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Predictive roles of intraoperative blood glucose for post-transplant outcomes in liver transplantation

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Abstract

Diabetogenic traits in patients undergoing liver transplantation (LT) are exacerbated intraoperatively by exogenous causes, such as surgical stress, steroids, blood transfusions, and catecholamines, which lead

to intraoperative hyperglycemia. In contrast to the strict glucose control performed in the intensive care unit, no systematic protocol has been developed for glucose management during LT. Intraoperative blood glucose concentrations typically exceed 200 mg/dL in LT, and extreme hyperglycemia (> 300 mg/dL) is common during the neohepatic phase. Only a few retrospective studies have examined the relationship between intraoperative hyperglycemia and post-transplant complications, with reports of infectious complications or mortality. However, no prospective studies have been conducted regarding the influence of intraoperative hyperglycemia in LT on post-transplant outcome. In addition to absolute blood glucose values, the temporal patterns in blood glucose levels during LT may serve as prognostic features. Persistent neohepatic hyperglycemia (without a decline) throughout LT is a useful indicator of early graft dysfunction. Moreover, intraoperative variability in glucose levels may predict the need for reoperation for hemorrhage after LT. Thus, there is an urgent need for guidelines for glucose control in these patients, as well as prospective studies on the impact of glucose control on various post-transplant complications. This report highlights some of the recent studies related to perioperative blood glucose management focused on LT and liver disease.

Key words: Blood glucose; Intraoperative; Liver transplantation; Outcome; Prediction

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Core tip: Despite the fact that blood glucose control is essential in critically ill patients, glucose levels are typically not managed effectively in patients undergoing liver transplantation. Currently, there are insufficient data from clinical studies on intraoperative glucose in liver transplantation to establish guidelines for glucose management of these patients. Intraoperative

features of blood glucose levels may be related to immediate and deleterious outcomes after liver transplantation. Identification of these associations will help to emphasize the prognostic role of intraoperative glucose, and stimulate the establishment of a standard protocol for intraoperative glucose management in liver transplantation.

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INTRODUCTION

Patients with end-stage liver disease have impaired glucose metabolism, which can manifest as glucose intolerance or full diabetes mellitus^[1,2]. Blood glucose status in these patients often worsens considerably during liver transplantation (LT). Sudden increases in intraoperative blood glucose can result from intrinsic diabetogenic traits and from a variety of exogenous factors, such as surgical stress, corticosteroids, glucose-containing fluid solutions, blood transfusions, and catecholamine vasopressors^[1,3,4].

Despite the strict guidelines used for blood glucose control in intensive care unit (ICU) patients^[5-7], intraoperative criteria for blood glucose control during LT have not yet been established. Although more than 20 units of insulin are typically administered during LT^[3,8], it is almost impossible to maintain blood glucose levels within a preoperatively sustained range. In fact, extreme hyperglycemia with blood glucose > 300 mg/dL is not uncommon during the neohepatic phase after reperfusion to the liver graft^[1,9].

Hyperglycemia can increase morbidity and mortality in critically ill patients^[10-12]. Clinical studies on the impact of perioperative blood glucose have been conducted in major surgical fields, particularly cardiac surgery^[13-15]. However, severe hyperglycemia in LT has not been rigorously investigated in terms of post-transplant sequelae. Therefore, this review examines the associations of intraoperative blood glucose with clinical outcomes during the immediate period after LT in order to encourage clinicians to pay more attention to the importance of blood glucose management in LT.

GLUCOSE DYSREGULATION

Insulin resistance in liver disease

Approximately 30%-60% of cirrhotic patients suffer from metabolic disorders related to blood glucose, known as "hepatogenic diabetes"^[16]. Its pathophysiologic bases include insulin resistance in muscle, hepatic, and adipose tissues, as well

as hyperinsulinemia. Whereas patients with liver cirrhosis show essentially normal hepatic production of glucose^[17,18], hypoglycemia can develop in cases of acute decompensated liver failure^[19]. Hypersecretion of glucagon can often compensate for this decrease in hepatic glucose production^[17].

Insulin resistance is associated with endothelial dysfunction in patients with cirrhosis, which increases hepatic vascular resistance and promotes portal hypertension^[20]. In addition, it contributes to the development of various complications, such as hepatic fibrosis, steatosis, hepatic carcinoma, and resistance to anti-viral treatments^[21]. Chronic hepatitis C virus infection, which is the leading cause for LT in Western countries, can lead to insulin resistance *via* upregulation of inflammatory cytokines, such as tumor necrosis factor- α ^[22], phosphorylation of insulin-receptor substrate-1^[23], upregulation of gluconeogenic genes, such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase 2^[24], and the accumulation of lipid droplets^[25]. Such insulin resistance results in hypersecretion of insulin in approximately 80% of patients with chronic liver disease, and oral glucose tolerance tests universally reveal high sensitivity for hyperinsulinemia in non-diabetic patients with nonalcoholic fatty liver disease^[26].

LT

During orthotopic LT, blood glucose concentrations typically increase abruptly from 110 ± 46 mg/dL to 204 ± 60 mg/dL in the preanhepatic phase (phase I), followed by a further increase to 384 ± 72 mg/dL during the neohepatic phase (phase III)^[27]. There are few data on blood glucose trends in living-donor LT. Figure 1 shows the perioperative blood glucose trend beginning from the preoperative day to post-transplant day 30 in patients who recently underwent living-donor LT at our center. Blood glucose concentrations peaked during the neohepatic phase, began to decline 3 h post-reperfusion near the end of LT, and then decreased abruptly two days post-transplantation.

Renal contributions: Although plasma insulin concentrations increase concomitantly with blood glucose, hyperinsulinemia does not effectively reduce hyperglycemia during the neohepatic phase^[4]. This may be because post-reperfusion hyperglycemia is not mainly due to insulin hyposecretion, but to peripheral insulin resistance in glucose metabolism, which is exacerbated by the hepatectomy. As the kidney and gut are also involved in gluconeogenesis^[28], the risk for hypoglycemia is increased with chronic renal failure, due to the suppression of renal glucose release and decreased glycogen storage^[29]. Thus, patients with renal failure usually have hyperinsulinemia due to decreased renal clearance and the effects of uremic toxin on the liver^[30]. Additionally, the subsequent malnutrition or muscle wasting may be more severe,

which decreases their hepatic glycogen stores and gluconeogenic capacity^[31]. Moreover, acidosis would limit the ability of the liver to compensate *via* hepatorenal reciprocity to maintain normoglycemia^[32]. As a result, blood glucose must be monitored closely during the anhepatic phase in patients with severely damaged renal function undergoing LT because of the risk of hypoglycemia.

Exogenous contributions: Corticosteroid administration can exacerbate preexisting insulin resistance^[33], and cause increased release of counterregulatory hormones, such as glucagon, adrenaline, noradrenaline, growth hormone, and cortisol. Therapeutic infusion of vasoactive drugs, such as epinephrine, norepinephrine, and dopamine, can also contribute to the increased blood glucose levels. Other sources include glucose within blood transfusions, and hepatic glucose released by the graft, which is accelerated during rewarming and after perfusion^[34]. Indeed, the abrupt aggravation of hyperglycemia during the neohepatic phase is mainly caused by glucose influx from the grafted liver^[4].

MANAGEMENT OF BLOOD GLUCOSE

Target levels in critically ill patients

Until the early 2000s, strict blood glucose control (targeting 80-110 mg/dL) was recommended as standard practice in ICUs^[5-7]. This protocol decreased patient morbidity and mortality compared to conventional management of blood glucose (targeting 180-200 mg/dL). However, the intensive insulin therapy was accompanied by a high risk of hypoglycemia^[10]. Updated guidelines for regulating blood glucose now advise treating ICU patients to achieve levels \leq 180 mg/dL^[35,36]. This guideline was formulated based largely on the results of the multicenter NICE-SUGAR trial conducted in Australia, New Zealand, and Canada, which reported a lower incidence of hypoglycemia and hospital mortality compared to stricter blood glucose control^[37].

Blood glucose during LT

Strict glucose control is not likely to be achieved during LT due to progressive hyperglycemia induced by exacerbated insulin resistance and exogenous intraoperative factors. Park *et al*^[9] found that an intraoperative blood glucose criterion threshold of $>$ 200 mg/dL was associated with post-transplant surgical site infection, whereas Ammori *et al*^[3] used a blood glucose criterion of $<$ 150 mg/dL, which appears to be a more reasonable goal^[38]. However, due to the lack of any specialized standard protocol, blood glucose control in LT is maintained in accordance with inpatient glycemic management guidelines. The Consensus Statement by the American Association of Clinical Endocrinologists and the American Diabetes

Association recommends initiating insulin infusions in critically ill patients at a blood glucose level no greater than 180 mg/dL^[39]. The target glucose level is 140-180 mg/dL, and levels below 110 mg/dL should be avoided, even if a lower target may be beneficial in some patient groups.

BLOOD GLUCOSE AND POST-TRANSPLANT OUTCOMES

Hyperglycemia and post-transplant infection

Two retrospective studies have documented an association between intraoperative hyperglycemia during LT and post-transplant infectious complications^[3,9]. In the study by Ammori *et al*^[3] in 2007 that included 184 patients undergoing LT, the overall infection rate (including superficial skin infection, pneumonia, blood stream infections, peritonitis, urinary tract infection) during the first 30 d post-transplant was significantly higher (48%) in the group with poorly controlled hyperglycemia compared to those with well-controlled blood glucose ($<$ 150 mg/dL; 30%). In the study of 680 LT patients by Park *et al*^[9] in 2009, severe hyperglycemia (\geq 200 mg/dL) increased the risk of surgical site infection during the immediate post-transplant period by more than twofold (RR = 2.25, 95%CI: 1.26-4.03)^[9].

Hyperglycemia influences major components of the immune system that combat infection. For example, early inflammatory responses to tissue injury are suppressed as a result of elevated expression of adhesion molecules, impaired complement activation, interference with the kininogen-bradykinin system, dysregulation of endothelial nitric oxide production^[40-42], and increased levels of proinflammatory cytokines, such as interleukins 1 β and 18 and tumor necrosis factor- α ^[43]. Hyperglycemia weakens macrophage phagocytosis, and reduces neutrophil adherence^[44,45], chemotaxis, and reactive oxygen species production^[46]. In addition, hyperglycemia interferes with the glycosylation of immune proteins and collagen^[47].

Glucose variability and post-surgical complications

Variability in blood glucose levels has been studied in association with mortality in the hospital or ICU^[48,49]. However, there are few studies examining surgical consequences with respect to perioperative variability in serial blood glucose measurements. A recent single-center, prospective cohort study of 1461 patients undergoing cardiac surgery found that postoperative glycemic variability increases the risk of major adverse events, such as death, myocardial infarction, reoperation, sternal infection, cardiac tamponade, pneumonia, stroke, and renal failure (RR = 1.3, 95%CI: 1.1-1.5)^[50]. Another retrospective study in 2013 revealed that large variability in preoperative blood glucose was associated with an increased rate of

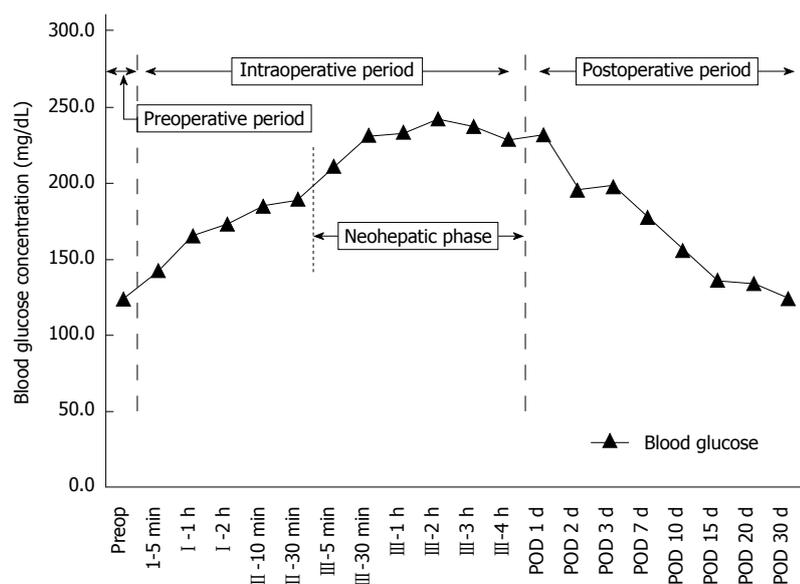


Figure 1 Perioperative trend of blood glucose during living-donor liver transplantation. Blood glucose concentrations were measured in 210 patients undergoing living-donor liver transplantation at St. Mary's Hospital (Seoul, South Korea) between 2009 and 2013. I : Preanhepatic phase; II : Anhepatic phase; III : Neohepatic phase; POD : Postoperative day; Preop : Preoperative.

reoperation (RR = 4.14, 95%CI: 1.30-13.33)^[51].

Only one study evaluated intraoperative glycemic variability in LT. In this retrospective study of 668 LT patients in 2010, intraoperative variability in blood glucose (SD \geq 55.0 mg/dL) nearly doubled the risk of reoperation for hemorrhage (RR = 1.9, 95%CI: 1.2-3.0)^[52]. However, the reason for this increased risk remains unclear. According to Hendriks *et al*^[53], surgical re-intervention in LT patients is related to intraoperative blood loss. It is possible that the turnover in body fluids due to massive blood loss results in an instability in blood glucose concentrations. *In vitro* studies indicate that rapid, wide swings in glucose levels can adversely affect normal cellular defenses and coagulation/fibrinolytic systems^[54,55].

Persistent neohepatic hyperglycemia and graft dysfunction

As graft-related problems are the most important determinant of initial prognosis after LT^[56], early detection of graft-related factors is important for improving post-transplant outcome. Since the early 1990s, blood glucose monitoring has been used as a sensitive indicator of early liver-graft function^[57]. In animals receiving partial liver allografts, graft function was predicted by intraoperative balance of glucose production and utilization in the liver, measured as the difference between hepatic glucose inflow (at the portal vein and hepatic artery) and outflow (from the hepatic vein, to the liver)^[58]. Impaired glucose uptake and continuous glycogenolysis causes persistent reperfusion hyperglycemia, which may be an early sign of impaired graft function^[59]. Therefore, blood glucose levels during the neohepatic phase can be associated with post-transplant liver function.

Moreover, a recent retrospective study found that hyperglycemia (> 200 mg/dL) maintained until the immediate post-transplant period was associated with liver allograft rejection within one year^[60]. The decline in intraoperative blood glucose that we observed near the end of the neohepatic phase during LT (Figure 1) has not been previously described. Future study is needed to determine whether this decline is associated with functional recovery of the grafted liver.

Prior reports indicate that pronounced insulin insensitivity and hyperinsulinemia in liver failure are attributable to pancreatic hypersecretion and reduced hepatic insulin clearance, secondary to hyperglucagonemia^[61]. These metabolic abnormalities disappear after successful LT^[62]. Thus, resolution of hyperglycemia would be expected at the end and immediately following LT upon recovery of liver graft function.

Mortality rate

The effect of intraoperative glucose management on mortality has primarily been examined in patients undergoing cardiac surgery. Such studies identified a benefit in patients with myocardial infarction who received intraoperative infusions of insulin and potassium^[63,64]. Additional studies have evaluated the effects of intensive glycemic control on mortality following coronary artery bypass grafting^[65-67]. The retrospective study by Ammori *et al*^[3] also reported one-year mortality rates, which were higher in patients with poorly controlled hyperglycemia compared to those with well-controlled glucose levels (21.9% vs 8.8%). A prospective clinical study of the relationship between intraoperative blood glucose and post-transplant mortality is thus warranted.

CONCLUSION

Patients with end-stage liver disease exhibit hepatogenic diabetes, which manifests as peripheral insulin resistance and hyperinsulinemia. During LT, additional exogenous factors lead to intraoperative refractory hyperglycemia, with peak blood glucose levels occurring after reperfusion. As there are no specific guidelines, conventional methods from other clinical fields are used for the intraoperative management of hyperglycemia in these patients. Retrospective studies demonstrate that intraoperative hyperglycemia is associated with increased risk for infection and one-year mortality. Furthermore, the variability in blood glucose level during LT may predict post-transplant outcomes. Diabetogenic traits return after successful LT, so persistent neohepatic hyperglycemia in association with early indicators of graft dysfunction should be examined in future studies, including prospective clinical studies on the influence of intraoperative blood glucose on post-transplant outcomes.

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