ORIGINAL RESEARCH PAPER

General Medicine

CORRELATION OF HBA1C, FASTING BLOOD SUGAR AND POST PRANDIAL BLOOD SUGAR, BMI AND DURATION OF DIABETES WITH CLINICAL MANIFESTATIONS OF PERIPHERAL NEUROPATHY AND RETINOPATHY

KEY WORDS: Diabetes; BMI; Diabetic neuropathy; Diabetic Retinopathy; Microvascular complications; Duration of Diabetes.

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ABSTRACT

BACKGROUND: Chronic complications of DM are responsible for the majority of morbidity and mortality associated with the disease. In this study we correlate BMI, FBS, PPBS and HbA1C with diabetic neuropathy and retinopathy using clinical and laboratory techniques.

METHODOLOGY: A Cross Sectional Analytical Study of 100 Type 2 diabetes mellitus patients who attended OPD/IPD at a MEDICAL COLLEGE AND HOSPITAL from October 2014 to September 2016. In this study we used Diabetic Neuropathy examination (DNE) score for detecting Diabetic Neuropathy and Fundoscopy for Diabetic Retinopathy. FBS, PPBS, HbA1C and various routine investigations were done using standard procedures.

RESULTS: Of the 100 participants in this study, 60% were males with mean age group of 56-60. The duration of diabetes ranged from 5 to > 15 years. 40% of the study group had diabetes for a period of 10-15 years, 36% had HBA1c of 8-10, 32% had DNE score > 3 and 22% had fundus picture of diabetic retinopathy. Out of 32 subjects with Diabetic neuropathy 72% had FBS >180. Out of 22 subjects with Diabetic Retinopathy 64% subjects had FBS > 180. In Subjects with BMI > 25, **85%** had DNE $\leq$ 3, and **15** had DNE >3. There is statistically significant correlation between levels of FBS, PPBS and HbA1C with diabetic neuropathy and retinopathy.

CONCLUSION: We can conclude that poor glycaemic control can cause increased risk of development of microvascular complications of diabetes like Diabetic Neuropathy and Retinopathy. Early diagnosis and tight control help in preventing microvascular complications.

INTRODUCTION:

Diabetes mellitus is a group of metabolic disorders that share the phenotype of hyperglycemia. Factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.

With an increasing incidence worldwide, DM is likely to continue to be a leading cause of morbidity and mortality in the future.

The number of people with type2 Diabetes mellitus is increasing rapidly and the latest figures are 387 million people with diabetes globally which is projected to rise to 592 million people in 2035(1). The disease burden due to diabetes is higher in low- and middle-income countries where four out of five people reside now. India, one of the largest countries in the Southeast Asian region, has more than 67 million people with diabetes, and this is expected to increase to 101 million by 2035[1].

Diabetes-related complications can be divided into vascular and nonvascular complications and are similar for type 1 and type 2 DM. The vascular complications of DM are further subdivided into microvascular and macrovascular complications.

Diabetic neuropathies are the most common complications of diabetes affecting up to 50% of older patients with Type2 diabetes. Up to 20% of patients with Type2 diabetes have retinopathy at the time of diagnosis because many were probably diabetic for an extensive period of time before diagnosis [2]. Diabetic nephropathy is the leading cause of ESRD and a leading cause of DM related morbidity and mortality [3].

The high rate of complications could be due to a variety of factors. The present study correlates the level of Fasting blood sugar, Postprandial blood sugar and HbA1C with microvascular complications like peripheral neuropathy and retinopathy and studying the role of duration of diabetes body mass index and Gender with the above complications.

The present study evaluates the need for tight glycaemic control for preventing microvascular complications of diabetes. Early detection and treatment of uncontrolled diabetes plays a significant role in preventing the complications.

Understanding the relation of duration of diabetes with development of complications, highlights the importance of early detection of diabetes. The role of increased body mass index in the development of microvascular complications is also studied here.

MATERIALS AND METHODS

STUDY DESIGN

The study design is Cross Sectional analytical Study.

STUDY SUBJECTS

100 Type 2 diabetes mellitus patients attended OPD/IPD at DR. B.R AMBEDKAR MEDICAL COLLEGE AND HOSPITAL from October 2014 to September 2016.

INCLUSION CRITERIA

- Duration of diabetes >5years
- Onset of type 2 diabetes>35 years of age

EXCLUSION CRITERIA

- Type 1 diabetes mellitus
- Chronic alcoholics
- Anaemia
- Hereditary neuropathy
- Patients with urinary tract infections
- Vitamin B-12 deficiency

TECHNIQUES

In this study the diabetic neuropathy examination (DNE) score is used for assessment of distal symmetrical polyneuropathy.

The Diabetic Neuropathy Examination Score:

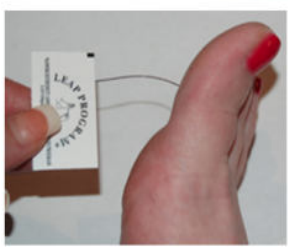
Scoring involves assessing muscle strength, reflex, sensitivity to pin pricks, touch, vibration and joint position by testing only the index finger, right leg and foot. Scoring ranges from 0 to 2, and the maximum score is 16 points where 0 is normal. Score of 1 equals mild/moderate deficit (Muscle strength: Medical Research Council scale 3–4), reflex is decreased but present, sensation is decreased but present. Score of 2 is severely disturbed/absent muscle strength (Medical Research Council scale 0–2), absent reflexes and sensation. A score of >3 indicates presence of polyneuropathy.

Muscle strength is assessed in 1. Quadriceps femoris by extension of the knee and 2. Tibialis anterior by dorsiflexion of the foot. **Reflex** is assessed in Triceps surae. **Sensation** is assessed in the index finger by testing for Sensitivity to pinpricks. **Sensation** is assessed in big toe by testing for Sensitivity to pinpricks, and touch, Vibration perception, Sensitivity to joint position. **Vibration sensation**: Tested bilaterally in patients with eye closed in unsupported dorsum of great toe over the bony prominence of the DIP joint using 128 Hz tuning fork and will be asked to indicate when they can no longer sense the vibration from the vibrating tuning fork. The examiner should be able to feel vibration from a hand held tuning fork for 5 seconds longer on his distal forefinger than a normal subject can at the great toe. If the examiner feels vibration for 10 or more seconds on his or her finger, then vibration is considered decreased. Vibration is scored as 1-present if the examiner senses the vibration on his finger for < 10seconds, 2-reduced if sensed for >=10, 3- absent/ no vibration detection.

Monofilament testing

The 10g monofilament is an objective, simple instrument used in screening the diabetic foot for loss of proprioceptive sensation [4].

Fig:4 Monofilament testing



10-g Semmes-Weinstein monofilament

Using the Monofilament[4]

Sensory examination should be done in a quiet and relaxed setting. First apply the monofilament on the patient's inner wrist so the patient knows what to expect.

The patient must not be able to see if and where the examiner applies the filament. The five sites to be tested on both feet are the pulp of the hallux and 3rd digit, and MPJs 1, 3 and 5.

Apply the monofilament perpendicular to the skin surface.

Apply sufficient force to cause the filament to bend or buckle.

The total duration of the approach, skin contact, and removal of the filament should be approximately 2 seconds.

Apply the filament along the perimeter of and not on an ulcer site, callus, scar or necrotic tissue. Do not allow the filament to slide across the skin or make repetitive contact at the test site.

Press the filament to the skin and ask the patient if they feel the pressure applied (yes/no) and next where they feel the pressure applied (left/right foot).

Loss of Protective Sensation = No Feeling in less than 8 sites.

Encourage the patients during testing.

Direct ophthalmoscopic examination of fundus

Fundus examination was done and results will be classified as normal, non-proliferative and proliferative retinopathy. It was confirmed by a senior ophthalmologist.

RESULTS AND ANALYSIS

Of 100 participants the study cohort had 60males (gender ratio 1:5) 14% of study subjects belong to the age group 40-45 out of which 50% males.

Out of 16% of the study subjects present in 46-50 age group 69% were males and 31% were females In 30% subjects of 51-55year age group, 60% were males and 40% were females.

38% of subjects were there in the 56-60 age group. In the 61-65 years age group 63% were males and 37% were females Our study shows that out of the 32 subjects with features of Diabetic neuropathy 6% of patients with FBS in the range of 80-130, 24% patients with FBS in the range of 130-180 and 66% of patients with FBS >180 had DNE >3. The p-value obtained is <0.001 i.e., the relation between FBS and Diabetic neuropathy was **statistically significant**.

Out of 36 subjects with FBS in the range of 80-130, 2(6%) had fundus picture of NPDR and the rest had normal fundus. Among the 29 subjects with FBS in the range of 130-180, 5(17%) had fundus feature of NPDR and 1(3%) had PDR. Out of 35 patients with FBS>180, 10(29%) had NPDR and 4(11%) had PDR.

It is inferred that out of 22 subjects who had Diabetic Retinopathy, 9% subjects had FBS 80-130. 27 % subjects who had Diabetic Retinopathy had FBS 130-180. 64% subjects had FBS more than 180. Association between FBS and Diabetic Retinopathy is statistically significant with P value being 0.011.

Here in the category of PPBS <180, only **3%** had DNE >3. But in the PPBS range of 180-300, **33%** of patients had DNE >3 and **78%** of patients with PPBS >300 had DNE >3. It was studied that out of 32 subjects with diabetic neuropathy, 3% had PPBS <180, 53% had PPBS 180-300 and 44% had >300. It is found that there is statistically significant correlation between PPBS and Diabetic neuropathy (p value <0.001)

Among the study group with PPBS<180 only 1**(i.e., 3%)** had features of NPDR in fundus and no patients had features of PDR. In the PPBS range of 180-300, **6(11%)** had NPDR and **2(4%)** had PDR. Out of patients with PPBS>300, **10(56%)** had NPDR and **3(16%)** had PDR. It is also studied that out of 22% subjects with diabetic retinopathy 5% had PPBS less than 180, 36% had PPBS 180-300 and 59% had PPBS more than 300. In our study it was observed that 22% of our study subjects had Diabetic retinopathy (17% Non-proliferative Diabetic Retinopathy-NPDR and 5% have Proliferative Diabetic Retinopathy-PDR).

In patients with HbA1C in the range 6-8, only **2 (4%)** subjects had DNE >3. **19 (53%)** of subjects with HbA1C 8-10 had DNE >3. In patients with HbA1C >10, **11(73%)** had DNE >3.

It is also studied that out of 32% subjects who had diabetic neuropathy, 6% were in the range of HbA1C 6-8; 60% had HbA1C 8-10 and 34% had HbA1C>10. The relation between HbA1C and Diabetic neuropathy was found to be statistically significant (p value<0.001)

In subjects with HbA1c in the range 6-8, **one (2%)** had features of NPDR and **no** other subjects in this range had PDR. In subjects with HbA1c in the range 8-10, **7(19%)** had NPDR and 1 **(3%)** had PDR. In subjects with HbA1c of more than 10, **9(60%)** had NPDR and **4(27%)** had PDR. Out of 22 subjects with diabetic retinopathy 5% were in the group of HbA1c 6-8, 36% subjects were in the group of 8-10, and 59% in the group of HbA1C >10. P value obtained was <0.001 which is **statistically significant.**

In our subjects with duration of diabetes with 5-10 years DNE score was more than 3 in **2(8%)** and less than or equal to 3 in **24 (92%).** In the group with duration of diabetes with 10-15 years **32(80%)** had DNE less than or equal to 3, and **8(20%)** had DNE of more than 3. In the group with duration of diabetes more than 15 years **12(35%)** had DNE less than or equal to 3 and **22(65%)** had DNE of more than 3. (Table 1)

Table1: Correlation Of Duration Of Diabetes With Diabetic Neuropathy And Retinopathy

Diabetic Neuropathy					Diabetic Retinopathy				
Years	≤ 3	≥3	Total	P-Value	Normal	NPDR	PDR	Total	P-Value
5-10	24 (92%)	2 (8%)	26	<0.001	25 (96%)	1 (4%)	0	26	0.003
10-15	32 (80%)	8 (20%)	40		34 (85%)	5 (13%)	1 (2%)	40	
>15	12 (35%)	22 (65%)	34		19 (56%)	11 (32%)	4 (12%)	34	
Total	68	32	100		78	17	5	100	

In our study subjects with a duration of diabetes of 5-10 years **1(4%)** had NPDR. In Subjects with a duration of diabetes of 10-15 years **5(13%)** had NPDR and **1(2%)** had PDR. Subjects with duration of more than 15 years **11 (32%)** had NPDR and **4 (12%)** had PDR. (Table 1)

In our subjects with normal BMI 33(65%) had DNE≤3 and 18(35%) had DNE>3. In subjects with Overweight (BMI of 23-24.9) **13(57%)** had DNE of less than or equal to 3 and **10 (43%)** had DNE of more than 3. In Subjects with Obesity (BMI more than 25), **22(85%)** had DNE less than or equal to 3, and **4(15%)** had DNE more than 3. P value is>0.05. So, it is **not statistically significant.) (**Table 2)

Table 2: Correlation Of Body Mass Index(BMI) With Diabetic Neuropathy And Retinopathy

Diabetic Neuropathy					Diabetic Retinopathy				
	≤ 3	≥3	Total	P-Value	Normal	NPDR	PDR	Total	P-Value
Normal	33(65%)	18(35%)	51	0.084	40 (78%)	9 (18%)	2 (4%)	51	0.746
Overweight	13(57%)	10(43%)	23		16 (70%)	5 (22%)	2 (9%)	23	
Obese	22(85%)	4(15%)	26		22(85%)		1(4%)	26	
Total	68	32	100		78	17	5	100	

In our subjects with normal BMI **9(18%)** had NPDR and **2(4%)** had PDR. In the overweight group (BMI -23-24.9), **5(22%)** had NPDR and **2(9%)** had PDR. In subjects with obesity (BMI of more than 25) **3(12%)** had NPDR and **1 (4%)** had PDR. p-value is 0.746 which **is not statistically significant** (Table 2)

DISCUSSION

The microvascular complications of DM results from chronic hyperglycemia. Large randomized clinical trials of individuals with DM have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or delays retinopathy, neuropathy and nephropathy.[5]

The risk of chronic complications of DM increases as a function of duration and degree of hyperglycemia. The plasma glucose measurements (fasting blood sugar-FBS and post pran-dial blood sugar-PPBS) provide a picture of short term glycemic control whereas the HbA1C reflects average glycemic control over the previous 2-3 months [5]

In the present study we used the Diabetic Neuropathy Examination Score (DNE), which was designed by Meijer for the evaluation of Diabetic neuropathy in our study subjects. The DNE is a sensitive, reproducible and well validated hierarchical scoring system that is fast and easy to perform in clinical practice[6]. We had excluded patients with hereditary neuropathy, Vitamin B12 deficiency and chronic alcoholics from our present study.

In the study, it was observed that 32% of our study subjects had a DNE score >3, i.e., presence of Diabetic neuropathy. It was found that there is a statistically significant correlation between fasting blood sugar, Post Prandial blood sugar and HbA1C with diabetic neuropathy (p value<0.001). From our study, it was evident that diabetic neuropathy increases with poor glycaemic control.

Tesfaye et al[7] in the European Diabetes Prospective Complications Study group (EURODIAB) showed that in their study the incidence of diabetic neuropathy as 23.5% and correlated this incidence with HbA1C value. Ramachandran et al [8] in their study on vascular complications in type 2 diabetes in India showed that higher HbA1c increases the risk of microvascular complications.

In our study it is observed that 22% of our study subjects had Diabetic retinopathy (17% Non-proliferative Diabetic Retinopathy-NPDR and 5% had Proliferative Diabetic Retinopathy-PDR). Association between FBS, PPBS, HbA1C and Diabetic Retinopathy was found to be Statistically significant From this study, we have inferred that Diabetic Retinopathy increases with poor glycaemic control and with prolonged duration of diabetes mellitus.

The prevalence of diabetic retinopathy was 29.6% in the study by Fredrick T et al [9] in a primary health centre based cross sectional survey in Tamilnadu. Gadkari SS[10] et al conducted a cross sectional study of diabetic patients under the initiative of All India Ophthalmological Society found out the prevalance of diabetic retinopathy as 21.7%. This result is similar to the prevalence of Diabetic Retinopathy in our study.

DCCT studies[5] showed strong relationships between the risks of developing these complications and glycemic exposure over time. Confirming the DCCT data the UKPDS showed a continuous relationship between the risk of microvascular complications and glycemia. For every percentage point decrease in HbA1c there was a 35% reduction in the risk of microvascular complications [5].

We have correlated Diabetic neuropathy and retinopathy with the duration of diabetes. The relation between diabetic microvascular complications and duration of diabetes was found to be statistically significant Zhaolan Liy[11] et al showed that after adjusting for age, the overall prevalence of diabetic complications significantly increased with disease duration.

Hence, the risk of chronic complications increases as a function of the duration and degree of hyperglycemia. Since type 2 DM often has a long asymptomatic period of

hyperglycemia, many individuals with type2 DM have complications at the time of diagnosis. The findings of DCCT, UKPDS and Kumomoto study strongly support. The idea that chronic hyperglycemia plays a causative role in the pathogenesis of diabetic microvascular complications [5] Holman et al[12] concluded that tight control of diabetes retarded or reversed the progression of the neuropathy

We have correlated the microvascular complications of diabetes with risk factors like gender and BMI and found to be statistically non significant.

But in a cohort study conducted by Tanaha S[13] et al in Japan , it was found that past obesity as well as current obesity were associated with increased risks of microvascular complications. Furthermore, there may be other factors influencing diabetic microvascular complications and obesity which was not taken into consideration in the present study. It may be responsible for this disparity.

In the present study we used Diabetic Neuropathy examination (DNE)score by Meijer for detecting Diabetic Neuropathy and Fundoscopy for Diabetic Retinopathy

These tests were easy to perform, cost effective, bedside tests and have given results correlating incidence of microvascular complications with levels of FBS, PPBS, HbA1C and with duration of diabetes similar as previous studies[10,15-18]

CONCLUSION AND SUMMARY

There is a statistically significant association between FBS, PPBS, HbA1C with diabetic neuropathy and retinopathy, however BMI doesn't have any significant association with development of microvascular complications. Despite BMI not having an effect, ***early diagnosis and tight glycemic control can still prevent or delay microvascular complications***.

DECLARATIONS:

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Conflict of Interest: Nil
Ethical Approval: Approved

REFERENCES

1. International Diabetic Federation, IDF- Diabetic Atlas Update Poster, 6th Edition
2. Rajeev Chawla,K.K. Pareek, Gurpreet S Wander, Progress in medicine 2016, medicine update 2016,9-10
3. Maxine A. Papadakis, Stephen J.Mc Phee, Rabow, Diabetes Mellitus and Hypoglycaemia, Current Medical Diagnosis and Treatment: 1218, 1219
4. Mayfield JA, Sugarman JR: The use of the Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in persons with diabetes. *J Fam Pract* **49**(Suppl. 11):S17–S29, 2002
5. Longo, Fauci, Kasper, Hauser, Jameson, Loscalzo; Harrison Principles of Internal Medicine 18TH Edition; Page 2980, 2981
6. Meijer JW, et al. Diabetic neuropathy examination: a hierarchical scoring system to diagnose distal polyneuropathy in diabetes.Diabetes Care. 2000
7. TesfayeS, ChaturvediN, Eaton SE, WardJD et al, EURODIAB, prospective complication study group, N Engl J Med 2005 jan 27,362(4):341-50
8. RamachandranA, SnehalathaC, SatyavaniK, Latha E et al journal of associations of physicians of india date dec, 1999 479(12) 1152-6. J Exp Med. 200861)
9. Fredrick T, Kaur P, Murthekar MV Et al National Med J India, 2016, jan –Feb, 29 (1): 9-13
10. Gadkari SS, MaskatiQB, Nayak et al, Indian J Ophthalmol, 2016 Jan64(1), 38-44
11. Zhaolan Liu et al diabetic complications and disease duration. J Exp Med. 2008
12. Holmon. R.R. S. Turner. R., diabetes. "The quest for normoglycemia Lancet. 1976;1:469
13. Tanaka S et al. J Diabetes Complication 2016, Maximum BMI and Microvascular complication in a cohort of Japanese patients with Type 2 Diabetes
14. Meijer JW, et al. Diabetic neuropathy examination: a hierarchical scoring system to diagnose distal polyneuropathy in diabetes.Diabetes Care. 2000
15. Spooren PF1, Lekkerkerker JF, Vermes I.Micral-Test: a qualitative dipstick test for micro-albuminuria. Diabetes Res Clin Pract. 1992 Nov;18(2):83-7.
16. Leong SO, et al, the use of semiquantitative urine strip test (micral test) for microalbuminuria screening in patients with diabetes mellitus, Singapore Med J, 1998
17. WuHY,etal, diagnostic performance of random urine samples using albumin concentration vs ratio of albumin to creatinine for microalbumin screening in patients with diabetes- meta analysis, JAMA Intern Med. 2014