher levels of glycosylated haemoglobin associated with impaired balance with increased risks of falls. Our study is somewhat similar to this study as in our study also the patients with diabetic neuropathy belonged to higher age groups and had statistically significant levels of glycosylated haemoglobin levels as compared to patients without diabetic neuropathy. Our study is different from this study as only 18% patients enrolled in our study had diabetic neuropathy and all the participants recruited in the study were newly diagnosed prticipants. Moreover, we wanted to find out presence of diabetic neuropathy in newly diagnosed patients whereas in this study, they also wanted to evaluated the risk of fall in these patients (4).

Another study done in Korea to look into the risk factors for neuropathy as well as to study the correlation with severity and gylcosylated haemoglobin level showed that participants with diabetic neuropathy had greater levels of glycosylated haemoglobin as well as belonged to higher age group. The study also demonstrated the positive correlation of age and glycosylated haemoglobin levels with higher propensity of motor and sensory nerve involvement of nerves of

lower limbs. The study also highlighted that duration of the disease was also one factor that had to be taken into consideration. The results of our study are also in similar lines as in our study also the patients with diabetic neuropathy had higher levels of glycosylated haemoglobin levels and plasma glucose levels. Our study also showed more propensity of involvement of lower limbs as compared to upper limbs. Our study differs from this study as in our study we laid emphasis on finding out newly diagnosed participants of T2DM afflicted with neuropathy (2).

A study done by Mojaddidi, et.al. for early diagnosi of impaired nerve functions, along with risk factor associated with neuropathy found that the mean duration of patients with diabetes of 14 years was related with development of neuropathy. Along with the duration of disease, higher age group, abnormal levels of glycosylated haemoglobin levels as well as abnormal plasma glucose level were associated with diabetes neuropathy. The study also showed a slight higher prevalence of neuropathy in females as compared to males. Our study is similar to the study as more number of females were affected, a higher age group was affected and the patients also had abnormal plasma glucose levels. Our study only studied the newly diagnosed patients and this study showed a positive correlation of duration of disease with neuropathic changes (6).

A study done by Lee, et.al. – The PROMISE cohort for prevalence of peripheral neuropathy and dysfunction of nerves for patients with higher risk for T2DM with the aid of MNSI and vibration perception threshold showed that prevalence of diabetic neuropathy in newly diagnosed patients with diabetes mellitus was 50%. The average age of the study population was 53 years with patients having neuropathy were older and had higher level of FPG as well as 2-hour plasma glucose. Our study is quite similar to this study as we found that the mean age of participants presenting in our study as 54years almost similar to that in the PROMISE cohort. The study also showed that participants with neuropathy were having a higher mean age and elevated fasting

plasma glucose and 2-hour plasma glucose, which is similar to this study. Our study differed from this study, as in our study we only included patient who were newly diagnosed diabetic patients with 18% cases of diabetic neuropathy, and we did not include the patients who were having normal glycemia or prediabetics. In our study we conducted NCV testing for all the patients as compared to PROMISE cohort where Vibration Perception Threshold was used (93).

Another study was done by Kakrani, et.al. in Western India to study the pattern of neuropathy as well as correlation with NCV studies in participants diagnosed with T2DM enrolled 50 patients. This study showed that in all patients lower limbs were involved with tibial and sural nerve most commonly afflicted. There were also few patients who had isolated involvement of either sensory or motor component of nerves of lower limbs. Our study is similar to this study as lower limbs were more commonly involved, with most commonly nerve affected for motor being peroneal nerve and for sensory being sural nerve in the study. In our study also we had 2 patients with sensory neuropathy and 4 patients with motor neuropathy. Our study is different from this study as we enrolled only those patients in our study who were newly diagnosed cases of type 2 diabetes mellitus as compared to already diagnosed patients with type 2 diabetes mellitus as duration of disease can affect the manifestation (1).

There are few limitations of our study; the sample size of the study was small – as this was a time based study so we could not enrol higher number of patients which could have shown a different result. Secondly, we did not have any intervention in our study, as keeping an intervention for patients with diabetic neuropathy would not have solved the aim of our study. The aim of our study was to evaluate the neuropathy in patients who are newly diagnosed. Thirdly, we did not have a control group, the patients who did not have diabetic neuropathy

served as control for the other group of participants and the purpose of our study was to find out diabetic neuropathy in patients with first time diagnosis of diabetes mellitus.

CONCLUSION

To conclude our study showed that all patients suffering from type 2 diabetes mellitus must be thoroughly examined for signs of neuropathy irrespective of duration of the illness. As many patients with T2DM are often asymptomatic and are diagnosed with the disease after several years of illness. This study demonstrated that 23% of first time diagnosed patients had abnormal clinical examination and when subjected to NCV testing 18% of patients were diagnosed with neuropathy when the disease was diagnosed. Approximately 1-in-5 newly diagnosed patients with T2DM is at increased risk of developing diabetic neuropathy. Females had slightly higher preponderance, and patients with abnormally high levels of glycosylated haemoglobin, plasma glucose levels and lower score on neuropathic scales had higher chance of developing neuropathy. These patients had a positive correlation of glycosylated haemoglobin levels with plasma glucose levels. The NCV findings of these patients showed prolonged latencies, reduced amplitudes and reduced conduction velocity suggestive of neuropathy. The most common presentation of cases with neuropathy was sensorimotor involvement and demyelinating type of neuropathy due to diabetes mellitus. The lower limbs were more commonly affected with involvement of common peroneal nerve, sural nerve and tibial nerve.

SUMMARY

The prevalence of type 2 diabetes mellitus (T2DM)is growing worldwide, and these patients may be without symptoms and present with complications at the first-time of diagnosis. Diabetic neuropathy is most common complication effecting the patients who may present with distal polyneuropathy at the time of diagnosis and also poor glycaemic control. The Diabetic peripheral polyneuropathy affects approximately 1 in every 10 newly diagnosed patients, whereas two third of patients with diabetes mellitus have clinical or subclinical neuropathy. As no treatment for diabetic peripheral neuropathy is available, so it's early detection and prevention assume utmost importance. So we designed this study to evaluatediabetic neuropathy Changes in Newly Diagnosed Patients of T2DM. This observational study was carried out in patients diagnosed with T2DM as per ADA criteria. The study was approved by IEC and consent was taken from all patients. A thorough clinical examination; Nerve conduction velocity testing; evaluation of plasma glucose and glycosylated haemoglobin;and aassessment of neuropathy by using the DNI and DNS was performed on all patients. Our study showed that that 18% of patients had signs of peripheral neuropathy as shown by NCV testing at the time of diagnosis. These patients had elevated levels of glycosylated haemoglobin, FPG and 2-hPG and lesser scores of DNI and DNS which were statistically significant. The most common neuropathy seen in these cases was sensorimotor involvement and demyelinating pattern of neuropathy with more involvement of lower limbs. The NCV studies showed reduced distal latency and prolonged amplitude as well as conduction-velocity in cases with diabetic neuropathy. There was positive correlation between glycosylated haemoglobin and fasting plasma glucose and 2-hour plasma glucose in patients with diabetic neuropathy. To conclude our study showed that approximately 1 in 5 newly diagnosed patients with T2DM and are at risk of developing diabetic neuropathy. Most common

presentation of patients with diabetic neuropathy was sensorimotor involvement and demyelinating type of neuropathy with lower limbs affected more as compared to upper limbs.

REFERENCES

References:

24. Kakrani AL, Gokhale VS, Vohra KV, Chaudhary N. Clinical and Nerve Conduction Study Correlation in Patients of Diabetic Neuropathy. Journal of the Association of Physician of India 2014; 62: 24-7.
25. Lee WJ, Jang S, Lee SH, Lee HS. Correlation between the Severity of Diabetic Peripheral Polyneuropathy and Glycosylated Hemoglobin Levels: A Quantitative Study Ann Rehabil Med 2016; 40: 263-70.
26. Kumar S, Aneja GK, Trivedi A, Atam V, Shankhwar SN, Panwar A, et.al. Correlation of Diabetic Nephropathy and HbA1C in Newly Diagnosed Type 2 Diabetic Patients of Western UP. International Journal of Scientific and Research Publications 2014; 4 (12): 1-4.
27. Timar B, Timar R, Gaiță L, Oancea C, Levai C, Lungeanu D. The Impact of Diabetic Neuropathy on Balance and on the risk of falls in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study. PLoS ONE 2016; 11(4): e0154654. doi:10.1371/journal.pone.0154654
28. Wiggin TD, Sullivan KA, Pop-Busui R, Amato A, Sima AAF, Feldman EL. Elevated Triglycerides Correlate With Progression ofDiabetic Neuropathy. Diabetes 2009; 58: 1634–40.
29. Mojaddidi MA, Aboonq M, AL Nozha OM, Allam A, El-Bab MF. Early Diagnosis of Diabetic Neuropathyin AlmadinahAlmunawwarah. Journal of Taibah University Medical Sciences 2011; 6: 121-31.
30. Bansal V, Kalita J, Misra UK. Diabetic neuropathy. Postgrad Med J 2006; 82: 95–100. doi: 10.1136/pgmj.2005.036137

31. Tomić M, Poljičanin T, Pavlić-Renar I, Metelko Ž. Obesity – A risk factor for Microvascular and Neuropathic Complication in Diabetes? DiabetologiaCroatica 2003; 32: 73-8.
32. Becker MG, Meardon S, Domire ZJ, Kim S, DeVita P. Virtual Time To Contact Is More Strongly Related To Disease Severity Than Sway Excursion In People With Diabetes And Diabetic Neuropathy. Available at url: web: http://www.ecu.edu/cs-hhp/exss/biomechlab.cfm
33. Gupta S, Jain P, Vij V. Correlation of Auditory and Visual Reaction Tiem with duration of Diabetes. World Journal of Pharmaceutical Research 2014; 3: 877-85.
34. Dolu H, Ulas UH, Bolu E, Ozkardes A, Odabasi Z, Ozata M, et.al. Evaluation of central neuropathy in type II diabetes mellitus by multimodal evoked potentials. ActaNeurolBelg 2003; 103: 206-11.
35. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, et.al. Vascular risk factors and diabetic neuropathy.N Engl J Med 2005;352:341–50.
36. Kempler P, Tesfaye S, Chaturvedi N, Stevens LK, Webb DJ, Eaton S, et.al. Autonomic neuropathy is associated with increased cardiovascular risk factors: the EURODIAB IDDM Complications Study. Diabet Med 2002; 19: 900–09.
37. Steinmetz A. Lipid-lowering therapy in patients with type 2 diabetes: thecase for early intervention. Diabetes Metab Res Rev 2008;24:286–93.
38. Dyck PJ, Davies JL, Litchy WJ, O'Brien PC. Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. Neurology 1997; 49: 229-39.

39. Powers AC. Diabetes Mellitus: Diagnosis, Classification and Pathophysiology. In Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison's Principle of Internal Medicine. 19th ed. New York: McGraw-Hill Education; 2015, pp. 2399-2407
40. Diabetes Mellitus. In Innes JA, Maxwell S, editor. Davidson's Essentials of Medicine. 2nd ed. Edinburgh: Elsevier Ltd; 2016, pp 381-411.
41. ICMR Guidelines for management of type 2 diabetes 2018. Available at url: https://medibulletin.com/wp-content/uploads/2018/05/ICMR.diabetesGuidelines.2018.pdf. (Last Accessed on 15th October 2018)
42. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: Prevalence, numerical estimates, and projections. Diab Care 1998; 21(9): 1414-31.
43. International Diabetes Federation. IDF Diabetes Atlas, 7 ed. Brussels, Belgium: International Diabetes Federation, 2015. (Available at url: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/13-diabetes-atlas-seventh-edition.html) (Last Accessed on 15th October, 2018)
44. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: Mechanisms to management. Pharmacol Ther 2008;120:1–34
45. Feldman EL, Stevens MJ, Russell JW, Peltier A, Inzucchi S, Porte JD, et.al. Somatosensory neuropathy. In The Diabetes Mellitus Manual. New York: McGraw-Hill, 2005, p. 366–84
46. Feldman EL. Diabetic neuropathy. Curr Drug Targets 2008;9:1–2

47. Masharani U. Diabetes Mellitus and Hypoglycemia. In Papadakis MA, McPhee SJ, Rabow MW, editors. Current Medical Diagnosis and Treatment. 57th ed. New York: McGraw-Hill Education; 2018, pp. 1222-68.

48. Mota M, Popa SG, Mota E, Mitrea A, Catrinoiu D, Cheta DM, et al. Prevalence of diabetes mellitus and prediabetes in the adult Romanian population: PREDATORR study. J Diabetes 2015; 8 (3): 336-44.

49. Al-Nozha MM, Al-Matouq MA, Al-Mazrou YY, Al-Harthi SS, Arafah MR, Khalil MZ, et.al. Diabetes Mellitus in Saudi Arabia. Saud Med J 2004; 25(11): 1603-10.

50. Alqurashi KA, Aljabri KS, Bokhari SA. Prevalence of diabetes mellitus in a Saudi community. Ann Saudi Med 2011; 31(1): 19-23.

51. Sadikot SM, Nigam A, Das S, et al. The burden of diabetes and impaired glucose tolerance in India using the WHO 1999 criteria: prevalence of diabetes in India study (PODIS). Diabetes Res Clin Pract 2004;66:301–7.

52. Pickup J, Wilham G. Epidemiology of diabetes. In: Guikshank K, ed. Textbook of diabetes. New York: Blackwell Science, 1991.

53. Bajaj M, Banerji MA. Type 2 diabetes in South Asians: a pathophysiologic focus on the Asian Indian epidemic. Curr Diab Rep 2004;4:213–8.

54. Zargar AH, Khan AK, Masoodi SR, Laway BA, Wani AI, Bashir MI, et al. Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in the Kashmir Valley of the Indian subcontinent. Diabetes Res Clin Pract. 2000;47:135–6.

55. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, et al. Diabetes Epidemiology Study Group in India (DESI): High prevalence of diabetes and impaired

glucose tolerance in India: Natioanl urban diabetes survey. Diabetologia. 2001;44:1094–101.

56. Anjana RM, Ali MK, Pradeepa R, Deepa M, Datta M, Unnikrishnan R, et.al. The need for obtaining accurate nationawide estimates of diabetes prevalence in India – Rationale for a national study on diabetes. Indian J Med Res 2011; 133 (4): 369-80.
57. Lagani V, Koumakis L, Chiarugi F, Lakasing E, Tsamardinos I. A systematic review of predictive risk models for diabetes complications based on large scale clinical studies. J Diabetes Complications 2013; 27(4): 407–13.
58. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res 2010; 107(9): 1058-70.
59. Turner R, Cull C, Holman R. United Kingdom Prospective Diabetes Study 17: A 9-year update of a randomized controlled trial on the effect of improved metabolic control of complications in non-insulin dependent diabetes mellitus. Ann Intern Med 1996; 124: 136-45.
60. Lehtinen JM, Uusitupa M, Siitonen O, Pyorala K. Prevalence of neuropathy inn newly diagnosed NIDDM and nondiabetic control subjects. Diabetes 1989; 38: 1307-13.
61. Deli G, Bosnyak E, Pusch G, Komoly S, Feher G. Diabetic neuropathies: diagnosis and management. Neuroendocrinology 2013;98:267-80.
62. Boulton AJ, Malik RA. Diabetic neuropathy. Med Clin North Am 1998; 82(4):909–29.
63. Poncelet AN, Diabetic polyneuropathy risk factors, patterns of presentation, diagnosis and treatment. Geriatrics 2003;58 (6): 16-8, 24-5, 30.
64. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diab Care 2006;29(7): 1518-22.

65. Ashok S, Ramu M, Deepa R, Mohan V. Prevalence of neuropathy in type 2 diabetes patients attending diabetes center in South India. J Assoc Physicians India 2002;50:546–50.
66. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014; 37(Suppl. 1): S81–90.
67. Insulin, Glucagon and Diabetes mellitus. In Hall JE, editor. Guyton and Hall Textbook of Medical Physiology.13th ed. Philadelphia: Elsevier ; 2016, pp 983-99.
68. Powers AC. Diabetes Mellitus: Management and Therapies. In Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison's Principle of Internal Medicine. 19th ed. New York: McGraw-Hill Education; 2015, pp. 2407-22.
69. NSPG. Harmonizing Hemoglobin A1c Testing: A better A1c test means better diabetes care. (Available at url: www.ngsp.org) (Last Accessed 15th October, 2018).
70. Selph S, Dana T, Blazina I, Bougatsos C, Patel H, Chou R. Screening for type 2 diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2015; 162 (11): 765-76.
71. Das S, Swain SK, Tripathy SK. Diabetes Complication in Indian Scenario – An Update. In Gupta P, editors. Medicine Update (Volume 28). New Delhi: Evangel; 2018, pp. 225-37.
72. Complications - Powers AC. Diabetes Mellitus: Complications. In Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison's Principle of Internal Medicine. 19th ed. New York: McGraw-Hill Education; 2015, pp. 2422-30.
73. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crisis in adult patients with diabetes. Diab Care 2009; 32 (7): 1335-43.

74. Bahl VK, Prabhakaran D, Karthikeyan G. Coronary artery disease in Indians. Indian Heart J 2001; 53 (6): 707-13.
75. Mishra TK, Das S, Patnaik UK, Routray SN, Behera M. Relationship of metabolic syndrome with quantum of coronary artery disease in Indian patients with chronic stable angina. Metab Syndr Relat Disord 2004; 2: 187-91.
76. Deepa R, Mohan V, Premanand C, Rajan VS, Karkuzhail K, Velmurugan K, et.al. Accelerated platelet activation in Asian Indians with diabetes and coronary artery disease: The Chennai urban population study (CUPS 13). J Assoc Physicians India 2006; 54: 704-8.
77. Kumar V, Madhu SV, Singh G, Gambhir JK. Post prandial hypertriglyceridemia in patients with type-2 diabetes mellitus with and without macrovascular disease. J Assoc Physicians India 2010; 58: 603-60.
78. Agarwal RP, Ola V, Bishnoi P, Gothwal S, Sirohi P, Agarwal R. Prevalence of micro- and macrovascular complications and their risk factors in type-2 diabetes mellitus. J Assoc Physicians India 2014; 62: 504-8.
79. Chawla R. Pathophysiology of diabetes complications: Indian prespective. In Joshi SB, editors, Medicine Update. The Association of Physicians of India. 2014; 24 (2): 1361-7.
80. Sosale A, Prassana Kumar KM, Sadikot SM, Nigam A, Bajaj S, Zarger AH, et.al. Chronic complications in newly diagnosed patients with type-2 diabetes mellitus in India (CINDI). Indian J Endocr Metab 2014; 18: 355-60.
81. Umamahesh K, Vigneswari A, Surya Thejaswi G, Stayavani K, Viswanathan V. Incidence of cardiovascular disease and associated risk factors among subjects with type-2 diabetes: A 11 year follow up study. Indian Heart J 2014; 66: 5-10.

82. Agarwal AK, Singla S, Singla S, Prevalence of coronary risk factors in type-2 diabetes without manifestation of overt coronary heart disease. J Assoc Physicians India 2009; 57: 135-42.
83. Davies TME, Millns H, Stratton IM, Holman RR, Turner RC. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Propsective Diabetes Study (UKPDS 29). Arch Int Med 1999; 159: 1097-103.
84. Das S, Chakrabarty SK, Patnaik M, Roul L, Mohanty J, Singh SC. The relationship of carotid plaque, intima media thickness (IMT), resistivity index (RI) and pulsatility index (PI) in Asian-Indian patients with acute ischemic srtoke with and without type-2 DM. International Journal of Clinical Medicine 2011; 2: 561-7.
85. Mohan V, Kumar RR, Rani SS, Deepa R. Intimal medial thickness of the carotid artery in South Indian diabetic and non diabetic subjects: The Chennai urban population study (CUPS). Diabetologia 2000; 43: 494-9.
86. Mohan V, Deepa R, Rani SS, Premalatha G. Prevalence of coronary artery disease and its relationship to lipids in a selected population in South India: The Chennai urban population study (CUPS NO 5). J Am Coll Cardiol 2001; 38: 682-7.
87. Sridhar GR. Diabetes in India: Snapshot of a panorama. Curr Sci 2002; 83: 791-2.
88. Padma MV, Bajaj JS. Diabetes and stroke. In Bansal BS, editors. Recent concepts in stroke. Medicine Update. The association of physicians of India: Mumbai 1999. Pp79-95.
89. Premlatha G, Shanthirani S, Deepa R, Markovitz J, Mohan V. Prevalence and risk factors of peripheral vascular disease in a selected South Indian population: The Chennai urban population study (CUPS). Diabetes Care 2000; 23: 1295-300.

90. Eshcol J, Jebarani S, Anjana RM, Mohan V, Pradeepa R. Prevalence, incidence and progression of peripheral arterial disease in Asian Indian type 2 diabetic patients. J Diabetes Complications 2014; 28: 627-31.
91. Hazra DK, Viswanathan V. Pathogenesis of microvascular complications of diabetes. In Chandalia HB, editor. RSSDI Text-book of Diabetes mellitus, 3rd Ed, Jaypee Brothers Medical Publishers 2014. pp. 918-34.
92. Madan R, Gupta B, Saluja S, Kansra UC, Tripathy BK, Guliani BP. Coagulation profile in diabetes and its association with diabetic microvascular complications. J Assoc Physicians India 2010; 58: 481-4.
93. Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V. Prevalence of diabetic retinopathy in urban India: The Chennai urban rural epidemiology study (CURES) eye study-1. Invest Ophthalmol Vis Sci 2005; 46: 2328-33.
94. Rajalakshmi R, Amutha A, Ranjani H, Ali MK, Unnikrishnan R, Anjana RM, et.al. Prevalence and risk factors for diabetic retinopathy in Asian Indians with young onset type-1 and type-2 diabetes. J Diabetes Complications 2014; 28 (3): 291-7.
95. Rema M, Saravanan G, Deepa R, Mohan V. Familial clustering of diabetic retinopathy in South Indian type-2 diabetic patients. Diabet Med 2002; 219: 910-6.
96. Rajapukar M, Dobhi M. Burden of disease: Prevalence and incidence of renal disease in India. Clin Nephrol 2010; 74: 9-12.
97. Chandrakanth MV, Das S, Rout SB, Mohanty R, Singh SC, Pattnaik M, et.al. Study of markers of atherosclerosis including insulin resistance in patients with chronic renal failure. Journal of Diabetes Mellitus 2012; 2 (2): 208-13.

98. Agarwal N, Sengar NS, Jain PK, Khare R. Nephropathy in newly diagnosed type-2 diabetes with special stress on the role of hypertension. J Assoc Physicians India 2011; 59: 145-7.

99. Unnikrishnan RI, Rema M, Pradeepa R, Deepa M, Shanthirani CS, Deepa R, et.al. Prevalence and risk factors of diabetic nephropathy in an urban South Inidan population: The Chennai urban rural epidemiology study (CURES 45). Diabetes Care 2007; 30 (8): 2019-24.

100. Mukhopadhyaya J, Ray S. Cardiac autonomic neuropathy in diabetes. Medicine Update. API. 2004; 14: 35-8.

101. Joshi SR, Saboo B, Vadivale M, Dani SI, Mithal A, Kaul U, et.al. Prevalence of diagnosed and undiagnosed diabetes and hypertension in India: Results from the Screening India's Twin Epidemic (SITE) study. Diabetes Technol Ther 2012; 14 (1): 8-15.

102. Amarpurkar D, Das HS. Chronic liver disease in diabetes mellitus. Tropical Gastroenterology 2002; 23: 3-5.

103. Das S, Singh SP, Parida P, Mallik RN. Non-alcoholic fatty liver disease in subjects with type 2 diabetes mellitus and non diabetics with special reference to insulin resistance and hepatic histopathological changes. Diabetes and Metabolic Syndrome: Clinical Research and Review 2010; 4: 226-9.

104. United Nations, Department of Economic and Social Affairs, Population division. World Population Prospects: The 2008 Revision; 2009. (Available at url: http://www.un.org/esa/population/publications/wpp2008/wpp2008_highlights.pdf) (Last Accessed 15th October, 2018)

105. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, et.al. Diabetes and tuberculosis: The impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health 2007; 7: 234

106. Vishwanathan V, Kumpatla S, Aravindalochanan V, Rajan R, Chinasamy C, Srinivasan R, et.al. Prevalence of diabetes and prediabetes and associated risk factors among tuberculosis patients in India. PLoS One 2012; 7 (7): e41367

107. Sridhar CB, Anjana S, Thomas MJ. Acute Infection. In Tripathy BB, Das AL, Rao PV, Madhu SV, Mohan V, editors. RSSDI Text Book of Diabetes Mellitus, 1st ed, Jaypee Publishers. 2002. Pp471-7.

108. Bhansali A, Chattopadhyaya A, Dash RJ. Mortality in diabetes: A retrospective analysis from a tertiary care hospital in North India. Diabetes Res Clin Pract 2003; 60: 119-24.

109. Mohan V. Epidemiology of complications in diabetes. In Chandalia HB, editor. RSSDI Text Book of Diabetes Mellitus, 3rd Ed. Jaypee Brother Medical Publishers. 2014, pp 169-83.

110. Sahoo R, Gantayat M. Diabetes neuropathy in tropics. In Samal KC, editor. Diabetes in the Indian Science 6 National Congress on Diabtes, Cuttack 1990. Pp. 83-92.

111. Das S. Introduction. In Das S, editor. Low Body Weight Type 2 Diabetes Mellitus Technical Series. Academic Wing of Association of Physician of India , Mumbai. 1999. Pp1-4.

112. Pradeepa R, Rema M, Vignesh J, Deepa M, Deepa R, MohanV. Prevalence and risk factors for diabetic neuropathy in an urban South Indian population: The Chennai urban rural epidemiology study (CURES-55). Diabet Med 2008; 25 (4): 407-12.

113. Baltzis D, Roustit M, Grammatikopoulou MG, Katsaboukas D, Athanasiou V, Iakovou I, et.al. Diabetic peripheral neuropathy as a predictor of asymptomatic myocardial ischemia in type 2 diabetes mellitus: A cross-sectional study. Adv Ther 2016; 33: 1840-7.

114. Mao F, Liu S, Qiao X, Zheng H, Xiong Q, Wen J, et.al. Sudoscan is an effective screening method for aymptomatic diabetic neuropathy in Chinese type 2 diabetes mellitus patients. J Diabetes Investig 2017; 8: 363-8.

115. Sung JY, Tani J, Chang TS, Lin CSY. Uncovering sensory axonal dysfunction in asymptomatic type 2 diabetes neuropathy. PLoS One 2017; 12 (2): e0171223.

116. Lee CC, Perkins BA, Kayaniyil S, Harris SB, Rethakaran R, Gerstein HC, et.al. Peripheral neuropathy and nerve dysfunction in individual at high risk for type 2 diabetes: The PROMISE cohort. Diabetes Care 2015; 38: 793-800.

117. Giard MH, Peronnet F, Auditory-Visual Integration during Multimodal Object Recognition in Humans: A Behavioral and Electrophysiological Study, Journal of cognitive neuroscience. 1999; 11: 473-90.

118. Shenvi D, Balasubramanian P. A comparative study of visual and auditory reaction time in males and females. Ind J PhysiolPharmacol, 1994; 38: 229-231.

119. Jensen, A. Clocking the mind: Mental chronometry and individual differences. Amsterdam: Elsevier, 2006.

120. Meijer JWG, Sonderen EV , Blaauwwiekel EE, et al. Diabetic Neuropathy Examination, A Hierarchical Scoring System To Diagnose Distal Polyneuropathy In Diabetes, Diabetes Care 2000; 23: 750-3.

121. Assessing diabetic peripheral neuropathy in primary care. Available at url: https://bpac.org.nz/bpj/2014/june/diabetic-peripheral-neuropathy.aspx. (Last Accessed 15th October, 2018)

122. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et.al. Diabetic neuropathy: A position statement by the American Diabetes Association. Diabetes Care 2017; 40: 136-54.

123. Petropoulos IN, Javed S, Azmi S, Khan A, Ponirakis G, Malik RA. Diabetic neuropathy and painful diabetic neuropathy in the Middle East and North Africa (MENA) region: Much work needs to be done. J Taibah Univ Med Sc 2016; 11 (4): 284-94.

124. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53

125. Spijkerman AM, Dekker JM, Nijpels G, Adriaanse MC, Kostense PJ, Ruwaard D, et.al. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: the Hoorn screening study. Diabetes Care 2003;26: 2604–8.

126. Kostev K, Jockwig A, Hallwachs A, Rathmann W. Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: a retrospective database analysis in Germany and U.K. Prim Care Diabetes 2014; 8: 250–5.