Fasting Plasma Glucose and Glycated Hemoglobin in the Prediction of Diabetic Retinopathy in a Rural Population

*Gnaneswaran.S[1], Kuberan.D[2], Vinodhini.V.M[3], Swamy Raj. S.V[1], Ebenezer William.W[3], Kumar.J.S[4]

[1]Department of Ophthalmology, SRM Medical College Hospital & Research Centre, Tamilnadu, India.
[2]Department of Community Medicine, SRM Medical College Hospital & Research Centre, Tamilnadu, India.
[3]Department of Biochemistry, SRM Medical College Hospital & Research Centre,
Tamilnadu, India.
[4]Department of Internal Medicine, SRM Medical College Hospital & Research Centre,
Tamilnadu, India

ABSTRACT

The presence of Diabetic Retinopathy is the best criterion from which to compare glycemic measures because it is a specific and early clinical complication of diabetes. The aim of this study was to assess the significance of fasting plasma glucose and HbA1c values in predicting retinopathy among Type 2 diabetics. 200 Type 2 diabetic patients were examined for presence of diabetic retinopathy. Out of these patients, 135 were negative for retinopathy (controls) and 65 were positive for retinopathy (cases). Of the study participants, 83% belonged to age group 41- 70 years. 55% of cases and 43% of controls were females. Diabetic Retinopathy was significantly associated with HbA1c values with a cut off of 7.0% between the cases and controls, with a higher HbA1c in cases than controls (chi square value = 14.35, df = 1, p=.000, Odds Ratio=4.46, 95% Confidence interval=1.97-10.106). Fasting plasma glucose (FPG) values with a cut off of 126 mg/dl (7mmol/l) did not show any significant difference in values among the cases and controls.

Key words: Diabetic Retinopathy, fasting plasma glucose, HbA1c

INTRODUCTION

Diabetes Mellitus (DM) is a major health problem with long term micro and macro vascular complications.[1] Diabetic retinopathy is one of the leading causes of blindness in the world that increases the chance of losing the sight about 25 times higher compared to normal individuals.[2]

The presence of diabetic retinopathy is the best criterion from which to compare glycemic measures because it is a specific and early clinical complication of diabetes.[3]

Both the World Health Organization (WHO)[4] and the American Diabetes Association (ADA) [5] use fasting plasma glucose (FPG) values of 7.0mmol/l (126mg/dl), to define diabetes. This criterion is based on an underlying assumption that there exists a clear glycemic threshold that separates persons at high and low risk of diabetic micro vascular complications.[6]

Approximately two decades ago, three pivotal epidemiological studies among Pima Indians,[7] Egyptians,[8] and the NHANES III[9] showed that retinopathy signs were rare below a FPG threshold of 7.0 mmol/l, but their prevalence increased dramatically above it.[9] A key observation was that the FPG cut-off of 7.0mmol/l had high sensitivity and specificity for identifying persons with and without retinopathy. This cut-off was therefore used by the World Health Organization (WHO) and American Diabetes Association (ADA) to diagnose diabetes.[9, 10]

Glycated hemoglobin (HbA1c) is a routinely used marker for long-term glycemic control. In accordance with its function as an indicator for the mean blood glucose level, HbA1c predicts the risk for the development of diabetic complications in diabetic patients.[11]

The amount of glycated hemoglobin (HbA1c) reflects the glycaemic control of a patient during the 6 – 8 weeks period before the blood sample was obtained. The amount of HbA1c correlates well with fasting and postprandial blood glucose levels. At present HbA1c is the best surrogate marker we have for setting goals of treatment.[12]

The level of HbA1c value 7.0% was said to be appropriate for reducing the risk of cardiovascular complications.[13]

HbA1c levels are being considered as an alternative diagnostic tool for diabetic diagnosis.[14] Unlike FPG, HbA1c does not require an overnight fast, is not affected by short-term lifestyle changes, and has less variability within individuals than FPG.[15, 16, 17] Nevertheless, few studies have examined the prevalence of retinopathy across the spectrum of HbA1c levels, which could assist in the designation of ideal HbA1c diagnostic cut points.[7,8]

The Diabetes Complications and Control Trial (DCCT) established glycated hemoglobin (HbA1c) as the gold

Table 1.Showing the age distribution of the participants

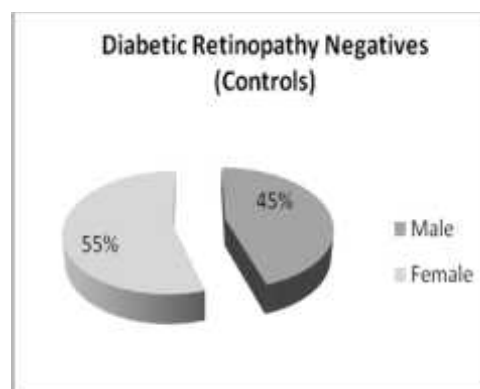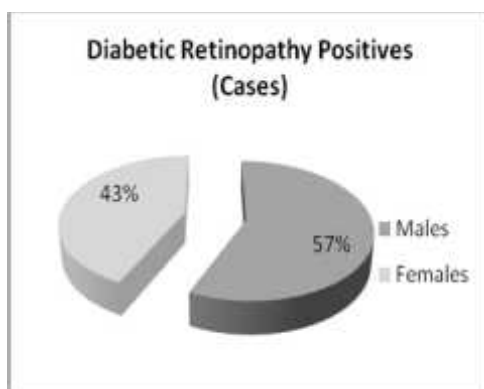| Age group(yrs)	Frequency	Percent (%)
21-30	3	1.5
31-40	24	12.0
41-50	56	28.0
51-60	64	32.0
61-70	46	23.0
71-80	7	3.5

Fig 1.Sex distribution among the cases and controls

standard of glycemic control, with levels 7.0% deemed appropriate for reducing the risk of vascular complications[18]. Australian Diabetes Society, has reported that the patients with DR had significantly higher HbA1c levels[19]

AIM OF THE STUDY

To assess the significance of fasting plasma glucose and HbA1c values in predicting retinopathy among Type 2 diabetics. Few studies have been done in India on this issue. Hence this study becomes imperative to know the trends in Indian population.

MATERIALS AND METHODS

200 Type 2 Diabetic patients who attended the ophthalmic outpatient services of S.R.M. Medical College Hospital and Research Centre for retinopathy screening from June 2012 to September 2012 were included in the study. An informed written consent was obtained from all the participants. The study was approved by the Institutional Ethical Committee. Patients with hypertension, ischemic heart disease, gestational diabetes mellitus, media opacity and previous history of cataract surgery were excluded from the study.

All subjects underwent detailed eye examination with slit lamp and fundus examination with +90D lens and Indirect Ophthalmoscopy. Based on the International Clinical Diabetic Retinopathy Severity Scale adopted by the American Academy of Ophthalmology (AAO) [20] and the International Council of Ophthalmology (ICO) [21], the patients were classified into two groups.
(1)Group A- diabetic retinopathy positive
(2)Group B- diabetic retinopathy negative.
5 ml of venous blood was collected from them after an overnight 12 hour fast and analysis of fasting plasma

glucose and HbA1c were carried out using standard kits in auto analyzer on the same day of sample collection.
Based on fasting plasma glucose, the respondents were classified into two groups.
(1)Group A- <126mg/dl (<7mmol/l)
(2)Group B- 126mg/dl (7mmol/l) [6]
Based on HbA1c, the respondents were classified into two groups.
(1)Group A-Good Glycemic Control 7.0%
(2)Group B- Poor Glycemic Control >7.0% .[22]

STATISTICAL ANALYSIS

All data were analyzed using SPSS 16.0. The mean, standard deviation and the statistical significance of biochemical parameters for the subjects were analyzed by using unpaired student 't' test and $p<0.05$ was accepted as statistically significant.

RESULTS

Among the 200 participants of the study, 65 patients (cases) had Diabetic Retinopathy (DR) and 135 patients (controls) were without Diabetic Retinopathy. 32% were in the age group 51- 60 years, 28% in the age group 41-50 years and 23% in the age group 61-70 years.
The mean age of the cases was 51.43 years (SD ±10.97) and controls was 55.62 years (SD ±11.22). With regard to sex distribution of the participants, 102 (51%) were females and 98 (49%) were males. 74 (55%) among the 135 controls and 28 (43%) among the 65 cases were females.
The mean value of HbA1c was 8.76% while SD was ±2.25 among all the respondents. Among the participants with HbA1c values of 7.0%, there were 52 (86.7%) controls with no DR and 8 (13.3%) cases with DR, whereas in the group with HbA1c values of >7.0%, there

Table 2. Showing statistical values of HbA1c and FPG among cases and controls

Parameters	Value	Diabetic retinopathy Status Negative (N=135)	Positive (N=65)	Statistical Values
HbA1c (%)	7	52	8	Mean=*8.76, SD=± 2.25* X^2=14.35 ,df=1, p=0.000
	>7	83	57	OR=4.46 95% CI=1.97-10.106
Fasting plasma Glucose (mg/dl)	<126	47	27	Mean= *170.8, SD= ± 79.34* X^2=0.851, df=1, p=0.356
	126	88	38	OR=0.751 95% CI=0.409-1.379

were 83 (59.3 %) controls with no DR and 57 (40.7%) cases with DR.

The mean HbA1c values among the cases with DR and the controls without DR were 9.18% and 8.56% respectively. In our study , HbA1c values with a cut off of 7.0% showed significant difference between the cases and controls with a higher HbA1c in cases than controls (chi square value = 14.35, df = 1, p=.000, OR=4.46, 95% CI=1.97-10.106)

The mean value of fasting plasma glucose was 170.8 mg/dl while SD was ±79.3 among all the respondents.

In the FPG group with values of <126 mg/dl (<7mmol/L), there were 47 (63.5%) controls with no DR and 27 (36.5%) cases with DR in comparison to the group 126mg/dl (7mmol/L), there were 88 (69.8%) controls with no DR and 38 (30.2%) cases with DR. The mean FPG values of the group with DR and the group without DR were 168.9mg/dl and 172.03mg/dl respectively. FPG values with a cut off of 126 mg/dl did not show any significant difference in values among the cases and controls.

In this study, out of 140 patients with HbA1c value >7.0%, 57 (41%) were positive for diabetic retinopathy. Among 60 patients with HbA1c 7.0%, only 8 (13%) were positive for retinopathy.

Patients with HbA1c >7.0% were at a higher risk of developing diabetic retinopathy compared to the group with HbA1c 7.0% with odds ratio being 4.46 and 95% CI=1.97-10.106.(Table 2.)

FPG values with a cut off of 126 mg/dl did not show any significant difference in values among the cases and controls with the odds ratio being 0.751 and 95% CI=0.409-1.379.

DISCUSSION

As a glycemic indicator, higher levels of glycated hemoglobin, (HbA1c) was found to be related to higher frequency of retinopathy.[23]

Hyperglycemia, as measured by HbA1c, is considered an important risk factor associated with DR and it was significantly associated with retinopathy in our study. In

our study , HbA1c values with a cut off of 7.0% showed significant difference between cases and controls with a higher HbA1c in cases than controls (chi square value =

14.35, df = 1, p=.000, OR=4.46, 95%CI=1.97-10.106). This is consistent with other studies.[24-36]

Many clinical trial results from the Diabetes Control and Complications Trial (DCCT) [34, 37]and the epidemiological data from the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) have emphasized the strong relationship of glycaemic control with the development and progression of DR.[37-41]

Many studies have clearly demonstrated the benefits of improving glycemic control, by reducing HbA1c concentration, in decreasing the complication rate. The United Kingdom Prospective Diabetes Study Group (UKPDS) reported that patients with intensive glucose control had reduction in retinopathy, a 25 percent drop in the overall micro vascular complications and for every 1 percent decrease in HbA1c, a 35 percent reduction in risk for micro vascular complications was observed. The authors concluded that slowing the progression of retinopathy with intensive control resulted in preservation of sight, decreased morbidity and fewer interventions.[36]

In a study done by Wong TY et al (2008), the authors found that FPG values with a cut off of 126 mg/dl did not show any significant difference in values among the cases and controls. A recent meta-analysis across three different populations found no consistent FPG threshold for retinopathy with the data instead of suggesting a continuous linear relationship and poor performance of the 7.0 mmol/l FPG cut-off point in discriminating the presence of retinopathy. Such findings raise doubts about the underlying premise of a uniform glucose threshold for retinopathy.[42]

Randomized controlled trials and observational studies have shown that glycated haemoglobin or HbA1c is also a good predictor of micro vascular complications,[7,22,43-45] is highly correlated with FPG[46] and does not require measurement in the fasting state.

Good control of hyperglycemia which is indicated by glycated hemoglobin level of <7.0% will help in preventing diabetic retinopathy, a micro vascular complication of diabetes.

CONCLUSION

The findings of this study show that glycaemic control as indicated by HbA1c level is a good predictor of diabetic retinopathy in diabetic patients. Good glycemic control of diabetes with target HbA1c of 7.0% and regular
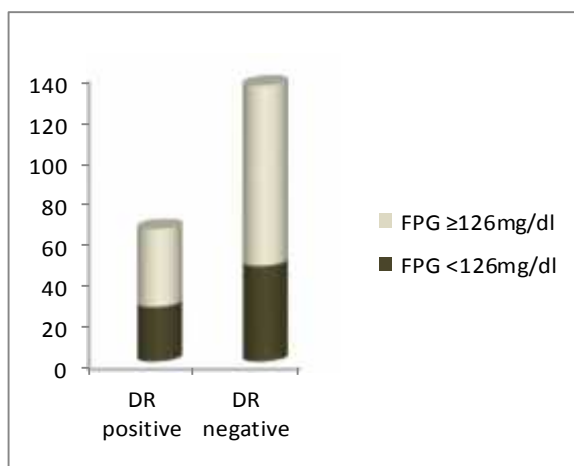
Fig 2.*Distribution of FPG level among the Diabetic retinopathy state*
Ophthalmic screening for diabetic retinopathy changes will reduce morbidity due to diabetic retinopathy.

Fig 3.*Distribution of HbA1c among the Diabetic retinopathy state*

REFERENCES
1. BilginÖzmen*, FeyzullahGüçlü*, SabriyeKafesçiler*,DilekÖzmen**, Zeliha Hekimsoy* The Relationship between Glycosylated Haemoglobin and Diabetic Retinopathy in Patients with Type 2 Diabetes Type 2 Diabetes Mellituslu Olgularda Glikozile Hemoglobin Diabetic Retinopati 2007; 11: 10-5
2. Taylor R, Williams R: Screening for Diabetic Retinopathy: An overview. Diabetic Medicine 1994, 13:946-952
3. McCance DR, Hanson RL, Pettitt DJ, Bennett PH, Hadden DR, Knowler WC .Diagnosing diabetes mellitus: do we need new criteria? Diabetologia1997;40:247–255
4. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. 2007. Available from URL: http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of %20diabetes_new.pdf Lancet. 2008 March 1; 371(9614): 736–743
5. American Diabetes Association. All about diabetes. Available from URL: http://www.diabetes.org/about#diabetes.jsp
6. Arky RA. Doctor, is my sugar normal? N Engl J Med 2005 October 6;353(14):1511–3. [PubMed:16207855]
7. McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, Bennett PH, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes .BMJ 1994 May 21;308(6940):1323 8. [PubMed: 8019217]
8. Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, et al.
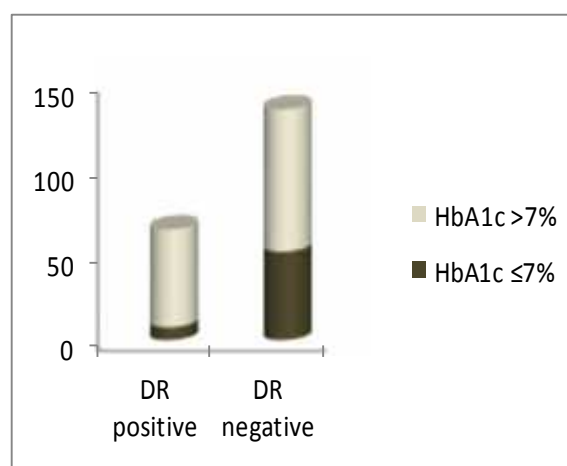9. Comparison off a sting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic

criteria and performance revisited. Diabetes Care 1997 May; 20(5):785–91. [PubMed: 9135943]
10. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997 July; 20(7):1183–97. [PubMed: 9203460]
11. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003 January; 26(Suppl 1):S5–20. [PubMed: 12502614]
12. Glycosylaed Haemoglobin, HbA1c .hptt:// clinlabnavi-gator.com/test interpretations/haemoglobin-a1c.html? (Updated on 18 June 2010).
13. Joslins Diabetes Mellitus 14th Ed Lippincott Williams & Wilkins Chapter 33: General approach to the treatment of diabetes mellitus.
14. Ram Vinod Mahato, "Association between glycaemic control and serum lipid profile in type 2 diabetic patients: Glycated haemoglobin as a dual biomarker," Biomedical Research., 2011, pp. 375-380.
15. Buell C, Kermah D, Davidson MB. Utility of A1C for diabetes screening in the1999–2004 NHANES population. Diabetes Care 2007;30:2233–2235
16. Petersen PH, Jørgensen LG, BrandslundI, De Fine Olivarius N, Stahl M. Consequences of bias and imprecision in measurements of glucose and HbA1c for the diagnosis and prognosis of diabetes mellitus. Scand J Clin Lab Invest Suppl 2005;240:51–60
17. Ollerton RL, Playle R, Ahmed K, DunstanFD, Luzio SD, Owens DR. Day-to-day variability of fasting plasma glucose in newly diagnosed type 2 diabetic subjects. Diabetes Care 1999;22:394–398
18. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. ClinChem2002;48:436–472
19. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A,Goldstein DE (2002) Defining the relationship between plasma glucose and HbA1c :

analysis of glucose profiles and HbA1c in the Diabetes Control and Complications trial. Diabetes Care 25:275–278

20. Retinopathy Sub-committee. Diabetes and Eye: Professional Guidelines. Australian Diabetes Society 1996; 3-30.

21. Rasmieh M. Al-Amer, Yousef Khader. Prevalence of risk factors of diabetic retinopathy among Jordanian patients with type 2 diabetes mellitus. Digital ophthalmology 2008, vol 14, no 2 august 2008.

22. BurakTurgut, FatihCemGulNevinIlhan. Comparison of serum glycosylated hemoglobin levels in patients with diabetic cystoids macular edema with and without serous macular detachment. Indian J Ophthalmol 2010; 58:381-384.

23. American Diabetes Association. Standards of Medical care in Diabetes 2007. Diabetes care. 2007; 30(suppl 1): S4-S40.

24. Dr. Al. Ramadhan a.n. Glycemic control (HbA1c) in patients with diabetic retinopathy Thi-qar medical journal (tqmj): vol(5) no(3):2011(103-108)103

25. Al Bdour M, Al Till M, Abu Khader I. Causes of blindness among adult Jordanian, A hospital-based study .Euro J Ophthalmol. 2002; 12(1): 5-10

26. Al-Till MI, Al-Bdour MD, Ajlouni KM. Prevalence of blindness and visual impairment among Jordanian diabetics. Eur J Ophthalmol. 2005; 15(1): 62-8.

27. Klein R, Klein BEK, Moss SE, et al. The Wisconsin epidemiolgic study of diabetic retinopathy prevalence and risk of diabetic retinopathy when age at diagnosis less than 30 years. Arch Ophthalmol. 1984; 102:520.

28. Sparrow JM, McCleod BK, Smith TDW, Birch M, Rosenthal R. The prevalence of diabetic retinopathy and maculopathy and their risk factors in the non-insulin treated diabetic patients of an English town. Eye.1993; 7:158-63.

29. 28)Kayani H, Rehan N, Ullah N. Frequency of retinopathy among diabetics admitted in teaching hospital of Lahore. Ayub Med Coll Abbott bad. 2003; 15(4):53-6.

30. Aghadoost D, Sadr F. Prevalence and risk factor for diabetic retinopathy in diabetic patients of Kashan Diabetic Center in 2002-2003.Feyz.Spring 2005; 33(13):115-20.

31. Abu El Asrar AM, Al-Rubeaan KA, Al-Amro SA, Kangave D, Moharram OA. Risk factors for diabetic retinopathy among Saudi diabetics.Int Ophthalmol.1999; 22:155-61.

32. El Haddad OA, Saad MK. Prevelance and risk factors for Diabetic Retinopathy among Omani Diabetics. Br J Ophthalmol.1998; 82:901-6.

33. Robyn J. Jonathan E. Alex H, et al. The prevalence of and factors associated with diabetic retinopathy in the Australian Population. Diabetes care. 2003; 26(6):1731-37.

34. Al-Shammari F, Al-Meraghi O, Alfred N, Al-Otaibi S. The prevalence of retinopathy and associated risk factors in type 2 diabetes Mellitus in Al-Naeem area: Kuwait. Middle East journal of family medicine. 2005; 3(2):42-48.

35. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of Diabetes on the development and progression of long-term complications in Insulin-dependent DM. N Engl J Med. 1993; 329:977-86.

36. Segato T, Midena E, Grigoletto F et al. the epedimiology and prevalence of diabetic retinopathy in the Veneto region of North East Italy. Veneto group for diabetic retinopathy. Diabet Med. 1991;8:511-6.

37. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998;317:703-713; erratum 1999;38:29.

38. Diabetes Control and Complications Trial Research Group: Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. Opthalmology1978; 85: p82-106.

39. Nathan DM. The pathophysiology of diabetic complications: how much does the glucose hypothesis explain? Ann Intern Med 1996; 124: 86-9.

40. Early Treatment Diabetic Retinopathy Study Research Group: Photocoagulation for diabetic macular edema: ETDRS Report Number 1.Arch Ophthalmol 1985; 103: 1796-806.

41. Early Treatment Diabetic Retinopathy Study Research Group: Grading diabetic retinopathy from stereoscopic color fundus photographs-An extension of modified Airilie House Classification. ETDRS report number1991; 98(Suppl:5): 786-806.

42. Klein R, Klein B, Moss S. The Wisconsin Epidemiological Study of Diabetic Retinopathy: a review. Diabetes Metab Rev 1992; 5: 1369-77.

43. Wong TY, Liew G, Tapp RJ et al (2008) Relation between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. Lancet 371:736–743

44. Tapp RJ, Zimmet PZ, Harper CA et al (2006) Diagnostic thresholds for diabetes: the association of retinopathy and albuminuria with glycaemia. Diabetes Res Clin Pract 73:315–321

45. Anonymous (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The diabetes control and complications trial research group. N Engl J Med 329:977–986

46. Anonymous (1998) Intensive blood-glucose control with sulphonyl ureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).UK Prospective Diabetes Study (UKPDS) Group. Lancet352:837–853

47. Ito C, Maeda R, Ishida S, Sasaki H, Harada H (2000) Correlation among fasting plasma glucose, two-hour

plasma glucose levels in OGTT and HbA1c   .Diabetes   Res   Clin   Pract   50:225–230