ORIGINAL ARTICLE

HbA1c Levels in Diabetic Patients with Chronic Liver Disease

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ABSTRACT

Objective: To investigate the accuracy of HbA1c in diabetic patients with chronic liver disease (CLD).

Study Design: Cross-sectional/ observational study.

Place and Duration of Study: Fauji Foundation Hospital, Rawalpindi (FFH), from July 2019-July 2020.

Materials and Methods: This study was carried out on 100 subjects divided in two groups i.e. Group A and Group B. Group A included diabetics with CLD (chronic hepatitis C) and Group B included diabetics without CLD. Each group consisted of 50 known type 2 diabetes mellitus (T2DM) participants, who were randomly selected from liver and medical OPD of FFH, Rawalpindi. Blood samples of the participants were analyzed for HCV, HbA1c and liver enzymes. Chemical analysis was carried out at the department of Pathology FFH, Rawalpindi. For statistical analysis version 21 of SPSS was used.

Results: Our study showed that HbA1c levels were low in group A (6.6±1.10% vs. 9.58±2.09% $p < 0.05$) when compared to group B. Group A showed significantly higher levels of alanine aminotransferase (ALT) than group B (74.65±21.84 U/L vs. 38.44±23.79 U/L $p<0.05$). Serum albumin was also lower in group A in comparison to group B (29.52±2.21g/L vs. 36.24±3.99 g/L $p<0.05$). HbA1c levels showed significantly negative association with ALT in group A (r-0.418 $p<0.05$) while in group B the negative correlation was not significant statistically (r-0.197 $p=0.171$). A significant negative association of HbA1c with Albumin was also seen in group A (r-0.391 $p<0.05$) Regression analyses showed a significant relationship between HbA1c and ALT in group A.

Conclusion: Our study concludes that HbA1c levels are significantly decreased in diabetic patients with CLD (chronic hepatitis C) than diabetics without CLD. Therefore, HbA1c is not a reliable predictor for long-term glycemic monitoring in diabetic patients having CLD.

Key Words: *Chronic Liver Disease, Chronic Hepatitis C, Cirrhosis, Diabetes Mellitus, HbA1c.*

Introduction

From a decade or so liver disease been recognized as a major complication of type 2 diabetes.[1,2] Chronic liver disease (CLD) generally takes the clinical form of chronic hepatitis, its long term complications include cirrhosis and hepatocellular carcinoma (HCC).[3] Chronic liver disease is accompanied by significantly impaired glucose homeostasis. In CLD, around 80% of patients show glucose intolerance, while in 30–60% of patients there is presence of frank diabetes. Hepatic glucose metabolism is significantly affected by CLD.[4,6]

There are many causes for CLD, of which Hepatitis C Virus (HCV) is most common.[7] HCV is one of the most alarming health problems globally, with an incidence of 200 million (3.3%) of the world's population.[8] "Till the year 2017 around 4 million individuals were infected with HCV in the United States and 2.7 million of them were careers."[9] Nearly 30,000 new cases of HCV have been diagnosed annually.[10] The HCV infected people in Pakistan is approximated to be more than 10 million.[11] The organ primarily affected by HCV is the liver which then progresses to cirrhosis, chronic liver failure and hepatocellular carcinoma.[12] Ghani ur Rehman et al. in 2017 revealed that almost one-third of the HCV patients were diabetic. Our data records showed that 26.42% of the HCV infected patients were found to have T2DM.[13] The high prevalence of hepatitis C in T2DM has been shown by multiple epidemiological studies, and have also postulated the progression of hepatitis C into development of DM. HCV infection & age as

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Funding Source: NIL; Conflict of Interest: NIL
Received: September 25, 2020; Revised: February 04, 2021
Accepted: February 12, 2021

documented by Mason et al. were independent predictors for DM.[14,19]

The American Diabetes Association (ADA) and World Health Organization (WHO), both, regard HbA1c as the most reliable chemical tool for diagnosis as well as prognosis of glycemic control in T2DM.[20] The use of HbA1c for the diagnosis of T2DM is supported by plenty of literature.[21] The turnover of erythrocytes is increased in CLD patients, while there is a decrease in serum albumin level.[22] Therefore, glycated albumin (GA) and HbA1c should not be utilized as tools in CLD diabetic patients for monitoring of chronic plasma glucose control.[23]

Literature search showed that many studies[24,29] have been carried out to see the reliability of HbA1c in diabetics with CLD in respect to cirrhosis but hardly any studies have been done to see accuracy of HbA1c in diabetic population having chronic hepatitis C infection and non-such study has been found to be carried out in Pakistan so far. Our study aimed to determine HbA1c accuracy in T2DM patients with chronic hepatitis C which is first stage of CLD to timely avoid complications like cirrhosis, hepatocellular carcinoma along with the subsequent death rate.

The objective of the present study was to provide information on how reliable is HbA1c in patients having diabetes with chronic hepatitis C and what alternative parameters can be utilized to check the previous 3-4 months control of diabetes in such patients.

Materials and Methods

This was a cross sectional/observational study. It was carried out at the pathology department FFH, Rawalpindi from July 2019 to July 2020 after approval from the institutional ethical committee. The inclusion criteria of the study were hundred known diabetic patients with and without CLD fulfilling criteria of chronic hepatitis C (Lasting > 6 months). The exclusion criteria included those who were free of illness like acute liver disease, renal disease/failure, hepatitis B or any other virus, pregnant females and those who did not want to be included in the study. The study subjects were split in two groups (group A & group B). Group A included diabetics with CLD (chronic hepatitis C) and Group B included diabetics without CLD. Each group consisted of 50 known diabetic participants.

Patients were randomly selected from liver and medical OPD of FFH, Rawalpindi. Proper consent was taken after explaining the aims and objectives of the study to all participants.

Blood sample was collected from all participants under aseptic conditions. Centrifugation of blood for 5 minutes at 4000rpm was carried out to separate the serum for the evaluation of liver function tests including ALT**,** ALP, albumin, and bilirubin. These parameters were measured using chemistry auto-analyzer Dimensions RxL. HbA1c was analyzed using fully automated analyzer Beckman Coulter.

Statistical analysis was carried out using version 21 of SPSS. Quantitative data was expressed as mean± Standard deviation (SD). Comparisons between the two groups were made using independent t-test. To show relationship of the variables with HbA1c Pearson's correlation co-efficient was used. Regression analysis was used to show the relationship between the dependent variables and the independent variables. Results were considered as significant with $p< 0.05$ and highly significant with $p<0.001$.

Results

Data was stated as mean± SD. Comparison of the two groups was done using independent t-test with considering $p < 0.05$ as statistically significant. The present study included 100 participants divided into group A and B. Group A, diabetics with chronic hepatitis C, included 50 participants with mean age of 61.32±10.70 years while group B, diabetics without chronic hepatitis C, also consisted of 50 participants with mean age of 57.44±11.08 years.

Low levels of HbA1c were seen in group A than group B (6.6±1.10% vs. 9.58±2.09% $p<0.05$).

Group A reported significantly higher level of serum ALT as compared to group B (74.65±21.84U/L vs. 38.44±23.79U/L $p<0.05$).

Group A also showed lower serum albumin as compared to group B (29.52±2.21g/L vs. 36.24±3.99g/L $p<0.05$). The comparison between the groups is summarized in Table I.The association of HbA1c with different parameters is shown in Table II. HbA1c levels were negatively associated with ALT in group A (r-0.418 $p<0.05$) while in group B the negative correlation was not significant statistically (r-0.197 $p=0.171$). Similarly, Albumin showed a significant negative correlation with HbA1c in group

A (r-.391 p<0.05), while negative correlation of ALP and bilirubin were not significant in both the groups. The correlation of ALT with HbA1c in group A is shown in Figure 1 with (r^2=0.175 p<0.05)) calculated by linear regression analysis while group B results are plotted in Figure 2 (r^2=0.039 p=0.171) The ALT results are plotted on x-axis and HbA1c on y-axis

Table I: Comparison of Demographic, Clinical and Biochemical Characteristics of the Study Groups

Variable	Diabetics with CLD	Diabetics without CLD	*P* value
Age (years)	61.32±10.70	57.44±11.08	0.078
ALT (U/L)	74.68±21.84	38.44±23.79	<0.05***
ALP (U/L)	159.96±36.10	172.08±55.56	0.199
Albumin (g/L)	29.52±2.21	36.24±3.99	<0.05***
Bilirubin (µmol/L)	10.64±5.37	9.92±5.90	0.525
HbA1c (%)	6.60±1.10	9.58±2.09	<0.05***

Note: *Significance at p <0.05, **Significance at p <0.01, ***Significance at p< 0.001

Table II: Correlation of HbA1c (%) with Different Parameters in the Study Groups

Variables	Group A (DM+CLD)		Group B (DM)	
	R	*P*	R	*P*
ALT (U/L)	-0.418	<0.05**	-0.197	0.171
ALP (U/L)	-0.048	0.740	-0.125	0.386
Albumin (g/L)	-0.391	<0.05*	-0.264	0.064
Bilirubin (µmol/L)	-0.160	0.268	-0.189	0.189

r is coefficient of correlation, * Significance at p<0.05, ** Significance at p<0.01, *** Significance at p<0.001

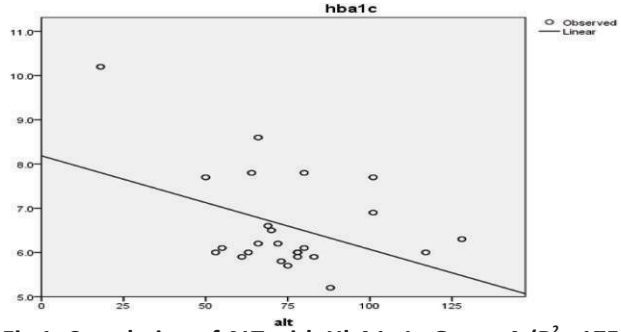

Fig 1: Correlation of ALT with HbA1c In Group A (R^2=.175 P=.003) Calculated by Linear Regression Analysis

Discussion

Chronic liver disease and diabetes are two major chronic illnesses afflicting a major segment of Pakistan's population.

The cost in terms of number of work hours lost due to illness is enormous. Moreover, both diseases require long term management and treatment. The average Pakistani can ill afford to bear the costs of such expensive treatments. Hence there was dire need to correlate HbA1c with CLD and see if the results of HbA1c in CLD depicted the actual levels or not.

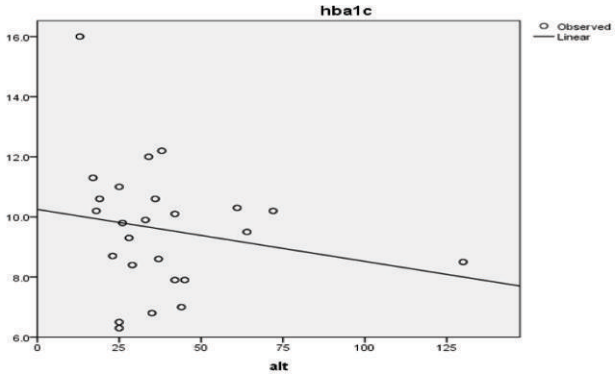

Fig 2: Correlation of ALT with HbA1c Group B (R^2=.039 P=.171) Calculated by Linear Regression Analysis

Multiple studies have been carried out to see the reliability of HbA1c in diabetics with CLD in respect to cirrhosis but hardly any studies have been done to see accuracy of HbA1c in diabetic population having chronic hepatitis C infection. Our study is aimed from this aspect as diabetes and chronic hepatitis C, account for major cause of chronic disease in Pakistan.

In our study it was observed that HbA1c level was significantly lesser in the diabetic patients with CLD in comparison to diabetic patients without CLD. ALT level was significantly more in the diabetics having CLD while serum albumin was seen to be significantly lower in this group, which may be sign of progression of the disease to cirrhosis.

Koga et al. in their study observed that in CLD patients the measured HbA1c levels were lower than estimated HbA1c levels.[23]

Lahousen et al. in their work measured HbA1c for the evaluation of long-term plasma glucose control in chronic hepatitis patients, with compensated cirrhosis and in ribavirin treated chronic hepatitis patients. The levels of HbA1c in all cases were seen to be below the diabetic range.[30]

The results of all these studies are in concordance with this study.

Nadelson et al. performed their study in 2016, in which they observed that HbA1c was not a reliable biomarker of glycemic index in cirrhotic patients with HbA1c levels ranging between 5-6%.[25]

MF Bashir et al. in their study showed that ALT was significantly higher in diabetics with hepatitis C (HCV) but they showed HbA1c higher in HCV plus diabetics. This could be because their patients did not fulfill the chronic hepatitis C criteria.[31]

Our study also showed a significant negative correlation of HbA1c with ALT and albumin in the diabetics with CLD as compared to diabetics without CLD. Similar results were shown by Christman et al. who observed that low HbA1c was associated with elevated liver enzymes (ALT) and low albumin levels.[32]

The limitation of our study includes a small sample size. It is suggested that HbA1c should be used with caution & fasting plasma glucose levels should be relied upon more along with liver function tests and red blood cell indices when prolonged glycemic control in type 2 diabetic patients with CLD is monitored. Studies to investigate newer options for monitoring glycemic levels are required in these patients.

Conclusion

We conclude that HbA1c is not a reliable tool for the long-term glycemic control in CLD patients with diabetes mellitus and clinicians should be aware of limitations of HbA1c as a marker of glycemic control in patients with CLD. For accurate monitoring of long-term glycemic control of such patients, HbA1c should only be evaluated in context with fasting plasma and post prandial glucose levels along with liver function tests.

REFERENCES

1. Tolman KG, Fonseca V, Tan MH, Dalpiaz A. Narrative review: hepatobiliary disease in type 2 diabetes mellitus. Annals of internal medicine. 2004;141(12):946-56.
2. Schnedl WJ, Wallner SJ, Piswanger C, Krause R, Lipp RW. Glycated hemoglobin and liver disease in diabetes mellitus. Wiener Medizinische Wochenschrift. 2005;155(17):411-5.
3. Burtis CA, Bruns DE. Teitz fundamentals of clinical chemistry and molecular diagnostics. 7th ed2014. 1075 / 2708 p.
4. Jaafar J, de Kalbermatten B, Philippe J, Scheen A, Jornayvaz FR. [Chronic liver diseases and diabetes]. Revue medicale suisse. 2014;10(433):1254, 6-60.
5. Baig NA, Herrine SK, Rubin R. Liver disease and diabetes mellitus. Clinics in laboratory medicine. 2001;21(1):193-207.
6. Blendea MC, Thompson MJ, Malkani S. Diabetes and Chronic Liver Disease: Etiology and Pitfalls in Monitoring. Clinical Diabetes. 2010;28(4):139.
7. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science (New York, NY). 1989;244(4902):359-62.
8. Saeed, Muhammad, Iram, Shagufta, Hussain, Shahida, et al. Hepatitis C in asymptomatic population. Professional Medical Journal. 2016;23(5):546-52.
9. CM F, S J, MA C, M E, Goldstein, BJ. Liver fibrosis as assessed by the FIB-4 index and metabolic markers in subjects with type 2 Diabetes. In hepatology 2017;66:1125A-6A.
10. Lavanchy D. The global burden of hepatitis C. Liver international : official journal of the International Association for the Study of the Liver. 2009;29 Suppl 1:74-81.
11. Saeed M, Hussain S, Rasheed F, Ahmad M, Arif M, Hamid Rahmani MT. Silent killers: Transfusion Transmissible Infections-TTI, among asymptomatic population of Pakistan. JPMA The Journal of the Pakistan Medical Association. 2017;67(3):369-74.
12. Hu KQ, Tong MJ. The long-term outcomes of patients with compensated hepatitis C virus-related cirrhosis and history of parenteral exposure in the United States. Hepatology (Baltimore, Md). 1999;29(4):1311-6.
13. Rehman GU, Ali M, Shah F, Iqbal A, Ahmad A, Hayat Z, et al. Prevalence of Diabetes Type 2 in Hepatitis C Infected Patients in Kpk, Pakistan. BioMed Research International. 2017;2017:2416281.
14. Simó R, Hernández C, Genescà J, Jardí R, Mesa J. High Prevalence of Hepatitis C Virus Infection in Diabetic Patients. Diabetes Care. 1996;19(9):998.
15. Knobler H, Stagnaro-Green A, Wallenstein S, Schwartz M, Roman SH. Higher incidence of diabetes in liver transplant recipients with hepatitis C. J Clin Gastroenterol. 1998;26(1):30-3.
16. Allison ME, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. Journal of hepatology. 1994;21(6):1135-9.
17. Ozyilkan E, Arslan M. Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection. The American journal of gastroenterology. 1996;91(7):1480-1.
18. Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology (Baltimore, Md). 1999;29(2):328-33.
19. Lecube A, Hernández C, Genescà J, Simó R. Glucose Abnormalities in Patients with Hepatitis C Virus Infection. Diabetes Care. 2006;29(5):1140.
20. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM, et al. Tests of Glycemia in Diabetes. Diabetes Care. 2004;27(7):1761.
21. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia. 2007;50(11):2239-44.
22. Jiao Y, Okumiya T, Saibara T, Park K, Sasaki M. Abnormally decreased HbA1c can be assessed with erythrocyte creatine in patients with a shortened erythrocyte age. Diabetes care. 1998;21(10):1732-5.
23. Koga M, Kasayama S, Kanehara H, Bando Y. CLD (chronic

liver diseases)-HbA1C as a suitable indicator for estimation of mean plasma glucose in patients with chronic liver diseases. Diabetes research and clinical practice. 2008;81(2):258-62.

24. Cacciatore L, Cozzolino G, Giardina MG, De Marco F, Sacca L, Esposito P, et al. Abnormalities of glucose metabolism induced by liver cirrhosis and glycosylated hemoglobin levels in chronic liver disease. Diabetes research (Edinburgh, Scotland). 1988;7(4):185-8.
25. Nadelson J, Satapathy SK, Nair S. Glycated Hemoglobin Levels in Patients with Decompensated Cirrhosis. Int J Endocrinol. 2016;2016:8390210-.
26. Nomura Y, Nanjo K, Miyano M, Kikuoka H, Kuriyama S, Maeda M, et al. Hemoglobin A1 in cirrhosis of the liver. Diabetes research (Edinburgh, Scotland). 1989;11(4):177-80.
27. Lahousen T, Hegenbarth K, Ille R, Lipp R-W, Krause R, Little R-R, et al. Determination of glycated hemoglobin in patients with advanced liver disease. World J Gastroenterol. 2004;10(15):2284-6.
28. Elkrief L, Rautou P-E, Sarin S, Valla D, Paradis V, Moreau R. Diabetes mellitus in patients with cirrhosis: clinical implications and management. Liver International. 2016;36(7):936-48.
29. Trenti T, Cristani A, Cioni G, Pentore R, Mussini C, Ventura E. Fructosamine and glycated hemoglobin as indices of glycemic control in patients with liver cirrhosis. Research in Clinic and Laboratory. 1990;20(4):261.
30. Lahousen T, Hegenbarth K, Ille R, Lipp RW, Krause R, Little RR, et al. Determination of glycated hemoglobin in patients with advanced liver disease. World journal of gastroenterology. 2004;10(15):2284-6.
31. Bashir M, Haider M, Rashid N, Riaz S. Association of Biochemical Markers, Hepatitis C Virus and Diabetes Mellitus in Pakistani Males. Tropical Journal of Pharmaceutical Research. 2013;12(5).
32. Christman AL, Lazo M, Clark JM, Selvin E. Low Glycated Hemoglobin and Liver Disease in the U.S. Population. Diabetes Care. 2011;34(12):2548.