World Journal of Transplantation

Submit a Manuscript: http://www.f6publishing.com

World J Transplant 2018 June 28; 8(3): 75-83

DOI: 10.5500/wjt.v8.i3.75

ISSN 2220-3230 (online)

SYSTEMATIC REVIEWS

Perioperative glucose management and outcomes in liver transplant recipients: A qualitative systematic review

Prani Paka, Sarah R Lieber, Ruth-Ann Lee, Chirag S Desai, Robert E Dupuis, Alfred Sidney Barritt

Prani Paka, Robert E Dupuis, Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, United States

Sarah R Lieber, Alfred Sidney Barritt, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, NC 27599, United States

Ruth-Ann Lee, Chirag S Desai, Division of Abdominal Transplant, Department of Surgery, University of North Carolina School of Medicine, Chapel Hill, NC 27599, United States

ORCID number: Prani Paka (0000-0002-4638-8202); Sarah R Lieber (0000-0001-8304-4479); Ruth-Ann Lee 0000-0002-6498-2037); Chirag S Desai (0000-0002-3784-0973); Robert E Dupuis (0000-001-8349-4138); Alfred Sidney Barritt (0000-0002-4200-3256).

Author contributions: Barritt AS contributed to this paper with conception and design of the study; Paka P, Lieber SR, Lee RA and Barritt AS contributed equally to literature review and analysis; Paka P and Lieber SR also contributed with drafting the transcript and with critical revision; all authors contributed to editing and approving the final draft.

Conflict-of-interest statement: Prani Paka was employed by University of North Carolina (UNC)/GlaxoSmithKline (GSK) as a fellow at the time the article was written (GSK markets the drug Rosiglitazone under the brand name Avandia). GSK is not involved in any part of this review. The authors have no other relevant conflicts to disclose.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Alfred Sidney Barritt, MD, Associate Professor, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Campus Box 7584, 130 Mason Farm Road, Chapel Hill, NC 27599, United States. barritt@med.unc.edu
Telephone: +1-919-9662516
Fax: +1-919-9661700

Received: January 23, 2018
Peer-review started: January 23, 2018
First decision: February 9, 2018
Revised: February 20, 2018
Accepted: April 1, 2018
Article in press: April 1, 2018
Published online: June 28, 2018

Abstract

AIM

To investigate the relationship between post-liver transplantation (LT) glycemic control and LT outcomes.

METHODS

A qualitative systematic review on relevant prospective interventions designed to control glucose levels including insulin protocols. Studies investigating an association between glycemic control and post-LT outcomes such as mortality, graft rejection, and infection rate were reviewed. PubMed, EMBASE, and other databases were searched through October 2016.

RESULTS

Three thousands, six hundreds and ninety-two patients from 14 studies were included. Higher mortality rate was seen when blood glucose (BG) $\geqslant$ 150 mg/dL (P = 0.05). BG $\geqslant$ 150 mg/dL also led to higher rates of infection. Higher rates of graft rejection were seen at BG > 200 mg/dL (P < 0.001). Mean BG $\geqslant$ 200 mg/dL was associated with more infections (P = 0.002).

Nurse-initiated protocols and early screening strategies have shown a reduction in negative post-LT outcomes.

CONCLUSION

Hyperglycemia in the perioperative period is associated with poor post-LT outcomes. Only a few prospective studies have designed interventions aimed at managing post-LT hyperglycemia, post-transplant diabetes mellitus (PTDM) and their impact on post-LT outcomes.

Key words: Diabetes; Liver transplant; Non-alcoholic steatohepatitis; Outcomes; Non-alcoholic fatty liver disease

Core tip: Despite the importance of post-liver transplantation (LT) glycemic control, there are no evidence-based guidelines on how to manage hyperglycemia in the post-LT period. The aim of this qualitative systematic review is to determine potential associations between glucose levels post-LT and outcomes such as mortality, graft rejection, infection rate, and other related post-LT outcomes. In addition, we analyzed methods for targeting glycemic control including specific therapeutic regimens or insulin protocols utilized in LT recipients.

Paka P, Lieber SR, Lee RA, Desai CS, Dupuis RE, Barritt AS. Perioperative glucose management and outcomes in liver transplant recipients: A qualitative systematic review. *World J Transplant* 2018; 8(3): 75-83 Available from: URL: http://www.wjgnet.com/2220-3230/full/v8/i3/75.htm DOI: http://dx.doi.org/10.5500/wjt.v8.i3.75

INTRODUCTION

Hyperglycemia after liver transplantation (LT) is a common phenomenon associated with increased risk of allograft rejection[1,2]. Poor glycemic control is also implicated in other post-LT complications including infection[3-5], acute kidney injury[6], new onset diabetes after transplantation (NODAT)[7,8], and malignancy, in addition to complications related to the metabolic syndrome including increased cardiovascular risk[9]. Despite the importance of post-LT glycemic control, there are no evidence-based guidelines on how to manage hyperglycemia in the post-LT period. Moreover, it is unclear what degree of glycemic control is associated with graft failure and complications such as infections. Similarly, predictors for poor glycemic control and NODAT in LT recipients have not been identified, apart from donor graft steatosis[9], post-LT immunosuppression[10-12], steroid use, and hepatitis C virus (HCV) infection[13]. These gaps in our existing knowledge necessitate a review of the literature on glycemic control and perioperative outcomes in LT recipients.

Given the increasing prevalence of non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome, many patients will arrive at transplant with some degree of insulin resistance. Post-LT hyperglycemic management will be essential to improving patient care and outcomes. The incidence of NODAT ranges from 20% to 44% among LT recipients, with rates varying depending on methodology used[8,9,11,14]. The aim of this qualitative systematic review is to analyze methods for targeting glycemic control including specific therapeutic regimens or insulin protocols utilized in LT recipients, and to determine associations between glycemic control and post-LT outcomes such as mortality, graft rejection, or infection rate. To achieve this goal, we reviewed prospective interventions targeting glucose control, as well as retrospective studies that examined the association between glucose control and relevant perioperative transplant outcomes.

MATERIALS AND METHODS

Overview

Our qualitative systematic review included *a priori* search criteria of journal articles and conference abstracts among adult (age ⩾ 18 years) human orthotopic or living donor LT recipients. Studies were limited to the English language and had to include at least one relevant outcome of interest such as patient survival, graft rejection, infection rate, acute kidney injury, and graft survival. Given the focus on perioperative glucose control, study outcomes were limited to glucose control during the first year post-LT.

Databases and search terms

A health sciences librarian with clinical input from our study team designed the *apriori* search strategy. PubMed (https://www.ncbi.nlm.nih.gov/pubmed), EMBASE (https://www.elsevier.com/solutions/embase-biomedical-research), SCOPUS (https://www.scopus.com), Clinical trials.gov (https://clinicaltrials.gov), and WHO ICTRP (http://www.who.int/ictrp/en) using the search terms outlined in Supplementary Table 1. Searches were performed on October 18, 2016 and updated in December 2017. All studies prior to this date were included.

Study selection

Using the various databases outlined above, our search yielded a total of 1624 results after removing duplicate results. Four reviewers (PP, SRL, RAL, and ASB) independently screened the titles and abstracts of 406 search results each for potential eligibility and a consensus was reached to include a total of 14 studies in the final analysis (Figure 1). Although the search strategy was designed to exclude patients receiving other transplants from this review, some of these studies included patients that received combined liver-

Table 1 Characteristics of retrospective studies

Ref.	Country	Year	*n*	Group 1	Group 2	Study outcome(s)	Comments
Ammori *et al*[5]	United States	2007	184	Strict glucose control (BG < 150 mg/dL)	Poor Glucose control (BG ⩾ 150 mg/dL)	Mortality Infection rate	
Chung *et al*[25]	South Korea	2014	211	BG decline during the Neohepatic Phase (Yes)	BG decline during the Neohepatic Phase (No)	Mortality, length of ICU stay, early allograft dysfunction, MELD Score recovery	Outcomes were assessed relative to the drop in hyperglycemia after the neohepatic phase
Gelley *et al*[21]	Hungary	2011	310	*De novo* diabetes	Control	HepC recurrence and association with NODAT	
Hartog *et al*[23]	United Kingdom	2014	430	DBD	DCD	NODAT	
Keegan *et al*[17]	United States	2010	161 (158 were available for analysis)	Pre-protocol	Protocol	Mortality Morbidity Graft function	
Linder *et al*[18]	United States	2016	114	PTDM	Non-PTDM	PTDM	BPAR, allograft failure, death, CMV infection are additional endpoints
Park *et al*[4]	United States/ Taiwan	2009	680	SSI (Yes)	SSI (No)	SSI	
Trail *et al*[20]	United States	1996	497	PTDM	Case-control	PTDM morbidity	PTDM leading to infections and graft rejection
Wallia *et al*[1]	United States	2010	144	BG > 200 mg/dL	BG < 200 mg/dL	Graft rejection, infection, and re-hospitalization	Graft survival and prolonged ventilation
Wallia *et al*[19]	United States	2011	73	Glucose management service	Non-Glucose Management Service	Graft rejection, infection, and re-hospitalization	Graft survival and prolonged ventilation
Yoo *et al*[6]	South Korea	2016	304	Normoglycemia (BG: 80-200 mg/dL)	Mild hyperglycemia (BG: 200-250 mg/dL)	AKI	Group 3: Moderate hyperglycemia (250-300 mg/dL) Group 4: Severe hyperglycemia (> 300 mg/dL)

DBD: Donated after brain death; PTDM: Post-transplant diabetes mellitus; Non-PTDM: Transplant diabetes mellitus free; DCD: Donated after circulatory death; NODAT: New onset diabetes after transplantation; AKI: Acute kidney injury.

kidney transplantation. These patients were included since the results were reported in a composite manner (*i.e.*, data for liver transplantation alone patients *vs* combined liver-kidney transplantation patients were not reported separately). Overall, the number of liver-kidney transplantation patients was relatively small, and the results were predominantly driven by LT recipients alone.

Quality assessment

Four reviewers independently assessed the risk of bias in each study. Selected studies were reviewed based on representativeness of study population, comparability of cohorts, adequate assessment of outcomes, sufficient length of follow-up, adequacy of follow-up, and source of study funding. The prospective randomized study was assessed using the Cochrane risk of bias tool and the Newcastle-Ottawa Scale (NOS) was used for the cohort/case-control studies[15,16].

RESULTS

This qualitative systematic review includes results from 14 full text articles. Of the 1624 records identified electronically, 780 were duplicates and 109 were eligible after abstract review. Of the 109, there were 22 articles that were reviewed and retrieved in full-text form. Of these, 8 were excluded and data from 14 full text articles (11 retrospective studies, 2 prospective studies and 1 cross-sectional study) were found to be eligible and included in this review (Figure 1).

Characteristics of included studies

The characteristics of the included studies are shown in Tables 1 and 2. A total of 3692 patients (3077 patients were retrospectively studied; 615 patients were prospectively studied) from 14 studies were included. The studies spanned 20 years from 1996 to 2016 with most occurring in the past decade and included transplants pe-

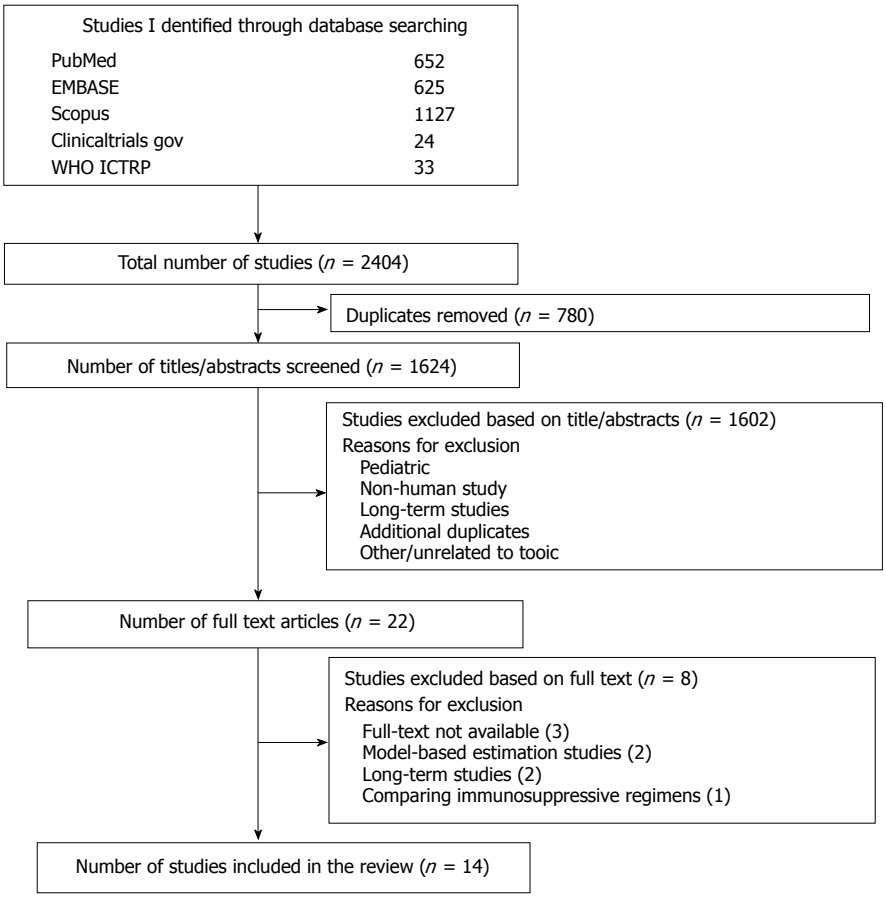

Figure 1 Consort diagram.

rformed in the United States, United Kingdom, Taiwan, Spain, South Korea, and Hungary.

Risk of bias in included trials

Supplementary Table 2 shows the risk of bias assessment of all the included trials. Of the 14 studies that were included, 11 were retrospective in nature and carry a potential to be inherently biased. NOS was used to assess risk of bias for the cohort/case-control studies and a modified version of the NOS was used for the single cross-sectional study. The single randomized prospective study, for the most part was deemed to have minimal bias utilizing the Cochrane risk of bias tool[15,16].

Study outcomes

Clinical outcomes for each trial are summarized in Table 3. Major outcomes of interest in relation to blood glucose (BG) level include mortality, graft rejection, infection rate, acute kidney injury (AKI), graft survival, post-transplant diabetes mellitus (PTDM), and NODAT.

Mortality

Three studies evaluated the relation between glycemic control and mortality in orthotopic liver transplantation (OLT) patients. Ammori *et al*[5] found a statistically significant association between glycemic control and mortality. The retrospective review compared patients with strict glycemic control (mean blood glucose < 150 mg/dL) *vs* those with poor control (mean blood glucose ⩾ 150 mg/dL). A total of 184 patients were analyzed (n = 60 for strict control, n = 124 for poorly controlled). The strict control group had a mean glucose of 135 mg/dL while the poorly controlled group had a mean glucose level of 184 mg/dL. Baseline donor and recipient characteristics for both groups were similar with the exception of recipient age (47 ± 2 years *vs* 53 ± 1 year; strict *vs* poor control, respectively). The Kaplan Meier survival analysis showed a significantly improved one-year survival rate in the strict glucose control group (91.2%) as compared to that in the poorly controlled group (78.1%). The one-year mortality rate was found to be 8.8% and 21.9% (P = 0.05) for patients in the strict controlled group and poorly glucose control group respectively.

Keegan *et al*[17] also evaluated the impact of perioperative glycemic control in OLT patients. This retrospective analysis studied the impact of the initiation of a nurse-initiated protocol for glycemic management (protocol group) *vs* glycemic management prior to the initiation of the protocol (pre-protocol group). Prior to the implementation of the protocol, a variety of insulin infusion protocols and ad hoc sliding scales were used at the discretion of the physician for glycemic control.

Table 2 Characteristics of prospective studies and the cross-sectional study

Ref.	Country	Year	*n*	Group 1	Group 2	Outcome	Comment
Alvarez-Sotomayor *et al*[24]	Spain	2016	344	Diabetes before transplantation	No diabetes before transplantation	PTDM	Cross-sectional study
Villanueva *et al*[22]	United States	2005	107	Rosiglitazone	-	PTDM	
Welsh *et al*[28]	United States	2016	164	Intensive glycemic control	Moderate glycemic control	Hypoglycemia	Insulin requirements

PTDM: Transplant diabetes mellitus.

Table 3 Summary of important findings of perioperative glucose control on liver transplant outcomes

Outcome of interest	Important findings	Data sources
Mortality	Mean BG ⩾ 150 mg/dL increases mortality	Ammori *et al*[5] (retrospective study)
	Nurse initiated insulin protocol did not impact mortality	Keegan *et al*[17] (retrospective study
	PTDM influenced glucose levels but did not change mortality	Linder *et al*[18] (retrospective study)
Graft rejection	Mean BG > 200 mg/dL increases risk of rejection	Wallia *et al*[1] (retrospective study)
	Although, mean BG were lower with the use of GMS, it did not lead to lower rate of rejection	Wallia *et al*[19] (retrospective study)
		Linder *et al*[18] and Trail *et al*[20] (retrospective studies)
	Conflicting evidence exists relating to the development of PTDM and its relation to rejection	
Infection rate	BG ⩾ 150 mg/dL is associated with higher infection rate	Ammori *et al*[5] (retrospective study)
	BG ⩾ 200 mg/dL increases risk of SSIs	Park *et al*[27] (retrospective study)
	Use of GMS led to lower rate of infection	Wallia *et al*[1] (retrospective study)
	Higher BG levels post-LT also led to increased incidence of HCV recurrence	Gelley *et al*[21] (retrospective study)
		Linder *et al*[18] (retrospective study)
	No association between BG levels and post-LT CMV infection	Trail *et al*[20] (retrospective study)
	Development of PTDM did not lead to higher infection rate	
Post-transplant diabetes mellitus/new onset diabetes mellitus	Rosiglitazone ± sulfonylurea is a potential option for the management of PTDM	Villanueva *et al*[22] (prospective study)
		Linder *et al*[18] (retrospective study)
	Post-LT hyperglycemia is associated with the development of PTDM	Alvarez-Sotomayor *et al*[24] (retrospective study)
	Insulin use was significantly higher in PTDM patients with inadequate BG	
Acute kidney injury and graft survival	High glucose variability is associated with post-LT acute kidney injury	Yoo *et al*[6] (retrospective study)
		Wallia *et al*[1] and Trail *et al*[20] (retrospective studies)
	No association between post-LT BG levels and graft survival	

BG: Blood glucose; PTDM: Post-transplant diabetes mellitus; GMS: Glucose management service; HCV: Hepatitis C virus; LT: Liver transplantation.

Under the protocol, a nurse would initiate a continuous intravenous (Ⅳ) insulin infusion within 48 h post-OLT if a patient's BG was greater than 130 mg/dL. The insulin infusion would be titrated as necessary (based on hourly readings) to reach a target BG goal of 80-130 mg/dL. The primary purpose of this quality improvement study was to identify the percentage of all measurements that were in the hypoglycemic (BG < 60 mg/dL) or severely hyperglycemia (BG > 250 mg/dL) range. These measurements were compared between pre-protocol and protocol groups. A total of 158 patients were available for analysis (n = 84 in the pre-protocol group; n = 77 in protocol group). Severe hyperglycemia was observed in 90 of the 581 measurements (15.5%) in the pre-protocol group and 15 of the 539 (2.8%) in the protocol group (OR for protocol group 0.16; CI: 0.09-0.28). Statistical significance, however, was not seen in one-year mortality between the protocol group and the pre-protocol group. Four out of 75 patients (5.3%) died in the protocol group, compared with 5 out of 83 patients (6.0%) in the pre-protocol group (OR for death in the protocol group, 0.89; 95%CI: 0.23-3.42; P = 0.86).

Linder *et al*[18] evaluated the insulin burden between liver transplant patients that developed PTDM *vs* patients that did not. BG levels between these two groups were reported as well as mortality rates. A total of 114 patients were retrospectively analyzed and while postoperative BG levels were similar in the ICU setting between the two groups, a statistically significant difference in floor (non-ICU) average BG levels (mg/dL) was seen between patients that developed PTDM and those that did not (184.7 ± 31.5 and 169.3 ± 31.4 respectively, P = 0.013). Statistically significant differences in one-month average BG levels were also seen-176.0 ± 31.1 for the PTDM group and 160.6 ± 28.0 for the non-PTDM group (P = 0.007). However, there was no significant difference in one-year mortality in the PTDM and non-PTDM groups.

Graft rejection

Four studies examined the association between glycemic

levels and graft rejection in liver transplant recipients. In a retrospective analysis conducted by Wallia *et al*[1] (n = 144), there was a statistically significant association between glucose level and graft rejection. Higher rates of rejection were seen in patients with a mean BG level > 200 mg/dL compared to those that had a mean BG level < 200 mg/dL (76.7% and 35.1% respectively; P < 0.001). A retrospective subgroup analysis by Wallia *et al*[19] (n = 73) studied the effect of a glucose management service (GMS) on blood glucose levels and its impact on clinical outcomes including graft rejection. The GMS consisted of a group of nurse practitioners supervised by an endocrinologist responsible for managing BG. The BG levels were managed by the primary transplant team in the non-GMS group. The mean inpatient BG level during the peri-transplant period was 189.0 ± 45.0 in the non-GMS group and 157.9 ± 32.3 in the GMS group (statistical significance data not provided). Although, patients in the non-GMS group had higher BG levels, hyperglycemia did not lead to higher rates of graft rejection (45% in the non-GMS group *vs* 29% in the GMS group, P = 0.156).

In the previously described retrospective analysis by Linder *et al*[18], biopsy-proven acute rejection (BPAR) was also studied as an outcome and there was a statistically higher incidence in PTDM *vs* non-PTDM patients (41.7% *vs* 24.2% respectively, P = 0.048). Similarly, a retrospective study by Trail *et al*[20] (n = 497), studied morbidity, including graft rejection, in DM patients after LT compared with matched control patients. Mean fasting blood glucose for patients with PTDM was 122.3 ± 5.0 mg/dL compared to 101.9 ± 3.9 mg/dL for the matched control patients (P < 0.01). Despite the statistically significant difference in glycemic levels between the PTDM group and matched control group, the number of rejection episodes was similar between the two groups, *i.e.*, rates of rejection were not significantly different between groups.

Infection

Six retrospective studies evaluated the association between glucose levels and infection. Park *et al*[4] studied the association between intraoperative hyperglycemia and surgical site infection (SSI) postoperatively in a retrospective study (n = 680). Of the 680 patients, 76 (11.2%) experienced SSI after LT. Severe hyperglycemia (defined as mean BG ⩾ 200 mg/dL) was seen in 37.8% of the 76 patients with SSIs compared to only 21.9% of the 604 non-SSI patients (P = 0.002) suggesting an association between the occurrence of SSIs and mean BG levels ⩾ 200 mg/dL. Similarly, In the study by Ammori *et al*[5], infectious complications when assessed 30 d post-LT were significantly associated with worse glucose control-among the strict glucose control group (mean BG < 150 mg/dL), there were 60 (30%) post-LT infections, compared to 124 (48%) infections in the poor glucose control group (mean BG ⩾ 150 mg/dL) (P = 0.02). The retrospective subgroup analysis by Wallia *et al*[19] found that the patients in the non-GMS group with higher BG levels exhibited higher rate of infection compared to the patients in the GMS group at one-year post-LT follow up (79% *vs* 51% respectively, P = 0.015). Gelley *at al*[21] found that higher early postoperative fasting plasma glucose led to higher incidence of HCV recurrence (diagnosed with histology criteria of the Knodell score), although no data was shown with regards to BG levels.

In contrast to the above studies, Linder *et al*[18] showed no association between glycemic level and post-LT CMV infection (patients with PTDM had higher BG levels compared to non-PTDM patients). Similarly, Trail *et al*[20] also showed no significant difference in infectious rates between patients with PTDM and those without PTDM. This study also evaluated the severity of infection as well as the type of infection and no differences were seen between the two groups.

Post-transplant diabetes mellitus and new-onset diabetes after transplantation

Villanueva and Baldwin evaluated the use of Rosiglitazone (ROSI) therapy for patients with PTDM. DM was diagnosed according to the American Diabetes Association (ADA) criteria (symptoms of hyperglycemia with post-prandial BG ⩾ 200 mg/dL, or fasting BG ⩾ 126 mg/dL on two separate occasions). The study followed 40 patients that developed PTDM that were initially stabilized by twice-daily NPH and regular insulin. These patients were subsequently started on ROSI 4 mg/d with the treatment goal to discontinue insulin while maintaining a target goal of HBA1c ⩽ 6.5%. Thirty of the patients that were initially treated with insulin were able to discontinue insulin within 3-4 mo. Three patients required chronic insulin therapy despite ROSI ± a sulfonylurea, and were considered insulin dependent. ROSI monotherapy was sufficient in 12 patients (30%), whereas 25 patients (62.5%) required ROSI + sulfonylurea to maintain insulin independence and normoglycemia. ROSI was continued at 4 mg/d in 25 patients while 15 patients required an increase to 8 mg/d. PTDM patients treated with ROSI maintained a mean HBA1C of 5.6% ± 0.8 (target BG levels were < 100 mg/dL for fasting glucose and < 140 mg/dL for post prandial glucose). A commonly seen side effect among patients treated with ROSI was edema (13%). These data suggest ROSI ± sulfonylurea may be a potential intervention that can reduce insulin burden in patients with PTDM[22].

Linder *et al*[18] also showed that patients who developed PTDM had significantly higher BG levels (1-mo average BG) suggesting post-LT hyperglycemia could play a role in the development of PTDM. Multivariate analysis for predictors of PTDM showed the use of Basiliximab was a negative independent predictor [AOR 0.182 (0.040-0.836), P = 0.03] and rejection was a positive independent predictor [AOR 3.237 (1.214-8.633), P = 0.019] for the development of

PTDM. Hartog *et al*[23] demonstrated that pulse high-dose steroids was an independent predictor of NODAT [OR 3.1 (1.7-5.6), P = 0.001]. In addition, this study also demonstrated donor graft type was associated with early occurrence of NODAT (within 15 d post-LT). Multivariate analysis showed donation after cardiac death (DCD) graft type was associated with significantly early occurrence of NODAT compared to donation after brain death (DBD) graft type [OR 6.5 (2.3-18.4), P = 0.001].

In addition to the previously mentioned outcomes, PTDM has also been associated with higher insulin use in post-LT patients. A cross-sectional study by Alvarez-Sotomayor *et al*[24] evaluated 344 patients of whom 141 patients experienced PTDM (157 total but 16 patients did not have HbA1c readings prior to enrollment). Patients with PTDM who had adequate glycemic control (defined as HbA1c < 7%), were significantly less dependent on insulin (39.4%) compared to patients with inadequate glycemic control (80.8%) (OR 6.6, 95%CI: 1.8-24.6, P < 0.001). Finally, Chung *et al*[25] found male sex, emergency surgery, surgical time (⩽ 9 h), and serum lactate (> 5 mmol/L) to be independent predictors for refractive hyperglycemia (RH), however, most post-LT outcomes were not significant in relation to RH.

Acute kidney injury and graft survival

Other outcomes of interest including AKI, graft survival, and complications related to hospitalization were not studied extensively. Three studies evaluated graft survival and no statistically significant association was seen between post-LT glycemic control and graft survival[1,19,20]. Similarly, no association was seen between BG levels and re-hospitalizations[1,19]. A study by Yoo *et al*[6] demonstrated no association between hyperglycemia and AKI in LT recipients; however, patients with greater glucose variability, as defined by the SD of blood glucose levels, more commonly presented with AKI (P = 0.019). Using SD as a surrogate marker for glucose variability, patients were divided into quartiles according to the SD of intraoperative and postoperative (initial 48 h of ICU admission) blood glucose levels. Patients with the lowest SD were assigned to the first quartile, ranging to those with the highest SD who were assigned to the fourth quartile. Glucose variability was significantly associated with AKI among patients in the third quartile (23.3% of patients with no AKI *vs* 30.3% with AKI, OR 2.47, CI: 1.22-5.00, P = 0.012) and fourth quartile (22.1% with no AKI and 31.1% with AKI, OR 2.16, CI: 1.05-4.42, P = 0.035).

DISCUSSION

This qualitative systematic review of 14 studies examined post-LT glucose control, interventions designed to target glucose control, and associations with post-LT outcomes including infection rate, PTDM, AKI, graft survival and mortality. Ultimately, this review concludes that perioperative hyperglycemia leads to unfavorable post-LT outcomes; however, the degree to which it plays a role may depend on the specific outcome in question. There is strong evidence to support an association between perioperative hyperglycemia and post-LT outcomes such as high infection rate and graft rejection[1,4,5,18-20,26]. A review by Park *et al*[27] that focused specifically on intraoperative hyperglycemia found a similar association between hyperglycemia and infection rate. In contrast, the strength of the evidence that exists to support an association between perioperative hyperglycemia and outcomes such as mortality and graft survival is not as well founded[1,5,17-20]. High glucose variability may also be a factor with the development of certain complications such as AKI[6]. In addition, donor graft type (DCD *vs* DBD) may also play a role in the early occurrence of NODAT (within 15 d post-LT)[23].

What was difficult to discern from these studies was the target BG level associated with poor post-LT outcomes. The studies in this review used different target BG levels to evaluate different outcomes, thus making it difficult to associate the degree of glycemic control with certain outcomes and also limiting comparisons that could be made between studies. The studies also varied in their definition of PTDM, the timing of glucose monitoring (immediate post-operative to days post-LT), and the medications used to manage hyperglycemia (ranging from insulin infusion to oral meds). The variability in the studies is what limits the comparisons that can be made and is the reason we can only perform a qualitative review of the literature. Additionally, most of the studies were retrospective observational studies and were not designed to study the specific association between hyperglycemia and post-LT outcomes. Finally, there were some studies that included a small number of combined liver-kidney transplant recipients and the results were reported in a composite manner, thereby making it difficult to detect LT-specific associations between glucose control and post-LT outcomes.

In this review, all of the relevant literature regarding glucose control and post-LT outcomes was compiled systematically using an apriori search strategy of the major medical literature databases. The data were compiled in a qualitative, descriptive manner due to the heterogeneity among research strategies and outcomes that exist in published literature

The conclusions from this review have robust implications for clinical practice. It is imperative to monitor glucose control pre- and post-LT. Along with hyperglycemia, it is also important to consider complications associated with strict glycemic control such as hypoglycemia and high insulin burden when deciding specific BG levels to target. Welsh *et al*[28] demonstrated the impact of hypoglycemia (defined as glucose ⩽ 70 mg/dL) pertaining to intensive and moderate glycemic control

in post-LT patients. There were a higher number of hypoglycemic patients in the intensive group and these hypoglycemic patients had significantly higher peak insulin drip rates, higher peak insulin glargine, and more importantly had significantly longer hospital stay. Therefore, it is crucial to target perioperative BG levels within a range that would limit complications associated with both hyper- and hypoglycemia. A reasonable target, based on our findings would be a range between 120 mg/dL to 150 mg/dL, given that BG $\geqslant$ 150 mg/dL were associated with negative post-LT outcomes. In addition, interventions through nurse-initiated glucose management protocols to achieve specific target BG levels, early screening to identify patients at high-risk for PTDM, and use of oral agents for management of PTDM seem to be a promising approaches to minimize post-LT outcomes[17,22,24]. Although not discussed extensively in this review, optimizing immunosuppression regimens may also play an important role as noted by the potential association between basiliximab and pulse steroids with PTDM[18,23]. Song *et al*[29] conducted a retrospective study in China and demonstrated that lower exposure of tacrolimus (measured by mean tacrolimus concentration at 6 mo) was associated with less risk of developing NODAT and its related complications. This suggested that not only optimizing the regimen important but also the dosing of immunosuppressive drugs utilized in the regimen need to be optimized. Such recommendations would be strengthened by prospective randomized data and thus highlights the need for further study in this area.

The need for close monitoring of glucose levels post-LT will become even more important in the future. More patients with insulin resistance will come to transplant in the coming years. NAFLD is the fastest growing indication for transplant and will become the leading indication over the next decade[30,31]. The change in disease etiology may also be accompanied by donor grafts from older patients with DM and obesity that may be more susceptible to poor outcomes from hyperglycemic stressors[32]. As NAFLD increases prevalence, the transplant community will see more NAFLD among both living donors as well. A reliable assessment of hepatic steatosis is of paramount importance for living donor selection as significant steatosis can impact the postoperative outcomes of recipients and safety of the donor[33]. Because of these challenges, the focus could be on developing and establishing a standardized protocol for the monitoring of blood glucose levels. The frequency of test like hemoglobin A1c, glucose tolerance test, and use of tools such as continuous glucose monitoring should be further explored.

Prospective clinical studies need to further examine the impact of perioperative glycemic control in LT recipients with specific attention to the outcomes listed above. An ideal target range for BG levels needs to be determined and specifically investigated in terms of reducing negative outcomes associated with both hypo- and hyperglycemia, as well as adverse events related to post-LT complications due to impaired glucose control.

ARTICLE HIGHLIGHTS

Research background

There are no standard guidelines to properly manage hyperglycemia in the perioperative period of liver transplantation.

Research motivation

Understanding the importance of blood glucose level and proper strategies to manage post-liver transplantation hyperglycemia could help reduce adverse outcomes

Research objectives

The primary objective was to identify an ideal blood glucose level to achieve in the perioperative period for patients undergoing liver transplantation. In addition, exploring treatment regimens to achieve the target blood glucose can help identify better strategies for the management of these patients in the future.

Research methods

This is a qualitative systematic review that utilized key search terms to find studies on PubMed and other common databases. The search terms were in relation to liver transplantation and blood glucose level management in the perioperative period.

Research results

A total of 14 studies fit the criteria to properly study the objectives. The findings from this qualitative review suggests that blood glucose levels greater than or equal to 150 mg/dL in the perioperative period generally leads to negative post-liver transplantation outcomes. Specifically, there was an increased risk of infections, graft rejection, PTDM, and mortality. Graft survival was not impacted by hyperglycemia and there was an increased risk of acute kidney injury with high glucose variability in the perioperative period.

Research conclusions

The findings from the compiled studies in this review suggest a blood glucose level between 120 mg/dL and 150 mg/dL could potentially be an ideal target to manage hyperglycemia post-liver transplantation. In addition, early screening, use of oral agents, and utilizing resources such as a glucose management service could be potential strategies to limit adverse outcomes post-transplantation.

Research perspectives

Future studies can validate the findings from this review through a prospective study while implementing some of the strategies discussed in this review to minimize post-liver transplantation outcomes.

ACKNOWLEDGEMENTS

The authors would like to thank Rachael Posey of The UNC Health Sciences Library for her assistance in designing the search strategy.

REFERENCES

1 **Wallia A**, Parikh ND, Molitch ME, Mahler E, Tian L, Huang JJ, Levitsky J. Posttransplant hyperglycemia is associated with increased risk of liver allograft rejection. *Transplantation* 2010; **89**: 222-226 [PMID: 20098286 DOI: 10.1097/TP.0b013e3181c3c2ff]

2 **Marvin MR**, Morton V. Glycemic control and organ transplantation. *J Diabetes Sci Technol* 2009; **3**: 1365-1372 [PMID: 20144390 DOI: 10.1177/193229680900300616]

3 **Nieto-Rodriguez JA**, Kusne S, Mañez R, Irish W, Linden P, Magnone M, Wing EJ, Fung JJ, Starzl TE. Factors associated with the development of candidemia and candidemia-related death among

liver transplant recipients. *Ann Surg* 1996; **223**: 70-76 [PMID: 8554421 DOI: 10.1097/00000658-199601000-00010]
4 **Park C**, Hsu C, Neelakanta G, Nourmand H, Braunfeld M, Wray C, Steadman RH, Hu KQ, Cheng RT, Xia VW. Severe intraoperative hyperglycemia is independently associated with surgical site infection after liver transplantation. *Transplantation* 2009; **87**: 1031-1036 [PMID: 19352123 DOI: 10.1097/TP.0b013e31819cc3e6]
5 **Ammori JB**, Sigakis M, Englesbe MJ, O'Reilly M, Pelletier SJ. Effect of intraoperative hyperglycemia during liver transplantation. *J Surg Res* 2007; **140**: 227-233 [PMID: 17509267 DOI: 10.1016/j.jss.2007.02.019]
6 **Yoo S**, Lee HJ, Lee H, Ryu HG. Association Between Perioperative Hyperglycemia or Glucose Variability and Postoperative Acute Kidney Injury After Liver Transplantation: A Retrospective Observational Study. *Anesth Analg* 2017; **124**: 35-41 [PMID: 27749341 DOI: 10.1213/ANE.0000000000001632]
7 **Galindo RJ**, Wallia A. Hyperglycemia and Diabetes Mellitus Following Organ Transplantation. *Curr Diab Rep* 2016; **16**: 14 [PMID: 26803650 DOI: 10.1007/s11892-015-0707-1]
8 **Wallia A**, Illuri V, Molitch ME. Diabetes Care After Transplant: Definitions, Risk Factors, and Clinical Management. *Med Clin North Am* 2016; **100**: 535-550 [PMID: 27095644 DOI: 10.1016/j.mcna.2016.01.005]
9 **Lv C**, Zhang Y, Chen X, Huang X, Xue M, Sun Q, Wang T, Liang J, He S, Gao J, Zhou J, Yu M, Fan J, Gao X. New-onset diabetes after liver transplantation and its impact on complications and patient survival. *J Diabetes* 2015; **7**: 881-890 [PMID: 25676209 DOI: 10.1111/1753-0407.12275]
10 **Lane JT**, Dagogo-Jack S. Approach to the patient with new-onset diabetes after transplant (NODAT). *J Clin Endocrinol Metab* 2011; **96**: 3289-3297 [PMID: 22058376 DOI: 10.1210/jc.2011-0657]
11 **Gosmanov AR**, Dagogo-Jack S. Predicting, managing and preventing new-onset diabetes after transplantation. *Minerva Endocrinol* 2012; **37**: 233-246 [PMID: 22766890]
12 **Driscoll CJ**. Risk factors for posttransplant diabetes mellitus: a review of the literature. *Prog Transplant* 2007; **17**: 295-300; quiz 301 [PMID: 18240695 DOI: 10.1177/152692480701700407]
13 **Räkel A**, Karelis AD. New-onset diabetes after transplantation: risk factors and clinical impact. *Diabetes Metab* 2011; **37**: 1-14 [PMID: 21295510 DOI: 10.1016/j.diabet.2010.09.003]
14 **First MR**, Dhadda S, Croy R, Holman J, Fitzsimmons WE. New-onset diabetes after transplantation (NODAT): an evaluation of definitions in clinical trials. *Transplantation* 2013; **96**: 58-64 [PMID: 23619735 DOI: 10.1097/TP.0b013e318293fcf8]
15 **Higgins JPT,** Green S (eds). Cochrane Handbook for System-atic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: URL: http://methods.cochrane.org/bias/
16 **Wells G,** Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
17 **Keegan MT**, Vrchota JM, Haala PM, Timm JV. Safety and effectiveness of intensive insulin protocol use in post-operative liver transplant recipients. *Transplant Proc* 2010; **42**: 2617-2624 [PMID: 20832556 DOI: 10.1016/j.transproceed.2010.05.156]
18 **Linder KE**, Baker WL, Rochon C, May ST, Sheiner PA, Martin ST. Evaluation of Posttransplantation Diabetes Mellitus After Liver Transplantation: Assessment of Insulin Administration as a Risk Factor. *Ann Pharmacother* 2016; **50**: 369-375 [PMID: 26847860 DOI: 10.1177/1060028015627662]
19 **Wallia A**, Parikh ND, O'Shea-Mahler E, Schmidt K, DeSantis AJ, Tian L, Levitsky J, Molitch ME. Glycemic control by a glucose management service and infection rates after liver transplantation. *Endocr Pract* 2011; **17**: 546-551 [PMID: 21324822 DOI: 10.4158/EP10343.OR]
20 **Trail KC**, McCashland TM, Larsen JL, Heffron TG, Stratta RJ, Langnas AN, Fox IJ, Zetterman RK, Donovan JP, Sorrell MF, Pillen TJ, Ruby EI, Shaw BW Jr. Morbidity in patients with posttransplant diabetes mellitus following orthotopic liver transplantation. *Liver Transpl Surg* 1996; **2**: 276-283 [PMID: 9346661 DOI: 10.1002/lt.500020405]
21 **Gelley F**, Zadori G, Firneisz G, Wagner L, Fehervári I, Gerlei Z, Fazakas J, Papai S, Lengyel G, Sarvary E, Nemes B. Relationship between hepatitis C virus recurrence and de novo diabetes after liver transplantation: the Hungarian experience. *Transplant Proc* 2011; **43**: 1281-1282 [PMID: 21620111 DOI: 10.1016/j.transproceed.2011.03.065]
22 **Villanueva G**, Baldwin D. Rosiglitazone therapy of posttransplant diabetes mellitus. *Transplantation* 2005; **80**: 1402-1405 [PMID: 16340782 DOI: 10.1097/01.tp.0000181165.19788.95]
23 **Hartog H**, May CJ, Corbett C, Phillips A, Tomlinson JW, Mergental H, Isaac J, Bramhall S, Mirza DF, Muiesan P, Perera MT. Early occurrence of new-onset diabetes after transplantation is related to type of liver graft and warm ischaemic injury. *Liver Int* 2015; **35**: 1739-1747 [PMID: 25349066 DOI: 10.1111/liv.12706]
24 **Alvarez-Sotomayor D**, Satorres C, Rodríguez-Medina B, Herrero I, de la Mata M, Serrano T, Rodríguez-Perálvarez M, D'Avola D, Lorente S, Rubín A, Berenguer M. Controlling Diabetes After Liver Transplantation: Room for Improvement. *Transplantation* 2016; **100**: e66-e73 [PMID: 27653229 DOI: 10.1097/TP.0000000000001399]
25 **Chung HS**, Lee S, Kwon SJ, Park CS. Perioperative predictors for refractory hyperglycemia during the neohepatic phase of liver transplantation. *Transplant Proc* 2014; **46**: 3474-3480 [PMID: 25498075 DOI: 10.1016/j.transproceed.2014.06.078]
26 **Morbitzer KA**, Taber DJ, Pilch NA, Meadows HB, Fleming JN, Bratton CF, McGillicuddy JW, Baliga PK, Chavin KD. The impact of diabetes mellitus and glycemic control on clinical outcomes following liver transplant for hepatitis C. *Clin Transplant* 2014; **28**: 862-868 [PMID: 24893750 DOI: 10.1111/ctr.12391]
27 **Park CS**. Predictive roles of intraoperative blood glucose for post-transplant outcomes in liver transplantation. *World J Gastroenterol* 2015; **21**: 6835-6841 [PMID: 26078559 DOI: 10.3748/wjg.v21.i22.6835]
28 **Welsh N**, Derby T, Gupta S, Fulkerson C, Oakes DJ, Schmidt K, Parikh ND, Norvell JP, Levitsky J, Rademaker A, Molitch ME, Wallia A. Inpatient hypoglycemic events in a comparative effectiveness trial for glycemic control in a high-risk population. *Endocr Pract* 2016; **22**: 1040-1047 [PMID: 27124695 DOI: 10.4158/EP151166.OR]
29 **Song JL**, Gao W, Zhong Y, Yan LN, Yang JY, Wen TF, Li B, Wang WT, Wu H, Xu MQ, Chen ZY, Wei YG, Jiang L, Yang J. Minimizing tacrolimus decreases the risk of new-onset diabetes mellitus after liver transplantation. *World J Gastroenterol* 2016; **22**: 2133-2141 [PMID: 26877618 DOI: 10.3748/wjg.v22.i6.2133]
30 **Yi Z**, Mayorga ME, Orman ES, Wheeler SB, Hayashi PH, Barritt AS Th. Trends in Characteristics of Patients Listed for Liver Transplantation Will Lead to Higher Rates of Waitlist Removal Due to Clinical Deterioration. *Transplantation* 2017; **101**: 2368-2374 [PMID: 28858174 DOI: 10.1097/TP.0000000000001851]
31 **Pais R**, Barritt AS 4th, Calmus Y, Scatton O, Runge T, Lebray P, Poynard T, Ratziu V, Conti F. NAFLD and liver transplantation: Current burden and expected challenges. *J Hepatol* 2016; **65**: 1245-1257 [PMID: 27486010 DOI: 10.1016/j.jhep.2016.07.033]
32 **Orman ES**, Mayorga ME, Wheeler SB, Townsley RM, Toro-Diaz HH, Hayashi PH, Barritt AS 4th. Declining liver graft quality threatens the future of liver transplantation in the United States. *Liver Transpl* 2015; **21**: 1040-1050 [PMID: 25939487 DOI: 10.1002/lt.24160]
33 **Kim JM**, Ha SY, Joh JW, Sinn DH, Jeong WK, Choi GS, Gwak GY, Kwon CH, Kim YK, Paik YH, Lee JH, Lee WJ, Lee SK, Park CK. Predicting Hepatic Steatosis in Living Liver Donors via Noninvasive Methods. *Medicine* (Baltimore) 2016; **95**: e2718 [PMID: 26886612 DOI: 10.1097/MD.0000000000002718]

P- Reviewer: Sanal MG, Tarantino G **S- Editor**: Wang XJ
L- Editor: A **E- Editor**: Tan WW

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com