Original Article

Preoperative Glycated Haemoglobin Level and Postoperative Morbidity and Mortality in Patients Scheduled for Liver Transplant

Mohd Qurram Parveez, Karthik Ponnappan, Manish Tandon[1], Ankur Sharma[2], Priyanka Jain[3], Akhil Singh[4], Chandra Kant Pandey[5], Varuna Vyas[6]

Department of Anaesthesiology, Institute of Liver and Biliary Sciences, [1]Dharamshila Narayana Superspeciality Hospital, New Delhi, [2]Department of Trauma and Emergency (Anaesthesiology), All India Institute of Medical Sciences, Jodhpur, Rajasthan, [3]Statistician, Institute of Liver and Biliary Sciences, [4]Departments of Anaesthesiology, All India Institute of Medical Sciences, New Delhi, [5]Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, [6]Department of Pediatrics (Endocrinology), All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

Abstract

Background: There is high prevalence of diabetes mellitus in patients of end stage liver disease and it has been implicated for complications in post-transplant patients. Glycated hemoglobin is now targeted as a modifiable preoperative risk factors for postoperative complications. Data describing the course and severity of postoperative liver transplant complication and their relation with pre-operative glycated hemoglobin level is sparse. In this study, we looked for co-relation between the preoperative HbA1c level and post-operative mortality and morbidity in patients scheduled for liver transplant. **Materials and Methods:** Retrospective data in 400 adult patients operated for liver transplant were retrieved. After exclusion, data were analyzed for 224 patients. Patients were divided into two groups on the basis of glycated hemoglobin levels (Group 1 (HbA1C ≥6.5) and Group 2 (HbA1C <6.5)). **Results:** Glycated hemoglobin levels were not associated with postoperative death during stay in intensive care unit, incidence of postoperative cardiovascular, renal, and central nervous complications. No difference was seen between 2 groups for need for renal replacement therapy, incidence of infections, rejection, need for re-exploration surgery and duration of intensive care unit and hospital stay. Glycated hemoglobin cannot predict 30 day survival (Area under curve {AUC} = 0.629, *P* value 0.05). **Conclusion:** Preoperative glycated hemoglobin level is not associated with postoperative morbidity and mortality in patients scheduled for liver transplant.

Trial Registration Number: CTRI/2018/04/012966.

Keywords: Diabetes mellitus, glycated hemoglobin, liver transplant

Introduction

Liver transplantation (LT) is the treatment of choice for end stage liver disease.[1-3] Shortage of deceased donor organs and long waiting period is bridged by living donor programs. The short term and long-term outcome of liver transplant has been consistent over the last decade with 80–90% survival at 3 months and at 5 years. Proportion of patients of end stage liver disease requiring LT and having metabolic syndrome is more prevalent than ever before, with non-alcoholic steato-hepatitis (NASH) now contributing to almost 30% of such patients. Diabetes mellitus (DM) is a manifestation of metabolic syndrome and can contribute to post-operative morbidity and mortality.

Post liver transplant recipients can have complications that can be attributed to preoperative comorbidies.[4-6] Long standing and uncontrolled DM is known to cause micro vascular and macro vascular damage and the association between DM and postoperative morbidity and mortality is established. There is high prevalence of DM in patients of cirrhosis of liver.[7] Patients of DM operated for LT are at increased risk of adverse cardiovascular event, infection, graft rejection, renal failure, neurological complication, and also of death.[8,9]

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_208_19

Address for correspondence: Dr. Ankur Sharma, Department of Trauma and Emergency (Anesthesiology), AIIMS, Jodhpur - 342 008, Rajasthan, India.
E-mail: ankuranaesthesia@gmail.com

How to cite this article: Parveez MQ, Ponnappam K, Tandon M, Sharma A, Jain P, Singh A, *et al*. Preoperative glycated haemoglobin level and postoperative morbidity and mortality in patients scheduled for liver transplant. Indian J Endocr Metab 2019;23:570-4.

Glycosylated hemoglobin (HbA1c) is now used to diagnose DM, pre-diabetes and ascertain long-term glycaemic control. Several studies have co-related pre-operative HbA1c level and post-operative outcomes. HbA1c is now therefore targeted as a modifiable risk factors for postoperative complications.[10-14]

However, HbA1c levels are affected by anemia and factors that has not been studied in patients of chronic liver disease. Data describing the course and severity of postoperative liver transplant complication and their relation with pre-operative HbA1c level is sparse. We thus in this retrospective study looked for co-relation between the preoperative HbA1c level and post-operative mortality and morbidity in patients scheduled for liver transplant.

Material and Methods

This study was planned in a tertiary care hospital of India after approval by the Institutional Ethics Committee. After registering this study in Clinical trial registry of India (Reg. No.-CTRI/2018/04/012966), data of adult patients (18–60 years) operated for LT due to end stage chronic liver disease, from year 2010 to 2016, was retrieved from the hospital information system. Data for patients with incomplete medical records, and patients operated for acute on chronic liver failure, and for acute liver failure were excluded. The American Diabetic Association (ADA) defines DM as HbA1c >6.5.[15] We divided the patients into 2 groups depending upon HbA1c level (Group 1 (HbA1C ≥6.5) and Group 2 (HbA1C <6.5)).

Primary outcome of this study was to see association between preoperative HbA1c level and post-operative mortality during stay in intensive care unit in recipients undergoing of liver transplant surgery. Secondary outcomes were various morbidity factors such as postoperative renal complications (post-operative acute kidney injury, urinary tract infection, need for renal replacement/dialysis therapy), respiratory complication (respiratory infection, pleural effusion), cardiovascular complication, neurological complication, sepsis, other infections (abdomen and cytomegalovirus), episodes of cellular rejection requiring steroid pulse therapy, re-intubatation, duration of ICU, and hospital stay.

Infection was defined using CDC (center for disease control criteria) definition.[16] Infection was further categorized on the basis of source of positive microbial cultures into respiratory tract, urinary tract and abdominal infection. Sepsis was defined using updated survival sepsis guidelines year 2016. Diagnosis of acute kidney injury (AKI) was made according to AKIN (acute kidney injury network) criteria.

Statistics

Statistical analyses were performed using SPSS Statistics 21 for Mac (IBM). Continuous variables were expressed as medians and interquartile range (IQRs). Continuous variables were compared with the student *t* test or Mann-Whitney test as appropriate. Differences between proportions derived from categorical data were compared with Chi-square or Fisher's exact test. Variables that correlated with HBbA1c levels and postoperative mortality and morbidity in the univariate analysis ($P < 0.05$) were included in the multivariate forward logistic regression analysis. *P* value of less than 0.05 was considered significant.

Results

Baseline characteristics

A total of 421 patients were operated for liver transplant during the study period from January 2010 to September 2016. Of these 421 patients, 58 patients were operated for acute liver failure (ALF) or were of age below 18 years, 32 for acute-on chronic liver failure (ACLF), were therefore not included. Data for 107 patients was incomplete and were therefore also not included. After exclusion, 224 patients were included in the data analysis. Based on ADA criteria, 24 patients were in Group 1 (HbA1C ≥ 6.5) and 200 patients in Group 2 (HbA1C < 6.5) [Figure 1].

Out of these 224 patients, 200 underwent live donor liver transplant and 24 underwent deceased donor liver transplant. The study group consist of 85.7% male with mean age of 45.9 ± 9.9 years. The average MELD (Model of end stage liver disease) score, MELD sodium and CTP (Child-Turcotte-Pugh) score was 19 ± 6, 22 ± 6 and 10.4 ± 1.6 respectively. Average Pre-operative HbA1c level was 5.88 ± 0.71.

Most common etiology for end stage liver disease (ESLD) was ethanol related CLD 92 (41%), followed by cryptogenic CLD 46 (20.5%), Hepatitis B virus 24 (10.7%), non-alcohol steatohepatitis 21 (9.3%), primary biliary cirrhosis 7 (3.1%), hepatitis C virus 18 (8%), primary sclerosis cholangitis 5 (2.2%), and other 11 (4.9%).

Primary analysis

No correlation of HbA1c was seen with age (P-0.15), gender (P- 0.85), BMI (P-0.08), and etiology (P-0.06).There was also no correlation seen of HbA1c with jaundice, preoperative ascites, hepatic encephalopathy, CTP score, MELD score, MELD Sodium score, pre-operative AKI, spontaneous bacterial peritonitis, hepatorenal, and hepatopulmonary syndrome [Table 1]. Significant correlation of HbA1c was seen with preoperative ascites (P-0.04), CTP score (P-0.03), MELD score (P-0.01), and MELD Sodium score (P-0.02)

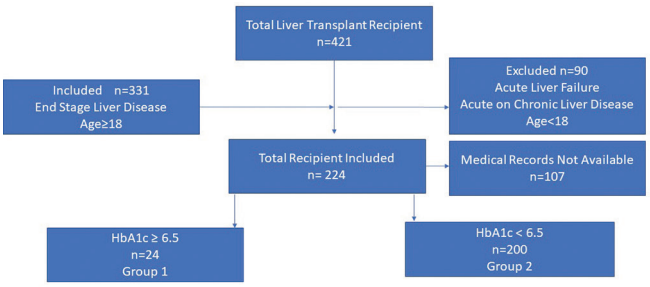

Figure 1: Flow Chart

Table 1: Demographic data and perioperative variables

Category	Total	Group 1 (HBA1C ≥6.5)	Group 2 (HbA1c <6.5)	*P*
Age (years) (Mean±SD)	45.9±9.9	49.65±5.6	46.7±9.6	0.156
Male (%)	192 (85.7)	20 (83.3)	172 (86)	0.857
BMI (Kg/m^2) (Mean±SD)	24.3±4.9	26.19±5.3	24.4±4.5	0.085
HbA1c (%) (Mean±SD)	5.88±0.71	7.34±0.88	4.79±0.63	0.031*
Diagnosed patients with diabetes mellitus (percent)	72 (32.1)	22 (91.7)	50 (25)	0.000
Fasting blood sugar (mg/dl)	110±51.6	175±112.6	110±51.6	0.000
Jaundice (%)	203 (90.6)	19 (79.1)	184 (92)	0.164
Ascites (%)	210 (93.8)	19 (79.1)	191 (95.5)	0.042*
Hepatic encephalopathy (%)	121 (54)	10 (41.6)	111 (55.5)	0.284
CTP Score (Mean±SD)	10.4±1.6	9.78±2	10.5±1.5	0.038*
MELD Score (Mean±SD)	19±6	15.6±7	26±20	0.019*
MELD Sodium (Mean±SD)	22±6	18.8±6.7	21.9±6.2	0.026*
Preoperative AKI (%)	67 (29.9)	6 (25)	61 (30.5)	0.672
Spontaneous bacterial peritonitis (%)	55 (24.6)	3 (13)	52 (26)	0.176
Hepatorenal syndrome (%)	21 (9.4)	1 (4.2)	20 (10)	0.383
Hepatopulmonary syndrome (%)	16 (7.1)	3 (12.5)	13 (6.5)	0.246

*Significant. BMI: Body Mass Index, HbA1c: Glycosylated hemoglobin, CTP: Child-Turcotte-Pugh, MELD: Model for End-Stage Liver Disease, AKI: Acute kidney injury

There was statistically significant difference in perioperative insulin requirement (100% patients in group 1 and 82.5% patients in group 2, $P = 0.03$). Post-operative glycemic control was insulin dependent and uncontrolled in group 1 (*P* value of 0.000) [Figure 2].

Secondary analysis

Multiple Logistic regression analysis was used to assess for the association of HbA1c with various outcomes like death etc. after adjusting for age, gender, and hemoglobin. There was no difference seen between 2 study groups, when compared to postoperative death (primary outcome), post-operative AKI, requirement of renal replacement therapy, cardiovascular complication, positive microbiology cultures from specimen drawn from respiratory, urinary tract, abdominal drain, incidence of cytomegalovirus infection, pleural effusion, sepsis, neurological complication, rejection, incidence of re-intubation, intensive care unit stay, and total hospital stay [Table 2]. Glycated hemoglobin cannot predict 30-day survival (Area under curve {AUC} = 0.629, *P* value 0.05).

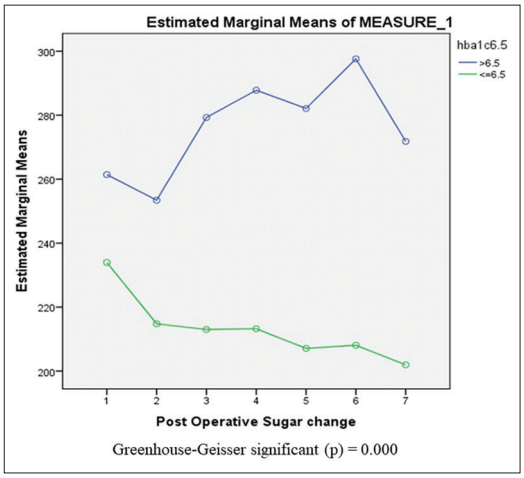

Figure 2: Post-operative glycemic control was insulin dependent and uncontrolled in group 1 with *P* value of 0.000

Discussion

In the present study, preoperative levels of glycosylated hemoglobin in patients of ESLD undergoing liver transplant is not associated with mortality and other complications, contrary to data on general surgical population.

An earlier study showed that HbA1c is not a reliable predictor of glycemic control in patients with decompensated cirrhosis, especially in those with severe anemia. We however found good correlation of HbA1c with fasting blood sugars in patients of ESLD posted for LT. Patients in our study population had a mean hemoglobin level of 8.8 mg/dL whereas in the previous study it was 11.8 mg/dL which probably explains the difference in conclusions drawn.[17]

Steroid used for immunosuppression after solid organ transplant tends to worsen glycemic control. In the present study, insulin was required in 187 (84.2%) patients after surgery. Out of these, only 72 were diagnosed DM in preoperative period reflecting precipitation of poor glycemic control upon stress of surgery and or institution of steroid based immunosuppreassion. We also found need for insulin supplementation in patients with or without history of DM attributed to use of steroid for immunosuppression. We found higher insulin requirement for regulation of blood glucose in group 1.[18]

Bragança[7] and colleagues also studied the correlation of preoperative DM and its impacts on a 3-month follow-up and if method of diagnosis of DM (Fasting Blood Glucose Vs GTT {glucose tolerance test}) had any impact on the outcome measures studied. Diabetes mellitus identified by oral GTT was associated with significantly higher prevalence of infectious

Table 2: Multiple Logistic Regression analysis of various intraoperative and post operative factors between two groups

Category	Total	Group 1 (HbA1c ≥6.5)	Group 2 (HbA1c <6.5)	aOR [95%CI]*	*P*
Post-operative AKI (%)	72 (32.1)	10 (41.6)	62 (31)	1.7 [0.7-4.3]	0.238
Post-operative Dialysis requirement (%)	13 (5.8)	1 (4.1)	12 (6)	0.74 [0.1-6.0]	0.753
Cardiovascular complication (%)	52 (23.2)	7 (29.1)	45 (23)	1.2 [0.4-3.7]	0.805
Neurological complication (%)	78 (35)	8 (33.3)	70 (35)	0.98 [0.4-2.5]	0.975
Sepsis (%)	61 (27.2)	5 (20.8)	56 (28)	0.75 [0.26-2.1]	0.532
Respiratory infection (%)	70 (31.2)	6 (25)	64 (32)	0.78 [0.3-2.1]	0.781
Pleural effusion (%)	86 (38.3)	11 (45.8)	75 (37.5)	1.62 [0.66-3.96]	0.253
Urinary tract infection (%)	28 (12.5)	3 (12.5)	25 (12.4)	1.1 [0.3-4.1]	0.867
Abdomen infection (%)	47 (21)	5 (20.8)	42 (20.9)	1.1 [0.4-3.3]	0.820
Cytomegalovirus infection (%)	27 (12.1)	4 (16.6)	23 (11.5)	1.6 [0.5-5.1]	0.442
Rejection (%)	20 (9)	1 (4.1)	19 (9.5)	0.6 [0.07-4.9]	0.635
Re-intubatation (%)	38 (17)	5 (20.8)	33 (16.5)	1.36 [0.47-3.95]	0.346
ICU days Stay Median (range)	11 (3-213)	10 (4-47)	11 (3-213)	-	0.634
Total hospital days stay Median (range)	22 (4-213)	20 (4-49)	23 (4-213)	-	0.577
Postoperative Death	21 (9.4)	4 (16.6)	17 (8.5)	2.38 [0.7-7.9]	0.164

*Adjusted for Hemoglobin values, age and sex, aor: Adjusted Odds Ratio

complications and deaths in a 3-month period ($P = 0.017$). In another study by Montano *et al*. hyperglycemia during the first 48 hours after liver transplantation was not associated with a higher risk for infection, rejection, and longer hospital stay.[19] Similarly in study by Tsai *et al*. no differences between diabetic and nondiabetic recipients were noted in terms of the incidence major infections.[20] We did not do GTT and instead relied only on preoperative fasting blood glucose and HbA1C levels to diagnose DM and also did not find any correlation of HbA1C levels with infective complications, postoperative respiratory, abdominal infections and incidence of culture positive sepsis. The reason for the observed lack of correlation with infection is probably aggressive glycemic control after surgery within prescribed limits of 140–180 mg/dl as also concluded by Ramos *et al*. coupled with good clinical practices including aseptic precautions that are practiced.[21]

In a study by John *et al*., 57 patients with preexisting DM undergoing LT were compared with age, sex, and race-matched patients without DM. Pretransplantation serum creatinine was significantly higher in the diabetic group compared with controls. Higher incidence in DM patients was seen for all complications including cardiovascular, major and minor infections renal, respiratory, neurologic complications. The duration of hospital stay, cost of hospitalization, retransplantation, and overall graft survival were similar.[22] In the present study, we did not find any correlation of preoperative DM and postoperative infectious, cardiovascular, renal, and neurologic complications. The duration of ICU and Hospital stay was also similar in patients with or without DM in this study.

John *et al*.[22] in their study found, higher incidence of acute rejection (50.9%) in patients with DM compared with 25.4% in controls ($P < 0.0009$). One-year (87% vs. 77%) and 2-year (81.6% vs. 70.1%) patient survival was similar. In another study by Zein *et al*.[23] no difference in rate of acute rejection was seen between patients with and without DM. Zein *et al*.[23] also did not find any impact of DM on overall survival after LT. We also did not find any difference in rate of acute rejection in patients with or without DM, probably due to refined immunosuppression practices. Survival at post-operative day 30 was also similar into two study groups.

Conclusion

Preoperative glycated hemoglobin level is not associated with postoperative morbidity and mortality in patients scheduled for liver transplant.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Zarrinpar A, Busuttil RW. Liver transplantation: Past, present and future. Nat Rev Gastroenterol Hepatol 2013;10:434-40.
2. Park GC, Song GW, Moon DB, Lee SG. A review of current status of living donor liver transplantation. Hepatobiliary Surg Nutr 2016;5:107-17.
3. Burra P, Senzolo M, Adam R, Delvart V, Karam V, Germani G, *et al*. Liver transplantation for alcoholic liver disease in Europe: A study from the ELTR (European liver transplant registry). Am J Transplant 2010;10:138-48.
4. Wei Y, Zhang L, Lin H, Li J, Li B, Yan L, *et al*. Factors related to post-liver transplantation acute renal failure transplant. Proc 2006;38:2982-4.
5. Hernandez MD, Martin P, Simkins J. Infectious complications after liver transplantation. Gastroenterol Hepatol (N. Y) 2015;11:741-53.
6. Moreno R, Berenguer M. Post-liver transplantation medical complications. Ann Hepatol Off J Mex Assoc Hepatol 2006;5:77-85.
7. Bragança AC, Alvares-da-Silva MR. Prevalence of diabetes mellitus and impaired glucose tolerance in patients with decompensated cirrhosis being evaluated for liver transplantation: The utility of oral glucose tolerance test. Arq Gastroenterol 2010;47:22-7.
8. Hernandez MD, Martin P, Simkins J. Infectious complications after liver transplantation. Gastroenterol Hepatol (N. Y) 2015;11:741-53.
9. Mells G, Neuberger J. Reducing the risks of cardiovascular disease in liver allograft recipients. Transplantation 2007;83:1141-50.

10. Abe T, Onoe T, Tahara H, Tashiro H, Ishiyama K, Ide K, *et al*. Risk factors for development of new-onset diabetes mellitus and progressive impairment of glucose metabolism after living-donor liver transplantation transplant. Proc 2014;46:865-9.
11. Selvin E, Steffes MW, Gregg E, Brancati FL, Coresh J. Performance of A1C for the classification and prediction of diabetes. Diabetes Care 2011;34:84-9.
12. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. WHO Guidelines Approved by the Guidelines Review Committee.Geneva: World Health Organization; 2011. PMID:26158184.
13. Mahmoodpoor A, Hamishehkar H, Shadvar K, Beigmohammadi M, Iranpour AS. Relationship between glycated hemoglobin, intensive care unit admission blood sugar and glucose control with ICU mortality in critically ill patients. Indian J Crit Care Med 2016;20:67-71.
14. Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. JAMA 2006;295:1688-97.
15. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2016;39(suppl 1):S1-106.
16. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309-32.
17. Nadelson J, Satapathy SK, Nair S. Glycated hemoglobin levels in patients with decompensated cirrhosis. Int J Endocrinol 2016;2016:8390210.
18. Kim SH, Kim JM, Lee KA, Park TS, Baek HS, Yu HC, *et al*. Effect of liver transplantation on glucose levels in patients with prediabetes or type 2 diabetes. Transplant Proc 2014;46:225-9.
19. Builes Montaño CE, Montoya JF, Londoño CA, Palacios Bayona KL, Restrepo Gutiérrez JC, Restrepo JG, *et al*. Complications associated with hyperglycemia in liver transplant patients. Rev Gastroenterol Méx 2014;79:180-6.
20. Tsai MS, Wang YC, Wang HH, Lee PH, Jeng LB, Kao CH. Pre-existing diabetes and risks of morbidity and mortality after liver transplantation: A nationwide database study in an Asian population. Eur J Intern Med 2015;26:433-8.
21. Ramos-Prol A, Hervás-Marín D, Rodríguez-Medina B, Rubio-Almanza M, Berenguer M, Moya-Herraiz Á, *et al*. Intensified blood glucose treatment in diabetic patients undergoing a liver transplant: Impact on graft evolution at 3 months and at 5 years. J Endocrinol Invest 2018;41:821-9.
22. John PR, Thuluvath PJ. Outcome of liver transplantation in patients with diabetes mellitus: A case-control study. Hepatology 2001;34:889-95.
23. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. J Hepatol 2000;32:209-17.