ORIGINAL ARTICLE

IS HBA1C A TRUE MARKER OF GLYCAEMIC CONTROL IN DIABETIC PATIENTS ON HAEMODIALYSIS?

Mehwish Sayed, Farzana Adnan, Muneeba Majeed
Department of Medicine, Liaquat National Hospital, Karachi-Pakistan

Background: HbA1c is generally conducted to check blood glucose control in diabetic patients. As reported by several recent studies, HbA1c may not be considered as a reliable assay for monitoring glycaemic status in haemodialysis patients. Multiple factors may result in artificially low HbA1c. We sought to confirm this observation by performing a study in which we saw the agreement between expected HbA1c values as indicated by the mean plasma glucose level and the measured HbA1c values of haemodialysis dependent Diabetic patients. **Methods:** This cross-sectional study was conducted on 45 patients. Daily three readings of capillary blood glucose were taken for three consecutive days in a week, every two weeks in a month for up to three months. Total 54 capillary blood glucose levels were checked in the duration of three months. Mean blood glucose level was calculated at the end of the study and it is used to calculate the 'expected HbA1c' levels using a formula. At the offset, HbA1c was measured (at 12 weeks) and was compared with the expected HbA1c. **Results:** On comparing the expected and measured HbA1c levels in 45 patients on haemodialysis. There is a significant difference between the two levels, with reduced levels of measured HbA_{1c} in majority of patients as compared to expected ones. **Conclusion:** HbA1c is not a true marker of glucose control in diabetic patients on regular haemodialysis.

Keywords: HbA1c; Haemodialysis; Glycaemic control; Capillary blood glucose; Diabetes Mellitus

Citation: Sayed M, Adnan F, Majeed M. Is HbA1c a true marker of glycaemic control in diabetic patients on haemodialysis? J Ayub Med Coll Abbottabad 2019;31(1):46–50.

INTRODUCTION

Glycated haemoglobin A1c (HbA1c) is generally conducted to check blood glucose control in diabetic patients. It is a form of haemoglobin that is measured to check the overall plasma glucose concentration over the prior three months period, and the Diabetes Control and Complications Trial (DCCT)[1]; United Kingdom Prospective Diabetes Study (UKPDS) have relied upon HbA_{1c} as a marker of blood glucose control. Doctors and patients greatly value haemoglobin A1c (HbA1c) test for assessing individual's average blood glucose level over the prior three months period.

The advantages of good glycaemic control have been given emphasis even in patients with end-stage renal disease (ESRD), after the onset of dialysis, as evidenced by a seven-year observational study.[2] As we know in Diabetic population, leading cause of death is cardiovascular disease. Researchers have reported that in patients with higher HbA1c values, who are on regular haemodialysis, there is higher rate of micro vascular complications and progressively increasing risk of cardiovascular death. Although it is subject to debate, but to date, recommended glycaemic targets and HbA1c in dialysis dependent patients are similar to the targets for general population.

Results of several recent studies have shown that, HbA1c may not be considered as a reliable assay for monitoring glycaemic status in haemodialysis patients and glycated Albumin may be a more appropriate marker of glucose control in this population of patients.[3,4] In patients on haemodialysis, the duration of RBC existence is reduced due to uremia, blood loss during dialysis and repeated blood sampling. This shortened RBC life span, shortens the time that sugar in the blood has to bind with haemoglobin, and thus causes lower HbA1c values. Additionally, erythrocytes production is suppressed; uremic milieu interferes with haemoglobin glycosylation and erythropoietin therapy all these factors may result in artificially low HbA1c level.[3,5,6]

As evidenced by various studies that HbA_{1c} test should not be considered as a dependable and true marker of sugar control in diabetic patients on hemodialysis[7,12], we sought to confirm this observation by performing a study in which we compared, the HbA_{1c} levels of patients on haemodialysis with a calculated HbA1c that is obtained by a mean blood glucose level of three months recording. By doing this we can provide further evidence regarding the reliability of HbA_{1c} in this population particularly in our part of the world, as no such studies have been done in our population. And still most of the doctors including nephrologists are relying on HbA_{1c} for the estimation of glycaemic status of diabetic patients on haemodialysis. To

generally apply this hypothesis, we need to conduct several single centred or multi-centred studies in our population. This study is done in a tertiary care hospital of Karachi, where the population being served reflects the diversity of the communities, so it will support the results of studies done previously on different ethnic groups, for example one such study done by Hoshino *et al*[8] in 2013. It will further verify the observations in our population. This would be helpful in guiding physicians, nephrologists and endocrinologists regarding the use of this test for assessing glucose control in patients on haemodialysis and in order to help these patients in monitoring the glycaemic control in a better way.

MATERIAL AND METHODS

It was a cross sectional study, conducted in the period of four months at Haemodialysis Unit, Department of Nephrology, Liaquat National Hospital, Karachi.

The obtained sample size is 44 patients, with the help of WHO software of sample size calculation, by using σ=1.44, μ_o=6.77, μ_1=7.68, Power=90%, and 95% confidence interval.[9]

[10]

Sampling technique: Non-probability purposive sampling

Inclusion Criteria:

- Diabetic patients (both type I and type II) with End stage renal disease on haemodialysis for more than 3 months
- Age limit: From 20 to 80 years

Exclusion Criteria:

- Non-diabetic patients
- Those on haemodialysis for less than three months.

The study was performed after the permission of ethical committee of the hospital and written informed consent for the study and the procedure was obtained from the patients. Patients were selected from the dialysis unit of Liaquat National Hospital according to the inclusion and exclusion criteria (Diabetic patients both type I and type II with End stage renal disease, i.e., stage 5 on maintenance haemodialysis for more than 3 months, having age from 20 to 80 years were included, while non-diabetic patients and those on haemodialysis for less than three months were excluded) and considering the willingness of patients to perform frequent blood glucose testing. They were advised to check capillary blood glucose, using Abbot freestyle optium glucose analyser provided to all study participants to be taken home for 3 months. Daily three readings of capillary blood glucose were checked for three consecutive days in a week, every two weeks in a month for up to three months; One in fasting and two in random state (two hours post prandial states and other at bed time). Total 54 capillary blood glucose levels were checked in the duration of three months, mean blood glucose value was calculated at the end of the study which was used to calculate the expected HbA_{1c} level using a formula which is as follows

HbA1c = 46.7 + average blood glucose (mg/dl) / 28.7

At the end HbA1c levels were checked by using Antibody based immunoassay at 12 weeks. Expected HbA1c level as indicated by Mean blood glucose value was compared with measured HbA1c levels at the end of study.

Data analyses were done by using SPSS version 21. Mean and standard deviation was computed for quantitative variable, i.e., age, duration of diabetes, expected HbA1c and measured HbA1c. Frequency and percentage was calculated for qualitative variables gender and treatment group. Dependent sample *t*-test was applied to see the significant mean difference of expected HbA_{1c} verses measured HbA1c and *p*-value <0.05 was considered as significant. Data was also stratified for gender, age groups, duration of diabetes groups and treatment group to see the significant mean difference of expected HbA1c verses measured HbA1c using dependent sample *t*-test and *p*-value <0.05 was considered as significant.

Independent sample *t*-test was applied to see the significant mean difference of expected HbA1c and measured HbA1c regards to gender, age groups, duration of diabetes groups and treatment group and *p*-value <0.05 was considered as significant.

RESULTS

This study was designed to compare the expected and measured glycosylated haemoglobin (HbA1c) levels in patients on dialysis.

For the purpose of this study, a sample of 45 individuals was selected. The mean age of the participants was 57.78±8.58 years. The distribution of the socio demographic characteristics has been illustrated in table-1 and figures-1 and 2.

The mean measured HbA1c levels measured were calculated to be 6.50±1.62. On the other hand, the expected HbA1c levels were 7.83+1.35 (Figure-1). An independent sample t test was used to assess the difference between expected and

measured HbA1c levels. There was a significant difference (1.33±0.31 mg/dl) between the two variables (p<0.001). The comparisons between expected and measured HbA1c levels as per different variables have been illustrated in table-2 and figure-3.

As illustrated in table-2, no significant difference was found between the measured and expected HbA_{1c} levels between men and women (p>0.05). Furthermore, the difference between the expected and measure HbA_{1c} levels in patients on diabetes for less than 15 years was found to be significant (p<0.05). The difference for the cohort that has had diabetes for more than 15 years was not significant (p>0.05).

When expected and measured HbA1c levels were compared between patients not taking insulin, the difference was not significant (p = 0.26) with a mean difference of 1.93 mg/dl between the two groups. On the other hand, the mean expected and measured HbA_{1c} levels for patients on insulin were significantly different (p<0.01) with a mean difference of 1.29.

Table-1: Socio-demographic characteristics of study population

	Mean±SD
Age (years)	57.78±8.58
Duration of Diabetes (years)	15.51±6.62
Expected HBA1c (mg/dl)	7.83±1.35
Measured HBA1c (mg/dl)	6.50±1.62
	Frequency (%) n=45
Gender	
Male	25 (55.6)
Female	20 (44.4)
Treatment	
On Insulin	42 (93.3)
Not on Insulin	3 (6.7)

Table-2: Independent variables according to HbA1c group

	Expected HbA1c (mg/dl)	Measured HbA1c (mg/dl)	*p*-value
	7.83±1.35	6.50±1.62	< 0.01
Gender			
Male	7.89±1.53	6.52±1.71	0.01
Female	7.75±1.11	6.46±1.54	0.01
Duration of Diabetes			
≤ 15 years	7.74±1.35	6.00±1.38	<0.01
> 15 years	7.95±1.38	7.11±1.72	0.1
Treatment			
On Insulin	7.83±1.34	6.54±1.63	< 0.01
Not on insulin	7.93±1.91	6.00±1.65	0.26

Table-3: Independent variables according to expected HbA1c

	Expected HbA1c (mg/dl)		*p*-value
Gender	**Male**	**Female**	0.72
	7.90±1.54	7.75±1.11	
Duration of Diabetes	**≤ 15 years**	**> 15 years**	0.61
	7.74±1.35	7.95±1.38	
Treatment	**On Insulin**	**Not on insulin**	0.94
	7.83±1.34	7.93±1.91	

Table-4: Independent variables according to measured HbA1c

	Measured HbA1c (mg/dl)		*p*-value
Gender	**Male**	**Female**	0.9
	6.53±1.71	6.47±1.54	
	7.00±1.53	6.10±1.61	
Duration of Diabetes	**≤ 15 years**	**> 15 years**	0.03
	6.01±1.38	7.11±1.72	
Treatment	**On Insulin**	**Not on insulin**	0.63
	6.54±1.63	6.00±1.65	

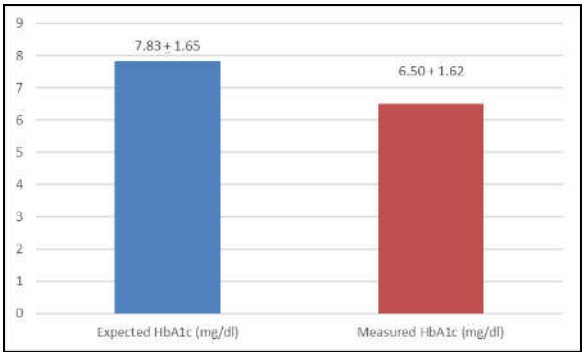

Figure-1: Expected and measured HbA_{1c} levels (mg/dl)

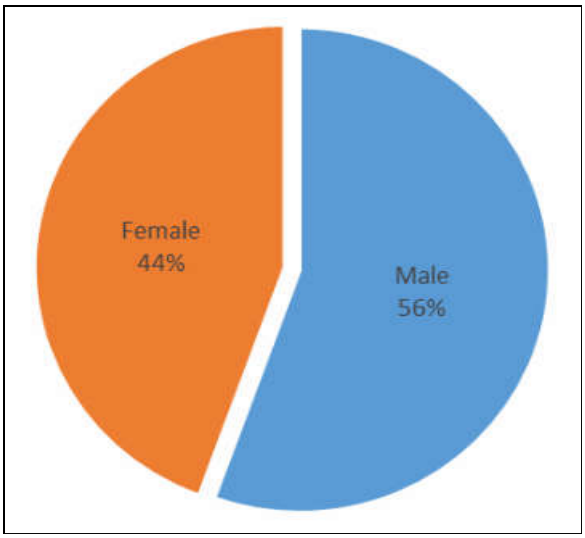

Figure-2: Gender distribution

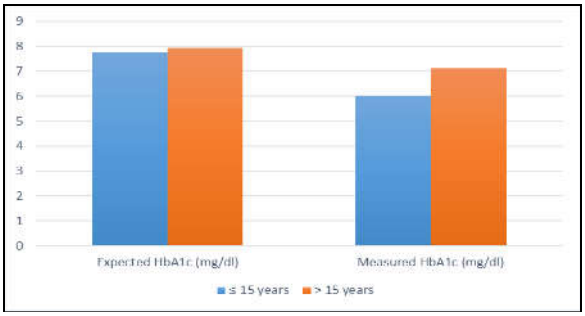

Figure-3: Expected and measured HbA1c B Levels as per duration of diabetes

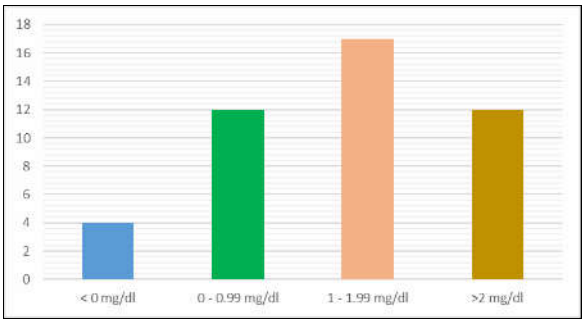

Figure-4: Difference between expected and measured HbA1c levels (mg/dl)

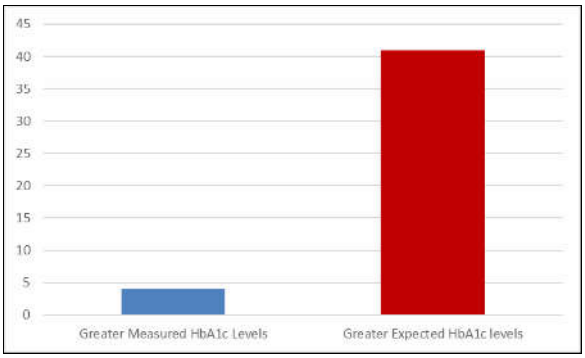

Figure-5: Difference in HbA1c levels (Expected – measured HbA1c levels) in mg/dl

The difference between the expected and measured HbA1c levels was calculated for all patients. Four of the patients had measured HbA1c levels greater than expected HbA1c levels. For the rest of the sample, the expected HbA1c levels were greater. These differences have been illustrated in figure-4. The difference between the two levels has been distributed into four groups. The first group illustrates the difference for patients who had greater measured expected HbA1c levels greater than measured levels.

DISCUSSION

The study at hand has shown that there is a significant difference between the two values of haemoglobin, i.e., expected and measured with reduced levels of measured HbA1c as compared to HbA_{1c} levels predicated by the mean plasma glucose levels. Such results were obtained in majority of the patients included in the study. This signifies the instability of HbA_{1c} in assessing the glycaemic control in haemodialysis dependent diabetic patients. It has been proposed by various other studies[3,4,11] that glycated albumin is a more appropriate marker of glucose control then glycated HbA1c.

Since the difference in HbA1c values between men and women was not significant. Therefore, gender is not a variable that warrants any further discussion with respect to our study. Furthermore, a significant difference between the measured and expected HbA1c levels was found for patients taking insulin with a mean difference of 1.93 mg/dl between the two groups. With a calculated mean difference of 1.29 mg/dl between the two groups, the difference was not significant for patients not on insulin. What needs to be taken into consideration is the small sample of patients in the cohort not on insulin (n=3). Any results obtained for such a small sample size cannot be taken as valid. Yet this relationship can be better explored by studying it on a larger no of patients not taking insulin.

An interesting finding was a significant difference between the two groups of patients who had diabetes for less than 15 years. The difference between the expected and measured HbA1c was significant with a *p*-value of <0.01. On the other hand, the patients who had diabetes for more than 15 years had no significant difference between the two groups. This has not been directly studied previously, further studies are required on a large scale to establish this association and also for elimination of the effect of confounding factors such as difference in levels of haemoglobin, no of haemodialysis and erythropoietin injections all of which contribute to the results.

However, the main idea has been studied by various studies done previously[12], but no such studies have been done in our population. So, we aimed to reaffirm this point by doing the study in a tertiary care hospital of Karachi on a considerable no of patients to see the pattern of HbA_{1c} in haemodialysis population. Due to unavailability of glycated Albumin testing in the city, we conducted the study using blood glucose levels to calculate HbA_{1c} (expected HbA1c). The main idea was to see how HbA_{1c} underestimates the glycaemic status in a patient who is on maintenance haemodialysis. Although this study gives us a good idea about the unreliability of HbA1c, a comparison study, using glycated albumin could have better delineated the relationship and would have the better strength. Moreover, since we did not have the data on the duration these patients have been on dialysis that could also be a potential factor to be discussed in terms of its effect on HbA1c of the two groups

CONCLUSION

Our study showed that glycated HbA1c is not a reliable marker of glycaemic status in haemodialysis dependent diabetic patients. We therefore, suggest that instead of relying on HbA1c, doctors especially, physicians, endocrinologist and nephrologist, who encounter such patients, should monitor multiple daily blood glucose levels for assessing glycaemic

status until other test, i.e., glycated albumin is widely available.

ACKNOWLEDGEMENT

Firstly, I am thankful to the staff of nephrology department particularly dialysis unit for supporting us in data collection. I am grateful to my colleague Dr. Shafaq Saleem for her efforts and support in data collection. Furthermore, I would like to acknowledge Mr. Mustansir Zaidi for his valuable input in data analysis. I am also immensely thankful to Dr. Mohammed Saeed for his help and assistance in designing of the study and Mr Mohammad Yousuf Sheikh in proof reading. Lastly, I would like to extend my gratitude to the administration of Liaquat National Hospital for funding my study.

AUTHORS' CONTRIBUTION

FA: Concept of the study, proof reading, arranged the grant from Hospital. MS: Literature search, study designing, data collection, data analysis and interpretation along with write-up. MM: Data collection, Data analysis and interpretation.

REFERENCES

1. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, *et al*. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993;329(14):977–86.
2. Oomichi T, Emoto M, Tabata T, Morioka T, Tsujimoto Y, Tahara H, *et al*. Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: a 7-year observational study. Diabetes Care 2006;29(7):1496–1500.
3. Inaba M, Okuno S, Kumeda Y, Yamada S, Imanishi Y, Tabata T, *et al*. Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: effect of anemia and erythropoietin injection. J Am Soc Nephrol 2007;18(3):896–903.
4. Fukuoka K, Nakaao K, Morimoto H, Nakao A, Takatori Y, Arimoto K, *et al*. Glycated albumin levels predict long-term survival in diabetic patients undergoing haemodialysis. Nephrology (Carlton) 2008;13(4):278–83.
5. Nakao T, Matsumoto H, Okada T, Han M, Hidaka H, Yoshino M, *et al*. Influence of erythropoietin treatment on hemoglobinA1c levels in patients with chronic renal failure on hemodialysis. Intern Med 1998;37(10):826–30.
6. Uzu T, Hatta T, Deji N, Izumiya T, Ueda H, Miyazawa I, *et al*. Target for glycemic control in type 2 diabetic patients on hemodialysis: effects of anemia and erythropoietin injection on hemoglobin A1c. Ther Apher Dial 2009;13(2):89–94.
7. Sany D, Elshahawy Y, Anwar W. Glycated albumin versus glycated hemoglobin as glycemic indicator in hemodialysis patients with diabetes mellitus: variables that influence. Saudi J Kidney Dis Transpl 2013;24(2):260–73.
8. Hoshino J, Molnar MZ, Yamagata K, Unara Y, Takaichi K, Kovesdy CP, *et al*. Developing an HbA_{1c}-Based Equation to Estimate Blood Glucose in Maintenance Hemodialysis Patients. Diabetes Care 2013;36(4):922–7.
9. Williams ME, Lacson E Jr, Teng M, Ofsthun N, Lazarus JM. Hemodialyzed type I and type II diabetic patients in the US: Characteristics, glycemic control, and survival. Kidney Int 2006;70(8):1503–9.
10. Ryan TP. Sample Size Determination and Power. New Jersey: John Wiley & Sons; 2013.
11. Abe M, Matsumoto K. Glycated hemoglobin or glycated albumin for assessment of glycemic control in hemodialysis patients with diabetes? Nat Clinc Pract Nephrol 2008;4(9):482–3.
12. Chujo K, Shima K, Tada H, Oohashi T, Minakuchi J, Kawashima S. Indicators with blood glucose control in diabetics with End-stage chronic renal disease: GHb vs. Glyvated albumin (GA). J Med Invest 2006;53(3-4):223–8.

Submitted: 7 December, 2017	*Revised: 22 April, 2018*	*Accepted: 19 June, 2018*

Address for Correspondence:

Dr. Mehwish Sayed, Department of Medicine, Liaquat National Hospital, National Stadium Road, Karachi-4800, Pakistan

Email: dr.mehwishsyed@gmail.com