Influence of Type 2 Diabetes Mellitus and Preoperative Hemoglobin A1c Levels on Outcomes of Liver Transplantation

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Liver transplant centers often establish hemoglobin A1c (HbA1C) criteria for candidates with type 2 diabetes mellitus (T2DM) based on data from other surgical specialties showing worse outcomes in patients with poor glycemic control. However, because of the reduced reliability of HbA1C in cirrhosis, it is unclear whether pretransplant HbA1C values are predictive of postoperative complications in liver recipients. We retrospectively examined the association between preoperative HbA1C and postoperative outcomes in 173 consecutive patients who underwent liver transplantation at the University of Cincinnati Medical Center between August 2012 and March 2015. Demographic correlates of pretransplant HbA1C included age, T2DM, native Model for End-Stage Liver Disease, hemoglobin, serum albumin, and nonalcoholic steatohepatitis as the indication for transplantation. No association was identified between pretransplant HbA1C and most outcome measures, including survival, length of stay, reoperation or readmission rates, rejection, bacteremia, and viremia. Significant correlates of HbA1C in liver recipients with diabetes were posttransplant insulin requirement and anastomotic biliary stricture formation. On multivariate analysis, HbA1C was the sole determinant of biliary strictures, with patients in the highest quartile (HbA1C >7.3%) exhibiting a 4-fold increased risk. Correlation of HbA1C with morning blood glucose levels was much tighter after versus before transplantation. *Conclusion:* Preoperative HbA1C is predictive of anastomotic biliary stricture formation and the need for insulin following liver transplantation. (*Hepatology Communications* 2019;3:574-586).

Glucose metabolism is commonly impaired in individuals with advanced liver disease, primarily as a result of increased peripheral insulin resistance and diminished insulin secretion.[1,2] As many as 80% of patients with cirrhosis have some degree of glucose intolerance, with up to one third manifesting overt diabetes mellitus.[3-5] In the majority of patients with cirrhosis, the observation that glycemic control markedly improves following liver transplantation[6] supports the notion that hepatic dysfunction is a principal contributor to the pathogenesis of altered glucose tolerance in patients with cirrhosis. Although required by many transplant centers, the need for and impact of strict blood sugar regulation on postoperative outcomes is not well established.[7]

A standard measure of diabetic control is hemoglobin A1c (HbA1C), which corresponds to the percentage of hemoglobin that is irreversibly glycosylated.[8] Maintenance of HbA1C levels below 7%

Abbreviations: ACR, acute cellular rejection; BMI, body mass index; CAD, coronary artery disease; CLD-A1C, chronic liver disease A1c; Corr. coeff., correlation coefficient; CX3CR1, C-X3-C motif chemokine receptor 1; GA, glycated albumin; HAT, hepatic artery thrombosis; HbA1C, hemoglobin A1c; HCC, hepatocellular carcinoma; MBG, morning blood glucose; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; POD, postoperative day; T2DM, type 2 diabetes mellitus.

Received September 22, 2018; accepted January 30, 2019.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep4.1323

Potential conflict of interest: Nothing to report.

has been associated with a decrease in microvascular complications[9,10] and cardiovascular events[11,12] in individuals with type 2 diabetes mellitus (T2DM). Elevated HbA1C levels have been directly correlated with worse outcomes following vascular,[13] coronary artery bypass,[14-18] colorectal,[19] and arthroscopic[20] surgeries, including increased rates of superficial and deep wound infections, major cardiovascular events, and in-hospital mortality. With regard to solid organ transplantation, elevated preoperative HbA1C levels have been strongly associated with worse survival in lung transplant recipients[21] and with late onset coronary artery disease (CAD) in the allograft of heart transplant recipients.[22]

The effect of aggressive glycemic management in liver transplant candidates on posttransplant outcomes has not been systematically evaluated. Because it is dependent on erythrocyte lifespan, HbA1C has been shown to be a less reliable marker of glucose control in patients with hepatic dysfunction.[23,24] This is because nutritional deficiencies and vascular shunting enhance erythrocyte survival and falsely elevate HbA1C levels, while hypersplenism, gastrointestinal bleeding, and hemolysis accelerate red blood cell turnover, thereby reducing HbA1C values. Previous studies have shown lower than expected HbA1C levels in patients with chronic liver disease[25,26]; this raises concern about the applicability of current HbA1C recommendations in patients with impaired liver function.

In the present study, we assess the predictive value of preoperative HbA1C values on the outcomes of liver transplant recipients and further examine the effect of transplantation on the correlation between blood glucose and HbA1C levels.

Patients and Methods

A retrospective chart review was performed on 184 consecutive patients who underwent liver transplantation at the University of Cincinnati Medical Center between August 2012 and March 2015. Over this time period, a single stable team of four surgeons performed all liver transplant operations, and all allografts were from deceased donors. Biliary reconstruction was performed by end-to-end choledocho-choledochostomy. Patients were excluded from the analysis if they did not have an HbA1C level measured within 3 months prior to liver transplantation (n = 11). If more than one HbA1C level was available, the result obtained closest to the time of transplant was selected.

All patients received standard immunosuppression consisting of corticosteroids, mycophenolate mofetil, and a calcineurin inhibitor (primarily tacrolimus). Goal trough levels for tacrolimus were 10 to 12 ng/mL for postoperative days (PODs) 1 to 30, 8 to 10 ng/mL for PODs 31 to 180, and 3 to 8 ng/mL thereafter. In patients who could not tolerate tacrolimus, cyclosporine was substituted with goal trough levels 150 to 200 ng/mL, 100 to 150 ng/mL, and 75 to 125 ng/mL, respectively. Mycophenolate mofetil was initiated immediately posttransplantation at a dose of 500 mg every 12 hours and continued indefinitely. Corticosteroids were gradually withdrawn over the first 3 months posttransplant according to the following protocol: intravenous methylprednisolone on PODs 0 to 3, oral prednisone taper from 50 to 20 mg daily over the first week to 10 mg daily over the first month, and then gradually off by POD 90. Liver recipients with impaired renal function or who were on hemodialysis at the time of transplantation

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received thymoglobulin with delayed introduction of tacrolimus starting on POD 7. Deviation from this protocol due to drug side effects/toxicity, infection, malignancy, or acute cellular rejection (ACR) was at the discretion of the treating physician.

Patient outcome measures included death and/or graft loss, hospital length of stay, reoperation (within 3 months of transplant), bile leak, biliary stricture, discharge to home, hospital readmission rates at 3 months and 1 year posttransplant, biopsy-proven ACR, cytomegalovirus viremia (by quantitative polymerase chain reaction), bacteremia or fungemia (positive blood culture), serum creatinine at 1 year (excluding patients on hemodialysis), need for hemodialysis at 1 year, ongoing insulin requirement (at 3 months and 1 year), and body mass index (BMI) at 1 year. Patients were considered to have an anastomotic biliary stricture if endoscopic retrograde cholangiopancreatography revealed an abnormal narrowing at the common bile duct anastomosis and subsequently required stent placement. Patients who died within 24 hours of transplant (n = 4) were censored from the outcome analysis, except for survival calculations. Subgroup analyses were performed on the recipient cohorts with and without T2DM prior to transplantation. Patients with hepatocellular carcinoma (HCC) were analyzed according to their underlying disease in addition to being analyzed as a separate cohort. In subjects who had an available morning blood glucose (MBG; defined as serum glucose drawn prior to 9 AM) level obtained within 3 months of both the pretransplant and posttransplant HbA1C, levels were correlated with the HbA1C. If more than one MBG was available, the median MBG value was used. This study was approved by the University of Cincinnati institutional review board (protocol CR4 2013-4309).

STATISTICS

Data were analyzed using a computer-based statistical package (SSI SigmaStat; Systat Software, Inc., San Jose, CA). For normally distributed data, one-way analysis of variance with Holm-Sidak post hoc analysis was used to correct for multiple hypothesis testing. For data that were not normally distributed, we used a nonparametric Kruskal-Wallis test. A Pearson Product Moment test was used for correlations between continuous variables. Multivariable analysis was performed by logistic regression that included parameters with correlations of $P < 0.10$.

Results

DEMOGRAPHIC CORRELATES OF T2DM IN LIVER TRANSPLANT RECIPIENTS

Of the 184 patients who underwent liver transplantation over the study period, 173 had a preoperative HbA1C measured within 3 months of surgery and were included in the analysis. Demographic information for the entire cohort as well as data stratified by presence or absence of pretransplant T2DM are shown in Table 1. The main indications for liver transplantation were chronic hepatitis C, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), and/or HCC (Fig. 1). Compared to recipients without diabetes, those with T2DM were significantly older, more often Caucasian, and more likely to have received a dual organ (liver–kidney) transplant. Patients with T2DM were also more likely to have CAD, higher HbA1C levels, and NASH as the indication for transplant. Median follow-up for the entire cohort was 2.1 years (range, 0-3.8 years). Follow-up was slightly longer in patients without T2DM compared to those with T2DM (2.3 versus 1.8 years, $P = 0.023$).

OUTCOMES OF LIVER TRANSPLANT IN RECIPIENTS WITH AND WITHOUT T2DM

Liver transplant outcomes for the entire population as well as for the cohorts with and without diabetes are displayed in Table 2. Compared to recipients without diabetes, those with T2DM had significantly higher creatinine (1.36 versus 1.19 mg/dL, respectively; $P = 0.012$) and BMI values (30.1 versus 28.3; $P = 0.030$) 1 year posttransplant and were more likely to develop an anastomotic biliary stricture (24.5% versus 11.1%; $P = 0.025$). Notably, all biliary strictures identified in the entire patient cohort were at the site of the choledocho-choledochostomy anastomosis. Patients with diabetes also had significantly higher readmission rates within 3 months of transplantation (66.0% versus 48.7%; $P = 0.041$) and were more

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

Characteristic (n; % of total)	All Subjects (n = 173)	Subjects Without Diabetes (n = 119)	Subjects With Diabetes (n = 54)	*P* Value
A. CATEGORICAL VARIABLES				
Male	117 (67.6)	76 (63.9)	41 (75.9)	0.118
Ethnicity				
Caucasian	148 (85.5)	96 (80.7)	52 (96.3)	0.007
Black	19 (11.0)	17 (14.3)	2 (3.7)	0.040
Other	6 (3.5)	6 (5.0)	0	0.095
Indication for transplant				
Hepatitis C	61 (35.3)	46 (38.7)	15 (27.8)	0.167
Alcohol	59 (34.1)	45 (37.8)	14 (25.9)	0.128
NASH	37 (21.4)	10 (8.4)	27 (50.0)	<0.001
HCC	40 (23.1)	31 (26.1)	9 (16.7)	0.177
Dual organ*	11 (6.4)	4 (3.4)	7 (13.0)	0.017
Status 1A†	2 (1.2)	2 (1.7)	0	0.344
Hemodialysis	34 (19.7)	21 (17.6)	13 (24.1)	0.327
CAD	14 (8.1)	6 (5.0)	8 (14.8)	0.030
DCD	12 (7.0)	6 (5.0)	6 (11.1)	0.162

	All Subjects (n = 173)		Subjects Without Diabetes (n = 119)		Subjects With Diabetes (n = 54)		
Characteristic	Median	Range	Median	Range	Median	Range	*P* Value
B. QUANTITATIVE VARIABLES							
Age	58.2	24.9-76.9	57.5	24.9-76.9	59.4	42.3-70.7	0.022
BMI	29.3	17.0-62.7	29.2	17.0-49.5	30.4	21.6-62.7	0.127
MELD (native)	22.0	6-40	23.0	6-40	21.5	8-24	0.332
HbA1C (%)	5.0	3.0-11.2	4.8	3.0-7.1	6.0	4.2-11.2	<0.001
Hemoglobin (g/dL)	9.8	6.4-17.5	9.7	6.4-17.5	10.3	7.1-16.3	0.332
Albumin (g/dL)	3.0	1.5-5.1	3.0	1.5-4.6	3.0	1.9-5.1	0.384
Creatinine‡ (mg/dL)	1.05	0.45-4.30	1.05	0.53-4.30	1.05	0.45-3.07	0.846
Total ischemia time (minutes)	366	119-922	361	119-922	373	150-756	0.924
Warm ischemia time (minutes)	37	20-60	36	27-56	37	20-60	0.751
Follow-up (years)	2.1	0-3.8	2.3	0-3.8	1.8	0-3.8	0.023

*Patients who received a simultaneous liver–kidney transplant.
†Patient listed at the highest priority for liver transplantation due to acute liver failure.
‡Patients on hemodialysis excluded.
Abbreviation: DCD, donation after cardiac death.

likely to require insulin at both 3 months (97.9% versus 51.3%; $P < 0.001$) and 1 year (89.1% versus 8.0%; $P < 0.001$). We found no association between T2DM and transplant-free survival, postoperative infection (either bacterial, fungal, or viral), length of posttransplant hospitalization, or re-operation rate.

CORRELATES OF PRETRANSPLANT HbA1C LEVELS

In the total cohort, pretransplant HbA1C correlated with T2DM, age, BMI, CAD, serum albumin and hemoglobin levels, and NASH as the indication for transplantation (Table 3). The only factor negatively associated with HbA1C was the native Model for End-Stage Liver Disease (MELD). A correlation between HbA1C and serum albumin was found in both liver recipients with diabetes and recipients without diabetes. In recipients with T2DM, HbA1C also correlated directly with BMI and inversely with native MELD and alcohol as an indication for transplant. Unique to recipients without diabetes were associations between pretransplant HbA1C and age, hemoglobin level, and HCC.

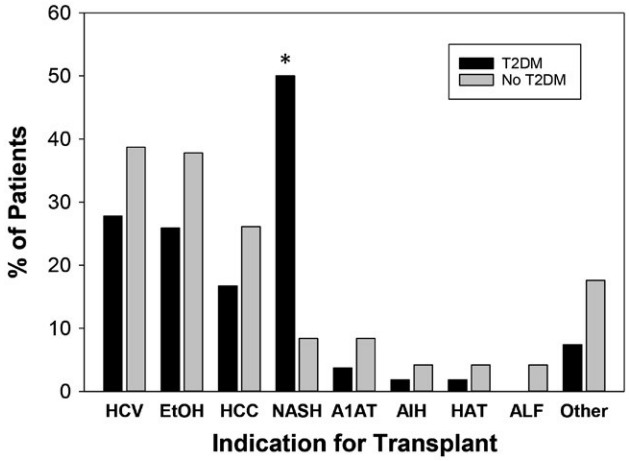

FIG. 1. Indications for liver transplantation. The percentage of all liver recipients with each indication for transplantation stratified by the presence (dark bars) or absence (gray bars) of T2DM prior to transplant. Because some patients had more than one indication, the total percentage exceeds 100. The category "other" includes diagnoses comprising less than 2.5% of cases, including chronic hepatitis B, primary sclerosing cholangitis, primary biliary cholangitis, drug-induced liver disease, polycystic liver disease, cryptogenic cirrhosis, hereditary hemochromatosis, sarcoidosis, human immunodeficiency virus, chronic cellular rejection, and primary graft nonfunction. *NASH as the indication for transplant was significantly more common in patients with T2DM ($P < 0.001$). Abbreviations: A1AT, alpha-1-antitrypsin; AIH, autoimmune hepatitis; ALF, acute liver failure; EtOH, ethanol; HCV, hepatitis C virus.

With regard to transplant outcomes in the entire patient cohort (Table 4), pretransplant HbA1C correlated with anastomotic biliary stricture formation ($P = 0.015$), serum creatinine at 1 year ($P = 0.013$), HbA1C levels at 3 months ($P = 0.019$), and the need for insulin therapy at both 3 months ($P < 0.001$) and 1 year ($P < 0.001$). These associations were mainly attributable to the subgroup of patients with T2DM, except for serum creatinine at 1 year, which correlated with pretransplant HbA1C levels only in the subgroup without diabetes ($P = 0.005$).

ASSOCIATION BETWEEN PRETRANSPLANT HbA1C AND ANASTOMOTIC BILIARY STRICTURES

A significant correlation between pretransplant HbA1C and anastomotic biliary stricture formation ($P = 0.022$) was confined to those recipients with T2DM (Fig. 2). Moreover, in the total cohort (Table 5), univariate analysis confirmed a significant correlation between anastomotic biliary stricture formation and preoperative T2DM ($P = 0.024$) as well as with insulin ($P = 0.011$) and oral hypoglycemic therapy ($P = 0.030$). By multivariable analysis, employing a model that included patient age, BMI, T2DM, hemoglobin, serum creatinine, dual organ transplant, native MELD, and NASH as the indication for transplant, HbA1C was identified as the only significant correlate of anastomotic biliary stricture formation ($P = 0.018$). Patients with HbA1C values in the highest quartile exhibited a 2.6-fold increased risk of developing an anastomotic biliary stricture compared with those in the lowest quartile (28.6% versus 10.7%, respectively) (Fig. 3A).

In the subset of patients with T2DM (Table 5), the two significant correlates of anastomotic biliary stricture formation identified by univariable analysis were pretransplant HbA1C level ($P = 0.022$) and warm ischemia time ($P = 0.026$). However, on multivariable analysis (taking into account additional correlates with $P < 0.1$, including dual organ transplant and hemodialysis), only HbA1C remained significantly associated with anastomotic stricture formation ($P = 0.048$). In support of this finding is the apparent dose-dependent relationship between pretransplant HbA1C and anastomotic biliary strictures in the subgroup of liver recipients with diabetes (Fig. 3B). Patients in the subgroup without diabetes also exhibited a dose-dependent relationship between HbA1C and biliary stricture formation when analyzed using identical HbA1C ranges as the subgroup with T2DM (Fig. 3C). Notably, total and warm ischemia times, as well as the proportion of patients receiving a donation after cardiac death organ were similar between patients with and without diabetes (Table 1A,B). None of the patients with T2DM received a transplant for acute liver failure or developed hepatic artery thrombosis (HAT) following transplantation (Fig. 1; Table 2A). There were no associations between anastomotic biliary stricture formation and pre-operative MELD score, recipient age, HAT, bile leak, or ACR.

CORRELATES OF RENAL FUNCTION 1 YEAR AFTER LIVER TRANSPLANTATION

Liver recipients with pretransplant T2DM manifested significantly higher creatinine levels 1 year

TABLE 2. COMPARISON OF OUTCOMES IN LIVER RECIPIENTS WITH OR WITHOUT PRETRANSPLANT T2DM

Characteristic (n; % of total)	All Subjects (n = 173)	Subjects Without Diabetes (n = 119)	Subjects With Diabetes (n = 54)	*P* Value
A. CATEGORICAL VARIABLES				
Death or retransplant	28 (16.2)	17 (14.3)	11 (20.4)	0.317
1-year transplant-free survival	154 (89.0)	108 (90.8)	46 (85.2)	0.280
Reoperation	62 (36.5)	45 (38.5)	17 (32.1)	0.426
Bile leak	20 (11.8)	13 (11.1)	7 (13.2)	0.697
Biliary stricture	26 (15.3)	13 (11.1)	13 (24.5)	0.025
HAT	7 (4.1)	7 (6.0)	0	0.071
Discharged to home	108 (65.5)	75 (65.2)	33 (66.0)	0.925
Readmission at 3 months	89 (53.9)	56 (48.7)	33 (66.0)	0.041
Readmission at 1 year	110 (67.5)	72 (63.2)	38 (77.6)	0.073
ACR	17 (10.0)	14 (12.0)	3 (5.7)	0.207
Bacteremia	40 (15.9)	19 (16.2)	8 (15.1)	0.852
Fungemia	7 (4.1)	6 (5.1)	1 (1.9)	0.328
CMV viremia	13 (7.7)	8 (6.8)	5 (9.4)	0.559
Hemodialysis at 1 year	7 (4.4)	5 (4.4)	2 (4.4)	0.987
Insulin at 3 months	106 (65.0)	59 (51.3)	47 (97.9)	<0.001
Insulin at 1 year	50 (31.4)	9 (8.0)	41 (89.1)	<0.001

	All Subjects (n = 173)		Subjects Without Diabetes (n = 119)		Subjects With Diabetes (n = 54)		
Characteristic	Median	Range	Median	Range	Median	Range	*P* Value
B. QUANTITATIVE VARIABLES							
Length of stay (days)	10	4-108	9	4-108	10	4-56	0.269
Creatinine at 1 year (mg/dL)*	1.22	0.60-3.89	1.19	0.60-3.75	1.36	0.70-3.89	0.012
HbA1C at 3 months (%)	5.2	4.0-7.8	5.2	4.2-7.0	5.7	4.0-7.8	0.348
HbA1C at 1 year (%)	5.4	4.3-11.0	5.2	4.5-6.2	5.4	4.3-11.0	0.544
BMI at 1 year	28.7	17.5-46.5	28.3	17.5-46.5	30.1	21.6-42.1	0.030

*Patients on hemodialysis excluded.
Abbreviation: CMV, cytomegalovirus.

posttransplant compared to those without diabetes (Table 2B) despite similar creatinine levels and rates of hemodialysis at baseline (Table 1). Within the entire cohort (Table 6), there were significant correlations between serum creatinine at 1 year and both baseline creatinine ($P < 0.001$) and age at transplantation ($P = 0.004$). Additional correlates included CAD, NASH as the indication for transplant, pretransplant insulin requirement, and the pretransplant HbA1C level. On multivariable analysis, taking into account all univariate correlates with a *P* value <0.1, pretransplant creatinine ($P < 0.004$) and age at transplantation ($P < 0.02$) were the only independent factors significantly associated with 1-year posttransplant creatinine, both in the entire population as well as in the subgroup with diabetes. In the subgroup with T2DM, there was no correlation between 1-year serum creatinine and either pretransplant or posttransplant measures of diabetic control (e.g., HbA1C level, need for insulin).

In the subgroup of patients without diabetes, there was a significant association between pretransplant HbA1C levels and creatinine at 1 year. This finding was validated on multivariable analysis, demonstrating that male sex ($P = 0.041$), pretransplant creatinine ($P < 0.001$), and HbA1C ($P = 0.01$) were the only significant correlates of 1-year creatinine.

CORRELATION OF HBA1C WITH MBG LEVELS BEFORE AND AFTER TRANSPLANTATION

In the entire cohort, 63 patients had both HbA1C and MBG levels measured both before and after liver

TABLE 3. DEMOGRAPHIC CORRELATES OF PRETRANSPLANT HbA1C LEVELS IN PATIENTS UNDERGOING LIVER TRANSPLANTATION

	All Subjects (n = 173)		Subjects Without Diabetes (n = 119)		Subjects With Diabetes (n = 54)	
Characteristic	*P* Value	Corr. coeff.	*P* Value	Corr. coeff.	*P* Value	Corr. coeff.
Age	<0.001	0.254	0.018	0.216	0.118	
Alcohol	0.078		0.854		0.027	–0.301
HCC	0.099		0.003	0.269	0.909	
NASH	<0.001	0.283	0.815		0.107	
MELD (native)	0.013	–0.189	0.142		0.043	–0.277
BMI	0.040	0.156	0.363		0.048	0.271
Hemoglobin	0.0066	0.206	0.031	0.198	0.069	
Albumin	<0.001	0.281	<0.001	0.349	0.033	0.291
T2DM	<0.001	0.588				
CAD	0.021	0.175	0.259		0.722	

TABLE 4. LIVER TRANSPLANT OUTCOME ASSOCIATIONS WITH HBA1C

	All Subjects (n = 173)		Subjects Without Diabetes (n = 119)		Subjects With Diabetes (n = 54)	
Characteristic	*P* Value	Corr. coeff.	*P* Value	Corr. coeff.	*P* Value	Corr. coeff.
Biliary stricture	0.015	0.187	0.274		0.022	0.315
Creatinine at 1 year	0.013	0.201	0.005	0.270	0.778	
HbA1C at 3 months	0.019	0.413	0.879		0.031	0.680
Insulin at 3 months	<0.001	0.495	0.297		<0.001	0.351
Insulin at 1 year	<0.001	0.551	0.092		0.048	0.186

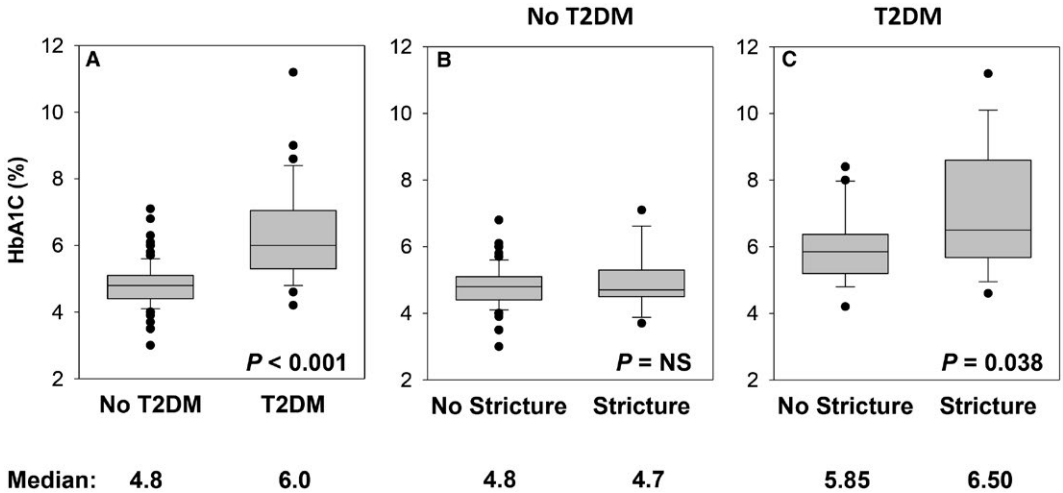

FIG. 2. Comparison of pretransplant HbA1C levels in liver transplant recipients with and without T2DM and, within those subgroups, patients who did or did not develop anastomotic biliary strictures. (A) Box (upper and lower quartiles) and whisker (farthest point within 1.5 interquartile ranges from the median) plots comparing pretransplant HbA1C levels in liver transplant candidates who carried the diagnosis of T2DM versus those who did not. The horizontal line reflects the median, and the dots reflect data points that lie outside the 10th and 90th percentiles. Median HbA1C levels were significantly higher in those with T2DM. (B,C) Similar plots comparing HbA1C levels in patients who did or did not develop anastomotic biliary strictures, stratified by the (B) absence or (C) presence of T2DM, respectively. Median HbA1C levels (displayed below the graphs) were significantly associated with stricture formation only in patients who carried the diagnosis of diabetes mellitus. Abbreviation: NS, not significant.

TABLE 5. DEMOGRAPHIC ASSOCIATIONS WITH BILIARY STRICTURE FORMATION

	All Subjects (n = 173)		Subjects Without Diabetes (n = 119)		Subjects With Diabetes (n = 54)	
Characteristic	*P* Value	Corr. Coeff.	*P* Value	Corr. Coeff.	*P* Value	Corr. Coeff.
HbA1C	0.015	0.187	0.274		0.022	0.315
T2DM	0.024	0.173				
Insulin therapy	0.011	0.196			0.187	
Oral agent	0.030	0.166			0.390	
Warm ischemia	0.219	0.020	0.909	–0.052	0.026	0.306

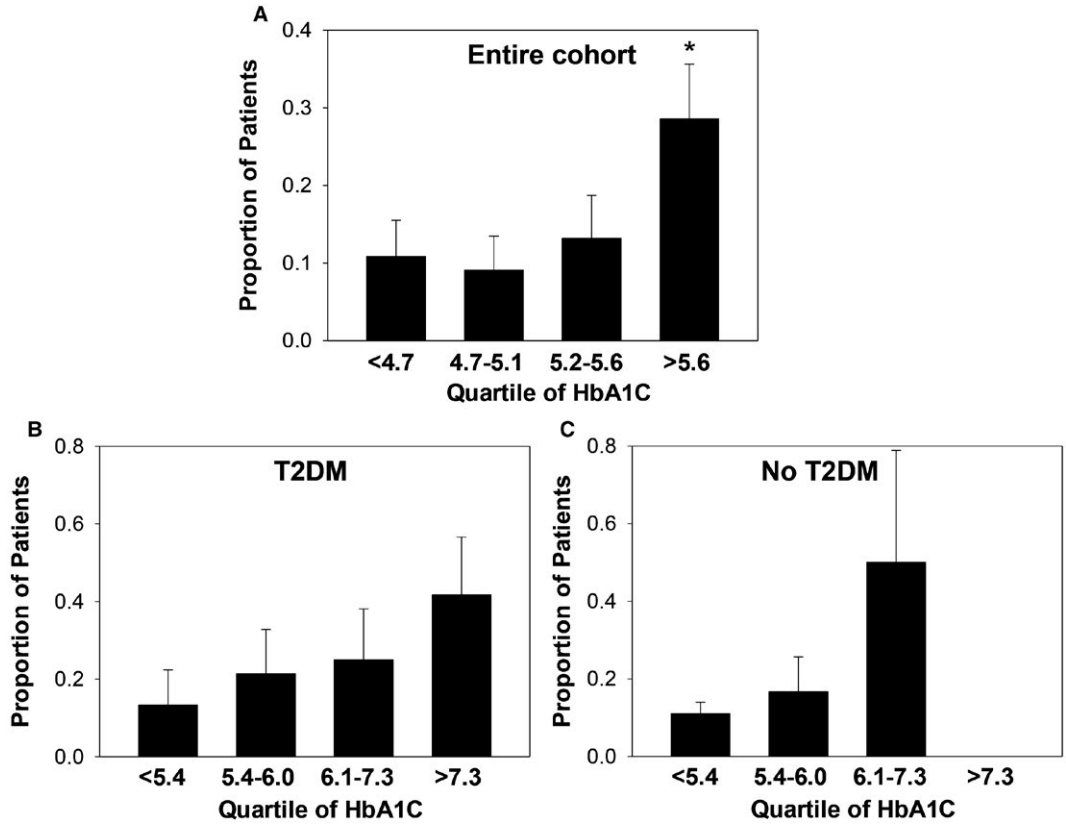

FIG. 3. Proportion of liver transplant recipients who developed biliary anastomotic strictures as stratified by quartile of pretransplant HbA1C. (A) Proportion of patients in the entire transplant cohort who developed an anastomotic biliary stricture plotted versus quartile of pretransplant HbA1C. (B) Similar plot for the subgroup of patients with pretransplant diabetes mellitus (T2DM). (C) Proportion of patients in the subgroup without diabetes who developed biliary strictures when stratified using the same quartile ranges as for the subgroup with diabetes. Only 4 patients in the subgroup without diabetes manifested an HbA1C above 6.0% (highest value 7.1%), and none fell within the fourth quartile. Bars represent the mean (± SEM). **P* = 0.037 versus all other quartiles.

transplantation. The demographics of this subgroup mirrored that of the entire transplant cohort: 43 (73%) were male individuals, 59 (94%) were Caucasian, and 28 (44%) carried the diagnosis of T2DM. Of the patients with diabetes mellitus, 17 (61%) were using insulin, 8 (29%) were taking oral hypoglycemic agents, and 3 (11%) were managed by diet alone. The median age at transplantation was 56.7 years (range, 17-71 years), BMI 29.6 (range, 16-63), native MELD 22 (range, 6-40), and hemoglobin 10.4 g/dL (7.6-15.3 g/dL). By univariate analysis, pretransplant MBG levels exhibited a significant correlation with T2DM (*P* = 0.002),

TABLE 6. CORRELATES OF SERUM CREATININE AT 1 YEAR

	All Subjects (n = 173)		Subjects Without Diabetes (n = 119)		Subjects With Diabetes (n = 54)	
Characteristic	*P* Value	Corr. coeff.	*P* Value	Corr. coeff.	*P* Value	Corr. coeff.
Age (years)	0.004	0.235	0.077		0.027	0.334
Male	0.083		0.026	0.214	0.597	
NASH	0.018	0.192	0.475		0.303	
HCV	0.083		0.861		0.005	–0.412
T2DM	0.008	0.251				
Insulin therapy	<0.001	0.276			0.058	0.288
Oral agent	0.680	0.166			0.040	–0.311
HbA1C	0.013	0.201	0.005	0.270	0.778	
Creatinine	<0.001	0.348	0.002	0.317	<0.001	0.575
CAD	0.017	0.194	0.090		0.246	
Hemodialysis	0.845		0.929		0.660	
Insulin at 3 months	0.099		0.432		0.478	
Insulin at 1 year	0.040	0.167	0.186		0.169	
HbA1C at 3 months	0.067	–0.388	0.114		0.238	
HbA1C at 1 year	0.208	–0.256	0.293		0.202	

Abbreviation: HCV, hepatitis C virus.

pretransplant BMI ($P = 0.043$), and the need for insulin at 1 year posttransplant ($P = 0.009$). Although there was a strong association between HbA1C and median MBG levels both before and after transplantation ($P < 0.0001$), the correlation was tighter (Fig. 4) and HbA1C values higher (Fig. 5) posttransplant. The improved correlation between HbA1C levels and MBG posttransplant was more pronounced in the cohort without diabetes (Fig. 6), as evidenced by a significant increase in median HbA1C levels (Fig. 7).

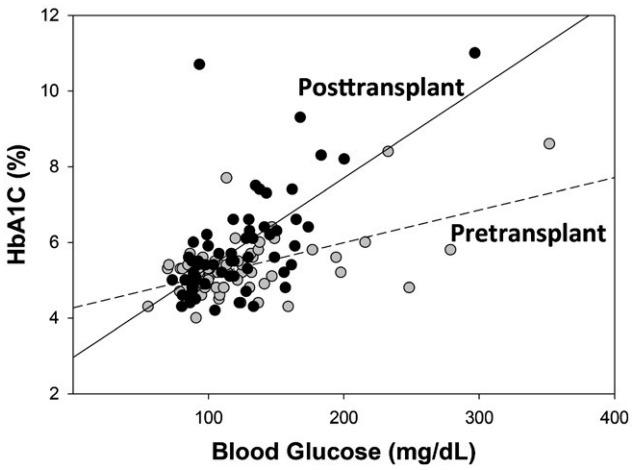

FIG. 4. Correlation between HbA1C and MBG levels before and after liver transplant. The median MBG is plotted against HbA1C levels obtained within 3 months prior to liver transplantation (gray symbols) and 1 year posttransplant (black symbols), with each circle representing an individual patient. Lines represent the results of linear regression analyses of pretransplant (dashed) and posttransplant (solid) data. R^2 values were 0.30 and 0.42, pretransplant and posttransplant, respectively. Results using minimum or maximum MBG levels (instead of median MBG) were highly concordant (data not shown).

Discussion

It is generally held that patients with diabetes mellitus have poorer outcomes following solid organ transplantation than those without diabetes. In liver transplant recipients, however, findings have been inconsistent, with some investigators reporting reduced 3- to 5-year survival and increased infectious and renal complications whereas others have shown minimal impact on outcomes.[27-33] We speculate that these discrepant results are due to several factors, including the effectiveness of pretransplant and posttransplant diabetic control, the duration of follow-up, and differences in patient selection, surgical technique, and medical management (both within and across studies). In the present analysis, we found that liver recipients with a history of T2DM had generally good outcomes although when compared to patients without diabetes were more likely to be readmitted within

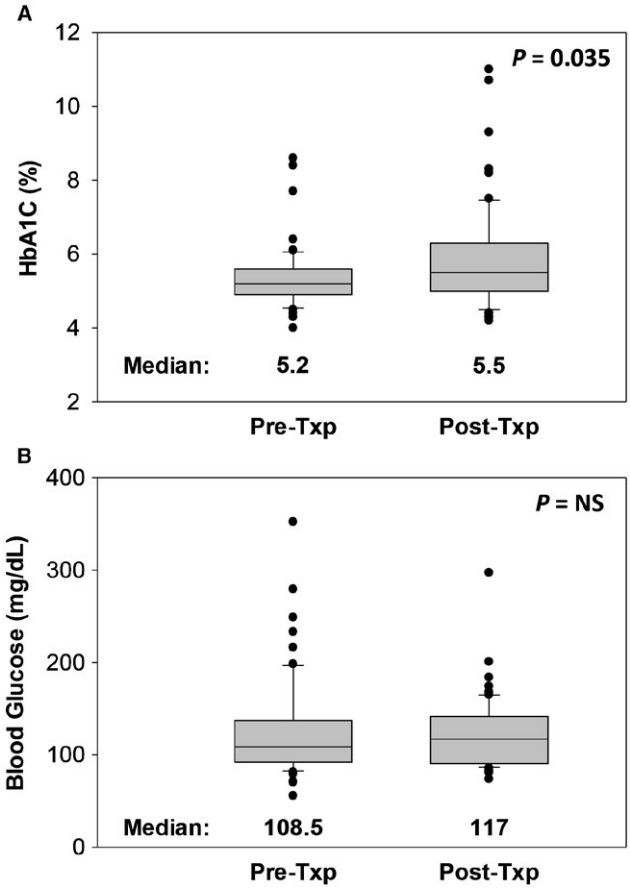

FIG. 5. Comparison of HbA1C and blood glucose levels in liver transplant recipients before and after transplantation. (A) Box and whisker plot comparing pretransplant and posttransplant HbA1C. (B) Similar analysis of median MBG levels. HbA1C levels were significantly higher 1 year posttransplant ($P = 0.035$) despite similar median MBG levels (P = NS). Abbreviations: NS, not significant; Txp, transplant.

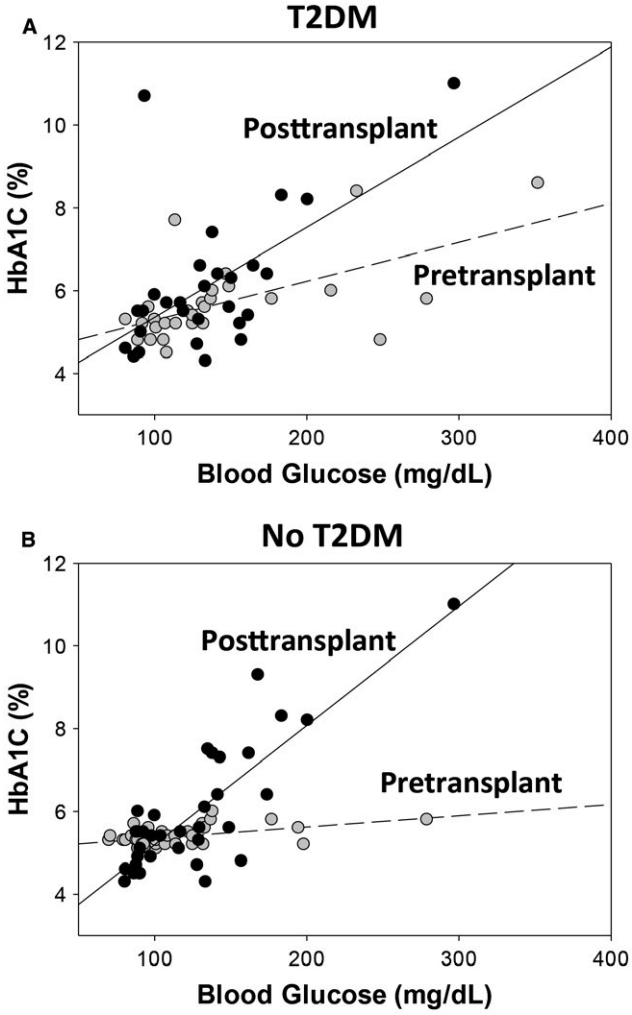

FIG. 6. Effect of liver transplantation on the association between HbA1C and MBG levels stratified by the presence or absence of T2DM diagnosis. (A,B) Median MBG is plotted versus HbA1C levels for (A) liver recipients with diabetes and (B) recipients without diabetes, as described in Fig. 4. Pretransplant and posttransplant R^2 values are 0.36 versus 0.23 and 0.34 versus 0.69, respectively. All correlations are highly significant ($P < 0.001$).

3 months of transplantation, to develop an anastomotic biliary stricture, and to have a higher BMI and ongoing insulin requirement at 1 year. Consistent with previous case-control studies,[27,31] we also noted that liver recipients with diabetes had significantly higher creatinine levels 1 year posttransplant. The presence of T2DM was not associated with nosocomial infections, length of stay, discharge disposition, or transplant-free survival.

A potential reason for the discrepant outcome data in previous reports for liver transplant recipients with T2DM is that most analyses did not consider the effect of pretransplant and posttransplant glycemic control. Our study is the first to specifically examine the correlation between HbA1C levels and liver transplant outcomes. The only prior investigation to address the impact of preoperative glycemia was by Katsura et al.,[34] who found that a preoperative fasting glucose of more than 100 mg/dL was associated with reduced 5-year (but not 1-year or 3-year) survival. We identified very few short-term adverse outcomes associated with pretransplant HbA1C in liver recipients with diabetes, namely the development of anastomotic biliary strictures and the need for insulin at 3 months and at 1 year.

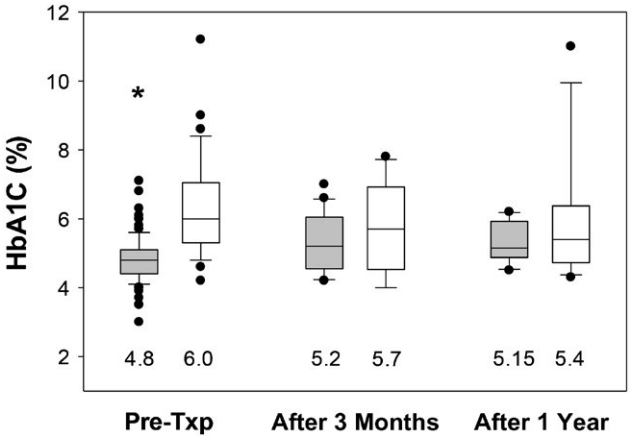

FIG. 7. Progression of HbA1C levels before and after transplantation in liver recipients with and without T2DM. Displayed is a box and whisker plot comparing pretransplant and 3-month and 1-year posttransplant HbA1C levels in the entire transplant cohort, as stratified by the presence (white boxes) or absence (gray boxes) of T2DM pretransplant. Median HbA1C levels are displayed. $^{*}P < 0.005$ versus all other groups. Abbreviation: Txp, transplant.

Consistent with prior studies,[27,31] we found that the serum creatinine at 1 year following liver transplant was higher in recipients with T2DM. There was no association with pretransplant or posttransplant HbA1C levels, suggesting that glycemic control is not a major determinant of renal function early posttransplant. Multivariable correlates of posttransplant creatinine were patient age and pretransplant creatinine level. Although recipients with T2DM had similar creatinine levels to recipients without diabetes at the time of transplant, those with diabetes were significantly older, which could explain (at least in part) the higher 1-year creatinine in this cohort. Patients with diabetes may also be more susceptible to calcineurin inhibitor nephrotoxicity, but as all the subjects in our cohort received calcineurin inhibitors, it was not possible to assess this hypothesis. Counterintuitively, we found that posttransplant creatinine strongly correlated with pretransplant HbA1C levels in subjects without diabetes. We speculate this is because HbA1C is serving as a marker of undiagnosed diabetes mellitus in this cohort. Also noteworthy is the strong association between HbA1C levels and the diagnosis of HCC, a finding that is concordant with a growing body of literature.[35,36]

Our most unexpected observation was the significant correlation between pretransplant HbA1C and the risk of anastomotic biliary stricture formation in liver recipients with diabetes mellitus. Although a number of donor and recipient factors have been suggested to increase the risk of anastomotic strictures,[37,38] this is the first description of an association with glucose intolerance. The strong correlation between biliary strictures and markers of diabetes as well as the apparent dose dependency with pretransplant HbA1C lend credence to the likelihood of a substantive effect. The absence of a significant association between biliary strictures and the HbA1C level 3 months and 1 year posttransplant suggests that posttransplant glycemic control is not a major determinate of stricture formation. In light of the well-established microvascular complications of diabetes mellitus, which are known to occur more commonly in patients with elevated HbA1C,[39] it seems plausible that such individuals would manifest an increased susceptibility to local ischemia at the site of surgical anastomosis. In support of this contention, Iacob et al.[40] identified a strong correlation between biliary stricture formation and the fractalkine receptor C-X3-C motif chemokine receptor 1 (CX3CR1)-249II allele in a cohort of 162 liver transplant recipients. CX3CR1 is the receptor for C-X3-C motif chemokine ligand 1 (CX3CL1), a chemokine that mediates angiogenesis.[41,42] Because the CX3CR1 V249I polymorphism disrupts CX3CL1 binding, the II genotype would be expected to manifest impaired microvascular ingrowth, thereby augmenting the risk of stricture formation. Indeed, the V249I polymorphism has been associated with fibrostenotic disease behavior in patients with Crohn's disease.[43] Because individuals with T2DM have an increased frequency of the V249I polymorphism,[44] we speculate that this could contribute to a higher incidence of anastomotic biliary strictures. If our finding is validated in other liver transplant cohorts, it raises the possibility that more aggressive preoperative glycemic control could ameliorate the risk of anastomotic biliary stricture formation.

Achievement of optimal blood glucose control in patients awaiting liver transplantation is challenging because the metabolic and hematologic derangements associated with advanced liver disease reduce the reliability of the most commonly employed long-term measures of glycemia, including HbA1C,[25,26,45] fructosamine,[46] and glycated albumin (GA).[25,47] To address this problem, Koga et al.[25] formulated

a chronic liver disease A1C (CLD-A1C) comprising the average of HbA1C and GA/3. Although these authors showed that CLD-A1C demonstrated improved accuracy over HbA1C or GA in estimating glycemic control in patients with cirrhosis, this finding has yet to be validated in larger cohorts, and thus the CLD-A1C has not been widely adopted. Continuous glucose monitoring would provide more accurate information regarding glycemic control in patients with advanced liver disease but is not used in routine practice. Our finding that HbA1C levels are significantly lower in patients before liver transplant versus those after liver transplant despite similar blood glucose levels is in line with other reports.[23-26] Notwithstanding the limitation of using MBG as a surrogate for fasting glucose levels, our study demonstrates that a robust correlation between HbA1C and MBG persists in patients with advanced liver disease, particularly in those with diabetes.

There are a number of limitations of the present study. The relatively short duration of follow-up (median 1.8 years for patients with T2DM) does not permit reliable assessment of the effect of glycemic control on longer term survival and cardiovascular and renal complications. In comparison with national averages, the transplant population at our center is skewed toward Caucasians and lower MELD scores, potentially impacting the generalizability of our findings. Attempts were made to mitigate against selection bias by including all transplant recipients over the study period. Because of the retrospective nature of the study, we used MBG as a surrogate fasting blood glucose (FBG). Despite potential shortcomings of this approach, the correlation between MBG and HbA1C were remarkably concordant with published data for FBG and HbA1C. Although a smaller subset of liver recipients was used to analyze the correlation between MBG and HbA1C, this cohort had statistically similar demographics to the entire study population. A key strength of our analysis is that the team of surgeons and immunosuppression protocols were stable and consistent throughout the study period, minimizing the impact of these factors on outcome measures.

In summary, although pretransplant HbA1C is a relatively poor predictor of most short-term outcomes of liver transplantation, recipients with higher HbA1C levels appear to be at increased risk for biliary stricture formation and long-term insulin requirement posttransplant. It remains to be determined whether improved pretransplant and posttransplant glycemic control can favorably impact these outcomes.

REFERENCES

1) Petrides AS, Vogt C, Schulze-Berge D, Matthews D, Strohmeyer G. Pathogenesis of glucose intolerance and diabetes mellitus in cirrhosis. Hepatology 1994;19:616-627.
2) Nielsen MF, Caumo A, Aagaard NK, Chandramouli V, Schumann WC, Landau BR, et al. Contribution of defects in glucose uptake to carbohydrate intolerance in liver cirrhosis: assessment during physiological glucose and insulin concentrations. Am J Physiol Gastrointest Liver Physiol 2005;288:G1135-G1143.
3) Megyesi C, Samols E, Marks V. Glucose tolerance and diabetes in chronic liver disease. Lancet 1967;2:1051-1056.
4) Conn HO, Schreiber W, Elkington SG, Johnson TR. Cirrhosis and diabetes. I. Increased incidence of diabetes in patients with Laennec's cirrhosis. Am J Dig Dis 1969;14:837-852.
5) Conn HO, Schreiber W, Elkington SG. Cirrhosis and diabetes. II. Association of impaired glucose tolerance with portal-systemic shunting in Laennec's cirrhosis. Am J Dig Dis 1971;16:227-239.
6) Perseghin G, Mazzaferro V, Sereni LP, Regalia E, Benedini S, Bazzigaluppi E, et al. Contribution of reduced insulin sensitivity and secretion to the pathogenesis of hepatogenous diabetes: effect of liver transplantation. Hepatology 2000;31:694-703.
7) Marvin MR, Morton V. Glycemic control and organ transplantation. J Diabetes Sci Technol 2009;3:1365-1372.
8) John WG, Bullock DG, MacKenzie F. Methods for the analysis of glycated haemoglobins: what is being measured? Diabet Med 1992;9:15-19.
9) Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al.; 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 diabetes mellitus. N Engl J Med 1993;329:977-986.
10) [No authors listed]. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-853. Erratum in: Lancet 1999;354:602.
11) Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643-2653.
12) Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med 2004;141:413-420.
13) O'Sullivan CJ, Hynes N, Mahendran B, Andrews EJ, Avalos G, Tawfik S, et al. Haemoglobin A1c (HbA1C) in non-diabetic and diabetic vascular patients. Is HbA1C an independent risk factor and predictor of adverse outcome? Eur J Vasc Endovasc Surg 2006;32:188-197.
14) Halkos ME, Lattouf OM, Puskas JD, Kilgo P, Cooper WA, Morris CD, et al. Elevated preoperative hemoglobin A1c level is associated with reduced long-term survival after coronary artery bypass surgery. Ann Thorac Surg 2008;86:1431-1437.
15) Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Kerendi F, Song HK, et al. Elevated preoperative hemoglobin A1c level is predictive of adverse events after coronary artery bypass surgery. J Thorac Cardiovasc Surg 2008;136:631-640.

16) Alserius T, Anderson RE, Hammar N, Nordqvist T, Ivert T. Elevated glycosylated haemoglobin (HbA1c) is a risk marker in coronary artery bypass surgery. Scand Cardiovasc J 2008;42:392-398.
17) Ehara N, Morimoto T, Furukawa Y, Shizuta S, Taniguchi R, Nakagawa Y, et al. Effect of baseline glycemic level on long-term cardiovascular outcomes after coronary revascularization therapy in patients with type 2 diabetes mellitus treated with hypoglycemic agents. Am J Cardiol 2010;105:960-966.
18) Knapik P, Ciesla D, Filipiak K, Knapik M, Zembala M. Prevalence and clinical significance of elevated preoperative glycosylated hemoglobin in diabetic patients scheduled for coronary artery surgery. Eur J Cardiothorac Surg 2011;39:484-489.
19) Gustafsson UO, Thorell A, Soop M, Ljungqvist O, Nygren J. Haemoglobin A1c as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery. Br J Surg 2009;96:1358-1364.
20) Stryker LS, Abdel MP, Morrey ME, Morrow MM, Kor DJ, Morrey BF. Elevated postoperative blood glucose and preoperative hemoglobin A1C are associated with increased wound complications following total joint arthroplasty. J Bone Joint Surg Am 2013;95:808-814, S801-S802.
21) Hackman KL, Snell GI, Bach LA. Poor glycemic control is associated with decreased survival in lung transplant recipients. Transplantation 2017;101:2200-2206.
22) Kato T, Chan MC, Gao SZ, Schroeder JS, Yokota M, Murohara T, et al. Glucose intolerance, as reflected by hemoglobin A1c level, is associated with the incidence and severity of transplant coronary artery disease. J Am Coll Cardiol 2004;43:1034-1041.
23) 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 J Gastroenterol 2004;10:2284-2286.
24) Inoue K, Goto A, Kishimoto M, Tsujimoto T, Yamamoto-Honda R, Noto H, et al. Possible discrepancy of HbA1c values and its assessment among patients with chronic renal failure, hemodialysis and other diseases. Clin Exp Nephrol 2015;19:1179-1183.
25) 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 Res Clin Pract 2008;81:258-262.
26) Nadelson J, Satapathy SK, Nair S. Glycated hemoglobin levels in patients with decompensated cirrhosis. Int J Endocrinol 2016;2016:8390210.
27) Trail KC, Stratta RJ, Larsen JL, Ruby EI, Patil KD, Langnas AN, et al. Results of liver transplantation in diabetic recipients. Surgery 1993;114:650-656.
28) Wahlstrom HE, Cooper J, Gores G, Rosen C, Wiesner R, Krom RA. Survival after liver transplantation in diabetics. Transplant Proc 1991;23:1565-1566.
29) Navasa M, Bustamante J, Marroni C, Gonzalez E, Andreu H, Esmatjes E, et al. Diabetes mellitus after liver transplantation: prevalence and predictive factors. J Hepatol 1996;25:64-71.
30) Shields PL, Tang H, Neuberger JM, Gunson BK, McMaster P, Pirenne J. Poor outcome in patients with diabetes mellitus undergoing liver transplantation. Transplantation 1999;68:530-535.
31) John PR, Thuluvath PJ. Outcome of liver transplantation in patients with diabetes mellitus: a case-control study. Hepatology 2001;34:889-895.
32) Samuelson AL, Lee M, Kamal A, Keeffe EB, Ahmed A. Diabetes mellitus increases the risk of mortality following liver transplantation independent of MELD score. Dig Dis Sci 2010;55:2089-2094.
33) Blanco JJ, Herrero JI, Quiroga J, Sangro B, Gomez-Manero N, Pardo F, et al. Liver transplantation in cirrhotic patients with diabetes mellitus: midterm results, survival, and adverse events. Liver Transpl 2001;7:226-233.
34) Katsura E, Ichikawa T, Taura N, Miyaaki H, Miuma S, Shibata H, et al. Elevated fasting plasma glucose before liver transplantation is associated with lower post-transplant survival. Med Sci Monit 2016;22:4707-4715.
35) de Beer JC, Liebenberg L. Does cancer risk increase with HbA1c, independent of diabetes? Br J Cancer 2014;110:2361-2368.
36) Donadon V, Balbi M, Valent F, Avogaro A. Glycated hemoglobin and antidiabetic strategies as risk factors for hepatocellular carcinoma. World J Gastroenterol 2010;16:3025-3032.
37) Verdonk RC, Buis CI, Porte RJ, van der Jagt EJ, Limburg AJ, van den Berg AP, et al. Anastomotic biliary strictures after liver transplantation: causes and consequences. Liver Transpl 2006;12:726-735.
38) Akamatsu N, Sugawara Y, Hashimoto D. Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome. Transpl Int 2011;24:379-392.
39) Zoungas S, Chalmers J, Ninomiya T, Li Q, Cooper ME, Colagiuri S, et al.; ADVANCE Collaborative Group. Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. Diabetologia 2012;55:636-643.
40) Iacob S, Cicinnati VR, Dechene A, Lindemann M, Heinemann FM, Rebmann V, et al. Genetic, immunological and clinical risk factors for biliary strictures following liver transplantation. Liver Int 2012;32:1253-1261.
41) Jones BA, Beamer M, Ahmed S. Fractalkine/CX3CL1: a potential new target for inflammatory diseases. Mol Interv 2010;10:263-270.
42) Imaizumi T, Yoshida H, Satoh K. Regulation of CX3CL1/fractalkine expression in endothelial cells. J Atheroscler Thromb 2004;11:15-21.
43) Sabate JM, Ameziane N, Lamoril J, Jouet P, Farmachidi JP, Soule JC, et al. The V249I polymorphism of the CX3CR43 gene is associated with fibrostenotic disease behavior in patients with Crohn's disease. Eur J Gastroenterol Hepatol 2008;20:748-755.
44) Bagci B, Bagci G, Huzmeli C, Sezgin I, Ozdemir O. Associations of fractalkine receptor (CX3CR44) and CCR44 gene variants with hypertension, diabetes and atherosclerosis in chronic renal failure patients undergoing hemodialysis. Int Urol Nephrol 2016;48:1163-1170.
45) Clarke M, Benmoussa J, Penmetsa A, Otterbeck P, Ebrahimi F, Nfonoyim J. Inaccuracies of hemoglobin A1c in liver cirrhosis: a case report. J Endocrinol Metab 2016;6:30-32.
46) Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan DM, Peterson CM, et al. Tests of glycemia in diabetes. Diabetes Care 2004;27(Suppl. 1):S91-S93.
47) Paroni R, Ceriotti F, Galanello R, Battista Leoni G, Panico A, Scurati E, et al. Performance characteristics and clinical utility of an enzymatic method for the measurement of glycated albumin in plasma. Clin Biochem 2007;40:1398-1405.