Original Research Article

A gender wise correlation analysis between glycated hemoglobin level and estimated glomerular filtration rate among type 2 diabetes patients

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ABSTRACT

Background: Studies found inconsistent relationship between glycated hemoglobin (HbA$_{1C}$) and estimated glomerular filtration rate (eGFR) in diabetes. Hence, population based studies are warranted. This study was aimed to find out the prevalence of good glycemic control and correlation of HbA1c level with eGFR in male and female type 2 diabetes patients.

Methods: A cross sectional study was designed among type 2 diabetes patients. Medical records of patients' in the inclusion criteria were abstracted for demographic characteristics, HbA1c and serum creatinine level. Patients were grouped into male and female and further sub grouped as with or without good glycemic control (HbA1c ≤ 7%). Data were statistically analyzed.

Results: A total of 465 diabetes patients (186 males and 279 females) were included. Among the total, more female patients were in good glycemic (p=0.0008) control. Gender wise comparison showed that HbA1c level was statistically significant between male and female patients in age groups below 60 years (p<0.05). HbA1c level, at >7%, showed an inverse correlation with eGFR in both male (r=- 0.3208, p=0.0008) and female patients (r =-0.3680, p<0.0001). For every 1% rise in HbA1c, eGFR declined by 10 ml/min/1.73 m^2 in males and 13 ml/min/1.73 m^2 in females.

Conclusions: More female patients were in good glycemic control. HbA$_{1c}$ level above 7% showed an inverse correlation with eGFR in both male and female patients. For every 1% rise in HbA1c, the eGFR declined by 10 ml/min/1.73 m^2 in male and 13 ml/min/1.73 m^2 in female patients.

Keywords: HbA$_1$c, Chronic kidney disease, Diabetes mellitus, Estimated glomerular filtration rate, Nephropathy

INTRODUCTION

Diabetes, a metabolic disease remains one of the leading causes of morbidity, mortality and impaired quality of life worldwide.[1] The prevalence of diabetes in India was alarmingly increasing in the last decade.[2] Despite the new medicines and treatment regimens are available in the management of the disease, advanced monitoring parameters are necessary to prevent the complications of the disease.[3] Among the complications, nephropathy is one of the leading causes for the incidence of end-stage renal disease in diabetes patients. In diabetes, it was found to be progressed silently and in most of the cases Chronic kidney disease (CKD) was found to be undiagnosed mainly in early stages of the disease. Most people exhibit no clinical presentations until the loss of 30-40% of kidney function. Therefore, early detection of kidney dysfunction is crucial to start the treatment and to minimize the progression of damages. Screening for CKD is recommended for high risk groups, such as people with heart disease, diabetes, hypertension and family history of kidney failure.

Direct glomerular filtration rate (GFR) measurement is considered as the most accurate way to detect changes in kidney function. However, measuring the GFR directly is complicated, time consuming, costly and requires experienced personnel. Thus, it is performed mainly in hospitals with advanced facilities and transplant centers. For this reason, the estimated GFR (eGFR) represents the best routinely available measurement for kidney function. National Kidney Foundation recommends creatinine involved CKD-Epidemiology Collaboration (CKD-EPI) equation for calculating eGFR in adults above 19 years and Schwartz equation in children below 18 years.[4,5] Among the various criteria available, CKD is diagnosed when the eGFR is less than 60 ml/min/1.73m^2 for more than three months.[4]

American Diabetes Association suggests self-monitoring of blood glucose and glycated hemoglobin A1c (HbA1c) level as the two parameters to evaluate the good glycemic control in the management of diabetes.[6] HbA1c level provides the mean glycemic control over the preceding 2–3 months.[7] In general, HbA1c $\leq 7\%$ has long been considered as good glycemic control in diabetes patients.[8] High burden of HbA1c and nephropathy are interlinked. Lowering of HbA1c has been associated with a reduction of micro-vascular, macro-vascular and neuropathic complications of diabetes.[9] Dodhia et al demonstrated that HbA1c level was inversely correlated with eGFR in type 2 diabetes patients.[10] But studies were found inconsistent relationship between HbA1c and GFR.[11,12] This may be associated with difference in race and gender which emphasizes the need for population based studies. This study was aimed to find out the prevalence of good glycemic control and correlation of HbA1c with eGFR in type 2 diabetic male and female patients.

METHODS

Study design and population

A descriptive cross sectional study was designed among type 2 diabetes patients, who visited the department of General Medicine, Mary Immaculate Mission hospital, Engandiyur, Thrissur, Kerala between December 2020 and June 2021. Patients (age between 40-85 year) undergoing diabetic treatment in the centre with details such as age, gender, HbA1c and creatinine available in their medical records were included in the study. Patients with acute or CKD, hemoglobinopathies, anemia (autoimmune, iron deficiency and hemolytic anemia), pregnancy, malignancies, liver cirrhosis, uremia, blood transfusion, malignant hypertension or incomplete in medical records were excluded from the study. The study was conducted according to Helsinki declaration, 1975 as revised in 2000.

Sample size calculation

Sample size was calculated after collecting one month data, the prevalence of diabetic patients with good glycemic control was calculated and sample size was calculated at 5% level of significance. Prevalence p=52, q=48, d=relative precision as 10% of p=5.2. The sample size was calculated using the equation n=Zα^2pq/d^2 and found as minimum 369.

Study procedure

Details of patients' who enrolled as per the inclusion criteria were abstracted from their medical records. Data including demographic characteristics such as age, sex, HbA1c (glycemic control) and serum creatinine were collected. HbA1c level determined using high pressure liquid chromatography technique was only selected. Patients were grouped into male and female and further sub grouped into with or without good glycemic control (HbA1c $\leq 7\%$). Estimated GFR was calculated using CKD-EPI equation [4] and its association with the HbA1c in both male and female patients (HbA1c level $\leq 7\%$) was analyzed. The HbA1c levels were also expressed in mean plasma glucose using the equation, mean plasma glucose (MPG) in mg/dl=(HbA1c) 28.7-46.7.[13]

Statistical analysis

All the parametric data were presented as mean ± SD. The data were analyzed using SPSS soft ware package (16v, IBM, CA, USA). Non-parametric data were presented as numbers and Chi square test was used in the analysis. Unpaired t test was used to find the significant difference between 2 quantitative data. While one way ANOVA with post test Bonferroni was used to compare more than 2 groups. Pearson correlation was used to find the correlation between HbA1c and eGFR levels, p<0.05 was considered significant.

RESULTS

A total of 465 diabetic patients (186 males and 279 females) were included in the study. The male to female ratio was 1:1.5 (Figure 1).
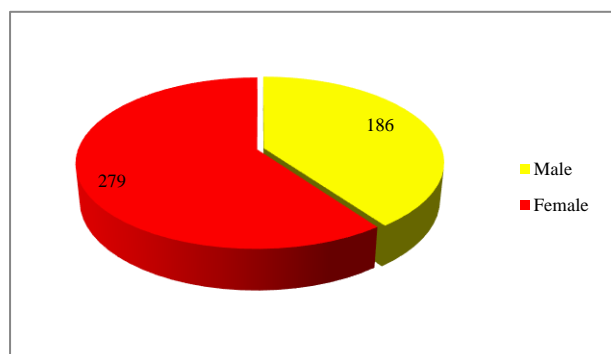

Figure 1: Distribution of gender.

Among the total patients, 221 were without good glycemic control. Among the total patients, 244 (81 males and 163 females) were in good glycemic control (HbA1c ≤7.0%). The gender wise distribution of good glycemic control is given in (Figure 2).
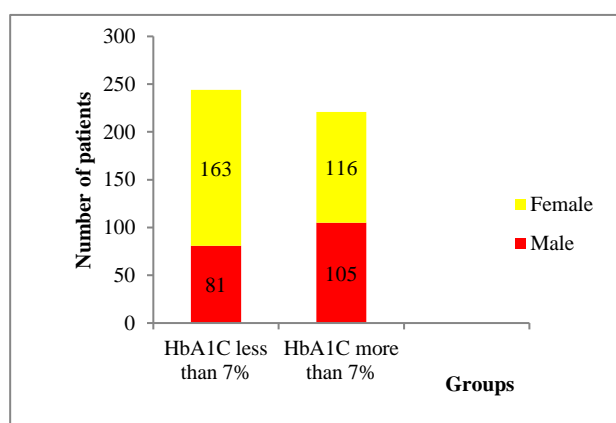

Figure 2: Distribution of patients with good glycemic control (HbA1C level ≤7%) and poor glycemic control (HbA1C level >7%), p=0.0008.

Among the total patients, more female patients (163/244, 66%) were in good glycemic control (HbA1c≤7%) than male patients (81/244, 33%). The difference was found statistically significant (Chi square 9.901, p=0.0008).

Distribution of age and HbA1c among male and female patients is depicted in (Table 1). Among the various age groups studied, HbA1c was found to be increased with increase in the age in female patients. However, significant decrease in HbA1c with increase in age was found in the males patients. Both observations was found statistically insignificant (p>0.05, ANOVA with post test Bonferroni). Gender wise comparison showed HbA1c was statistically significant between male and female patients in the below 60 years age groups.

Table 1: Distribution of age and HbA1c level among male and female patients.

Age (years)	Male		Female		P value
	N	HbA1c level (%)	N	HbA1c level (%)	
40-50	21	8.10±2.85	19	6.47±1.34	0.014
50-60	77	8.04±2.20	100	7.09±2.03	0.001
60-70	41	7.01±2.38	74	7.44±2.61	0.192
70-80	47	7.75±2.30	86	7.33±2.28	0.156

Distribution of age and eGFR among male and female patients was depicted in (Table 2). eGFR in male and female patients was found decreased as the age advances. Comparison of eGFR between various age groups in male showed statistically significant difference from that of 70-80 age group (p<0.05). In the female patients, the eGFR was found to be decreased as the age advances. Gender wise comparison of eGFR in the 50-60 and 60-70 age groups showed a statistically significant difference.

Number of male and female patients with good glycemic control (HbA1c ≤ 7%) is given in (Table 3-4). A negative correlation was found between the HbA1c and eGFR in male patients with HbA1c above 7% (Figure 3). A statistically significant negative correlation was found among male patients with HbA1c above 7% (p<0.008) (Table 3). Similarly, a negative correlation was found between the HbA1c and eGFR in female patients with HbA1c above 7% (Figure 4). Similarly, a statistically significant negative correlation was found among female patients with HbA1c above 7% (p<0.0001) (Table 4). Distribution of HbA1c level and mean plasma glucose (MPG) among male and female patients is given in table 5. MPG was high in the male patients with 40-50 years age and it was high in female patients with 60-70 years age.

DISCUSSION

Results of the study revealed that among the total of 465 type 2 diabetes patients, 52% were with good glycemic control (HbA1c ≤7%) and 48% were with poor glycemic control. Among the total patients, more female patients were in good glycemic control than male patients. Gender wise comparison of HbA1c level showed a significant difference between male and female patients below 60 years of age. eGFR in male and female patients was found decreased as the age advances. CKD-EPI equation is currently recommended to calculate eGFR in adults (age 19-85 years) and can be corrected for age, race and sex. It can also apply across all eGFR range (normal or mildly reduced) and is found superior to MDRD.[4]

The relationship between HbA1c and eGFR was found inconsistent. Therefore, variability of HbA1c on eGFR in type 2 diabetes is still debatable. Previous study by Haque et al found a positive correlation of HbA1c with eGFR.[14]

Table 2: Distribution of age and eGFR level among male and female patients.

Age (years)	Male		Female		P value (unpaired t test)
	N	eGFR (ml/min/1.73 m²)	N	eGFR (ml/min/1.73 m²)	
40-50	21	72.95±29.79	19	63.89±20.07	0.135
50-60	77	64.76±20.83**	100	58.71±22.16***	0.033
60-70	41	64.02±18.29**	74	56.87±20.64*	0.033
70-80	47	48.61±19.34***	86	46.66±19.48**	0.290

Values are mean SD, **p<0.01 and ***p<0.001 (ANOVA with post test Bonferroni) eGFR significantly different from that of 70-80 age group in male, **p<0.01 eGFR of 70-80 age group v/s 40-50 age group, ***p<0.001 eGFR of 50-60 age group v/s that of 70-80 age group and *p<0.05 eGFR of 60-70 age group v/s that of 70-80 age group in female.

Table 3: Correlation between HbA1c level and eGFR among male patients with glycemic control below and above 7%.

| Groups	eGFR (ml/min/1.73 m²)	Pearson correlation (% 95 CI)	P value
HbA1c ≤7%, 5.81±0.93, N=81	71.69±19.15	r=- 0.001477 (-0.2198 to 0.2170), r²=0	0.9896
HbA1c >7%, 9.28±1.91 , N=105	51.31±18.59	r=- 0.3208 (-0.4828 to -0.1375), r²= 0.1029	0.0008

Table 4: Correlation between HbA1c level and eGFR among female patients with glycemic control below and above 7%.

Groups	eGFR (ml/min/1.73 m²)	Pearson correlation (% 95 CI)	P value
HbA1c ≤7%, (5.69±0.81) N=163	63.90±15.94	r =-0.03019; (-0.1880 to 0.1291), r²=0.00911	0.7111
HbA1c >7%, (9.27±1.83) N=116	47.05±17.43	r=-0.3680; (-0.5151 to -0.1998), r²=0.1354	0.0001

Table 5: Distribution of HbA1c level and mean plasma glucose among male and female patients.

Age (Years)	Male		Female	
	HbA1c level (%)	Mean plasma glucose (mg/dl)	HbA1c level (%)	Mean plasma glucose (mg/dl)
40-50	8.10±2.85	185.77±35.09	6.47±1.34	138.98±8.24
50-60	8.04±2.20	184.04±16.44	7.09 ±2.03	156.78±11.56
60-70	7.01±2.38	154.48±21.60	7.44±2.61	166.82±28.20
70-80	7.75±2.30	175.72± 19.31	7.33±2.28	163.67±18.73

Mean plasma glucose (MPG) in mg/dl = (HbA1c) 28.7-46.7
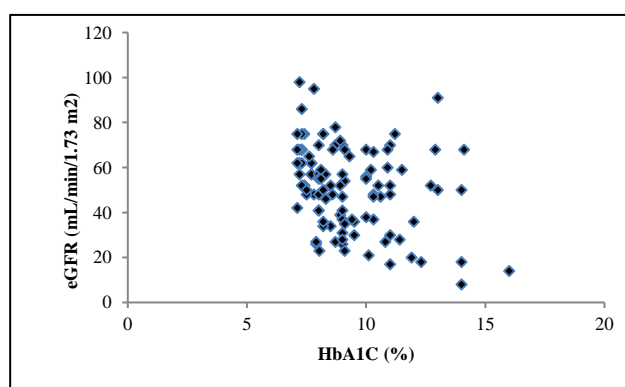
Figure 3: Scatter plot of HbA1c and eGFR among male patients with glycemic control above >7.

But such positive correlation was not statistically significant (p=0.158). The result of this study is consistent to the result of Dodhia et al who demonstrated that glycemic control can affect the progression of kidney disease in type 2 diabetes patients.[15] They found an inverse relation between HbA1c and eGFR. We also found a significant inverse relation in patients with HbA1c above 7%. Cummings et al demonstrated that fluctuation in HbA1c level will be the strongest predictor of change in eGFR, when it is >7% (p=0.02).[16]

According to American diabetes association, HbA1c ≤7% was considered as good glycemic control in subjects with diabetes and is associated with reduced microvascular complications of type 1 and type 2 diabetes.[17] A hospital-based descriptive study in India on 622 newly diagnosed type-2 diabetic patients who received treatment showed only 7.4% in good glycemic control.[18] In our study on a cross section of diabetic patients from the central Kerala population showed 52% (81 males and 163 females) in good glycemic control. Among the total, more female patients were found with good glycemic control. This supports the hypothesis that variation in HbA1c other

than glycemia includes age, gender (sex hormones), ethnic and racial differences.[19]
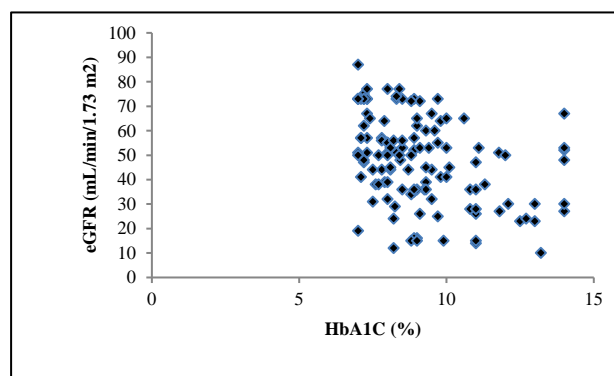

Figure 4: Scatter plot of HbA1c and eGFR among female patients with glycemic control above 7.

Diabetic nephropathy is considered as the major chronic complication in uncontrolled type 1 and type 2 diabetes among others. There is a spectrum of changes in CKD, which progress from hyperfiltration to micro to macro albuminuria and finally renal failure. In early stage of renal disease, classical markers like serum urea and serum creatinine may be normal, but early glomerular changes like matrix materials deposition in the renal mesangium, thickening of basement membrane and nodular deposits with consequent microalbuminuria (MA) occurs. An early pharmacological intervention can reverse the pathological changes at this stage of disease. So, newly detected or known type 2 DM patients need strict monitoring for HbA1c, with simultaneous monitoring for GFR and MA. Monitoring the HbA1c approximately every 4 months (in patients with unstable glycemic control) is recommended to determine whether a patient's metabolic control is maintained within the target range.[20] Most of the previous studies reported that the GFR declines steadily with aging. The decline begins at age 30-40 years and increased after age 65-70 years.[21,22] In this study, we found high decrease in eGFR after 70 years in males (~16 ml/min/1.73m^2) but less in female patients (~10 ml/min/1.73m^2). Davies and Shock reported the average decline in GFR was 0.96 ml/min/year or about 10 ml/min/decade.[23] The decline can be ascribed to structural changes as well as reduction in the actual number of functioning glomeruli in aging.[24] The expected findings in normal aging such as global glomerulosclerosis, progressive loss of nephron mass, arteriolo-nephrosclerosis and an increase in interstitial volume were reported in previous study.[25] The decline was not modulated by changes in systolic blood pressure or cardiac index in healthy normotensive subjects.[26]

Limitations

Limitations of current study were information about proteinuria, duration of diabetes and BMI were not consistently available and hence could not be included in the study. We also could not do the multiple regression analysis to ignore the interference of age as a confounding factor in eGFR. Furthermore, the study period was short to monitor the exhibited correlation. Therefore, a longitudinal study design in a large group of patients is warranted.

CONCLUSION

Among the total patients, more female patients were in good glycemic control. Gender wise comparison showed that HbA1c level was statistically significant between male and female patients in all age groups below 60 years. eGFR in both male and female patients was decreased as the age advances. Correlation between HbA1c level and eGFR showed an inverse correlation to HbA1c level in both male and female patients when it was more than 7%. For every 1% rise in HbA1c level (above 7%), the eGFR was declined by 10 ml/min/1.73 m^2 in male and 13 ml/min/1.73 m^2 in female patients.

REFERENCES

1. International Diabetes Federation. International Diabetes Federation diabetes atlas. Available at: https://idf.org/e-library/epidemiology-research/diabetes-atlas.html. Accessed on 2 May 2021.
2. International Diabetes Federation. Available at: 2019. https://www.idf.org/our-network/regions-members/south-east-asia/members/94-india.html 2019. Accessed on 20 August 2019.
3. Cummings DM, Larsen LC, Doherty L, Lea CS, Holbert D. Glycemic control patterns and kidney disease progression among primary care patients with diabetes mellitus. J Am Board Fam Med. 2011; 24(4):391-8.
4. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. CKD-EPI. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
5. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34(3):571-90.
6. American Diabetes Association. Management of diabetes in pregnancy. Diabetes Care. 2017;40(1): S114-9.
7. 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. Clin Chem. 2002;48:436-72.
8. American Diabetes Association: Standards of medical care for patients with diabetes mellitus. Diabetes Care. 1999;22:S32–41.

9. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE: Defining the relationship between plasma glucose and HbA$_{1c}$: analysis of glucose profiles and HbA$_{1c}$ in the Diabetes Control and Complications Trial. Diabetes Care. 2002;25:275-8.
10. Dodhia SS, Barasara JD, Joshi VS. Glycemic control affects progression of kidney disease in patients with type 2 diabetes mellitus. Int J Med Sci Public Health. 2016;5:1305-8.
11. Rigalleau V, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P, et al. Glucose control influences glomerular filtration rate and its prediction in diabetic subjects. Diabetes Care. 2006;29:1491-5.
12. Yokoyama H, Kanno S, Takahashi S, Yamada D, Itoh H, Saito K, et al. Determinants of decline in glomerular filtration rate in nonproteinuric subjects with or without diabetes and hypertension. Clin J Am Soc Nephrol. 2009;4:1432-40.
13. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. A1c-derived average glucose study group translating the A1c assay into estimated average glucose values. Diabetes Care. 2008;31:1473-8.
14. Haque N, Debnath BC, Ibrahim M, Sirajuddin K, Majumder M, Hossain M S. Association of HbA1c with urinary ACR & eGFR in type-2 diabetes mellitus. Pulse. 2011;5:6-11.
15. Dodhia SS, Barasara JD, Joshi VS. Glycemic control affects progression of kidney disease in patients with type 2 diabetes mellitus. Int J Med Sci Public Health. 2016;5:1305-8.
16. Cummings DM, Larsen LC, Doherty L, Lea CS, Holbert D. Glycemic control patterns and kidney disease progression among primary care patients with diabetes mellitus. J Am Board Fam Med. 2011;24:391-8
17. American Diabetes Association. Standards of Medical Care in Diabetes 2010. Diabetes Care. 2010; 33(S1):S1-S61.
18. Patel M, Patel IM, Patel YM, Rathi SK. A hospital-based observational study of type 2 diabetic subjects from India. Indian J Clin Prac. 2013;2:141-8.
19. Roy S, Bhattacharjee K. A Cross-sectional Retrospective Analysis of Glycemic Burden and Nephropathy in an Indian Population and Formulation of a New Plan Using eGFR/HbA1c Grid Formation. Cureus. 2019;11:e5378.
20. 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. Clin Chem. 2002; 48:436-72.
21. Macias-Nunez J-F, Lopez-Novoa JM. Physiology of the healthy aging kidney. In: Oreopoulos DM, Cameron JS, Macias Nunez JF, eds. Aging Kidney in Health and Disease. New York: Springer; 2008:93-112.
22. Glassock RJ, Winearls C. Ageing and the Glomerular Filtration Rate: Truths and Consequences. Trans Am Clin Climatol Assoc. 2009;120:419-28.
23. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males. J Clin Invest. 1950;29:496-504.
24. Hoang K, Tan JC, Derby G, Blouch KL, Masek M, Ma I, Lemley KV, Myers BD. Determinants of glomerular hypofiltration in aging humans. Kidney Int. 2003;64:1417-24.
25. Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva F. The ageing kidney. Kidney Int. 2008;74:710-20.
26. Danziger RS, Tobin JD, Becker LC, Lakatta EE, Fleg JL. The age-associated decline in glomerular filtration in healthy normotensive volunteers. Lack of relationship to cardiovascular performance. J Am Geriatr Soc. 1990;38:1127-32.

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