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REVIEW ARTICLE

Hyperglycemia in the Perioperative Period of Liver Transplantation: A Scoping Review

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ABSTRACT

Objectives: To find evidence on the influence of hyperglycemia in the perioperative period of liver transplantation. **Methods:** This is a scoping review of the PubMed, VHL, and Web of Science databases. The following descriptors were used: "Liver transplantation," "Hyperglycemia," and "Blood Sugar Control," with the Boolean operator "AND," and articles of relevance to the topic were selected. Initially, 139 articles were selected, all published in the last 20 years, in Portuguese and English. After analysis, 10 articles corresponded to the proposed objective. **Results:** In comparing strict control and conventional glucose control in patients undergoing liver transplantation, the average intraoperative glycemia was 143.3 mg/dL in the conventional group and 130.7 mg/dL in the strict control group, which received more insulin. The intensive care unit stay was similar with a mean of 3 days, but survival improved significantly with mean intraoperative glycemia ≤ 120 mg/dL. Patients with postreperfusion syndrome required insulin infusion more often. New-onset diabetes mellitus and early bacteremia were more frequent in the postreperfusion syndrome group. AST and ALT levels were higher in hyperglycemic patients. Surgical site infection rates correlated with postoperative hyperglycemia, with 20% for glycemia < 200 mg/dL and 52% for glycemia ≥ 200 mg/dL. Patients with postoperative glucose < 200 mg/dL had a lower rejection rate than those with glucose ≥ 200 mg/dL. Patients with diabetes had higher preoperative glycemia than patients without diabetes, with a gradual reduction after liver transplantation, whereas patients without diabetes had a peak on days 2 and 3 before returning to baseline levels. High glucose levels 48–72 h post-transplant were associated with higher mortality and a worse response to insulin treatment in the first week. **Conclusion:** Strict glycemic control in patients undergoing liver transplantation resulted in lower intraoperative glycemia and significantly better survival for those with glycemia ≤ 120 mg/dL, as well as lower rates of infection, rejection, and mortality, especially in patients without diabetes.

Descriptors: Hyperglycemia, Liver Transplantation, Glycemic Control.

Hiperglicemia no Perioperatório de Transplante de Fígado: Uma Revisão de Escopo

RESUMO

Objetivos: Encontrar evidências sobre a influência da hiperglicemia no perioperatório de transplante de fígado. **Métodos:** Trata-se de uma revisão de escopo na base de dados PubMed, BVS e Web of Science. Foram utilizados os descritores: "*Liver transplantation*", "*Hyperglycemia*" e "*Blood Sugar Control*" com o operador booleano "*AND*", e selecionados artigos de relevância para o tema. Inicialmente, foram selecionados 139 artigos, todos publicados nos últimos 20 anos, em português e inglês. Após análise, 10 artigos corresponderam ao objetivo proposto. **Resultados:** Na comparação entre controle rigoroso e controle convencional da glicose em pacientes submetidos a transplante de fígado, a média de glicemia intraoperatória foi de 143,3 mg/dL no grupo convencional e 130,7 mg/dL no grupo de controle rigoroso, que recebeu mais insulina. A permanência na unidade de terapia intensiva foi similar, com média de 3 dias, mas a sobrevida melhorou significativamente com glicemia intraoperatória média ≤ 120 mg/dL. Pacientes com síndrome pós-reperfusão necessitaram mais frequentemente de infusão de insulina. O diabetes mellitus de início recente e a bacteremia precoce foram mais frequentes no grupo com síndrome pós-reperfusão. Níveis de AST e ALT foram mais elevados em pacientes hiperglicêmicos. As taxas de infecção do sítio cirúrgico correlacionaram-se com a hiperglicemia pós-operatória, sendo 20% para glicemia < 200 mg/dL e 52% para glicemia ≥ 200 mg/dL. Pacientes com glicose pós-operatória < 200

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mg/dL tiveram menor taxa de rejeição em comparação com glicose ≥ 200 mg/dL. Os pacientes com diabetes apresentaram glicemia pré-operatória mais alta que pacientes sem diabetes, com redução gradual após o transplante de fígado, enquanto os pacientes sem diabetes tiveram um pico nos dias 2 e 3 antes de retornarem aos níveis basais. Níveis elevados de glicose após 48–72 h pós-transplante foram associados a maior mortalidade e pior resposta ao tratamento com insulina na primeira semana. **Conclusão:** O controle rigoroso da glicemia em pacientes submetidos a transplante de fígado resultou em uma glicemia intraoperatória mais baixa e uma sobrevida significativamente melhor para aqueles com glicemia ≤ 120 mg/dL, além de menores taxas de infecção, rejeição e mortalidade, especialmente em pacientes sem diabetes.

Descritores: Hiperglicemia; Transplante de Fígado; Controle Glicêmico.

INTRODUCTION

During liver transplantation (LT), hyperglycemia is a common complication, with an incidence of between 6.7% and 94%, with 45.9% of recipients developing severe hyperglycemia with a value above 241.2 mg/dL in the neohepatic phase[1]. This glycemic instability results from surgical stress, corticosteroids, fluid solutions containing glucose, blood transfusions, vasopressors, and the onset of gluconeogenesis after reperfusion of the new graft[2]. Postreperfusion syndrome (PRS) causes severe circulatory and metabolic deterioration during reperfusion of the liver graft after removal of the portal vein clamp, contributing to the development of hyperglycemia and negatively affecting the postoperative recovery of these patients[3]. This occurs because hyperglycemia intensifies the costimulation and presentation of antigens, aggravates ischemic damage and the inflammatory response associated with reperfusion, increases the production of cytokines and the expression of adhesion molecules, as well as activates dendritic cells.[4]

Liver cirrhosis and diabetes mellitus (DM) are closely related clinical conditions. When it coexists with cirrhosis, diabetes is called hepatogenous diabetes (HD), which differs from type 2 DM. It has a later onset, no family history of DM, a lower body mass index, a lower frequency of diabetic complications such as retinopathy, cardiovascular, and kidney disease, as well as insulin resistance. Common causes of death from HD are related to liver disease[5]. Patients with end-stage liver disease often have impaired glucose metabolism, manifesting as glucose intolerance or DM[6]. In patients on the waiting list for LT, diabetes is present in up to 65% of them. During LT, the glycemic status of these patients tends to worsen due to their intrinsic diabetogenic state. In the post-transplant period, the prevalence of diabetes is around 38%[4]. Hyperglycemia is a frequent complication, associated with a higher risk of graft rejection and various post-LT complications, such as infection, acute kidney injury, new-onset diabetes, malignancies, and increased cardiovascular risk, characteristic of metabolic syndrome[7]. Although glycemic control is essential in this context, there is a lack of evidence-based guidelines for the appropriate management of hyperglycemia, and the impact of the degree of glycemic control on graft failure and the development of complications remains unclear.

Therefore, the aim of this scoping review was to find evidence in the literature on the effects and management of hyperglycemia in the perioperative period of LT.

METHODS

This is a scoping review, which is defined as a type of study that seeks to explore the main concepts of the topic in question, ascertain the size, scope, and nature of the study, condensing and publishing the data in order to expose existing research gaps. This review was structured on the basis of the methodological framework of the Joanna Briggs Institute (JBI) and the PRISMA Checklist for Scoping Reviews (PRISMA-ScR), which establish the following steps: 1) define and align the objectives and research question; 2) develop and align the inclusion criteria with the objectives and questions; 3) describe the planned approach to search, selection, data extraction, and presentation of evidence; 4) search for evidence; 5) selection of evidence; 6) extraction of evidence; 7) analysis of evidence; 8) presentation of evidence; and 9) summary of evidence on the purpose of the review, conclusions, and observations of any implications of the findings.[8,9]

Accordingly, the guiding question was formulated according to the PCC strategy, which represents a mnemonic for identifying the Population, Concept, and Context. Thus, the following research question was developed: What are the implications of hyperglycemia in the perioperative period of patients undergoing LT?

The bibliographic search was carried out systematically in the following databases: PubMed, Web of Science, and the Virtual Health Library (VHL), with scientific articles from Medline found in the latter. The following descriptors validated by the Health Sciences Descriptors (DeCS) were used: "Liver transplantation," "Hyperglycemia," and "Blood Sugar Control." The descriptors were interchanged using the Boolean operator "AND," and the time frame was limited to include only articles published in the last

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20 years. The use of descriptors in English is due to the way the databases work and the fact that most of the indexed articles are available in English, which means that searching with descriptors in Portuguese limits the results only to articles that have both Portuguese and English versions available.

The descriptors used in PubMed, VHL, and Web of Science were expanded to all fields, and 89, 48, and 2 articles were found, respectively. In the end, 139 articles were retrieved. Due to time constraints, other manual sources were not used.

For the systematized selection of articles, the Rayyan tool was employed, considering the PRISMA Statement 2020 search strategy in accordance with the CARE Guidelines for systematic reviews outlined by the Equator Network (Fig. 1).[10]

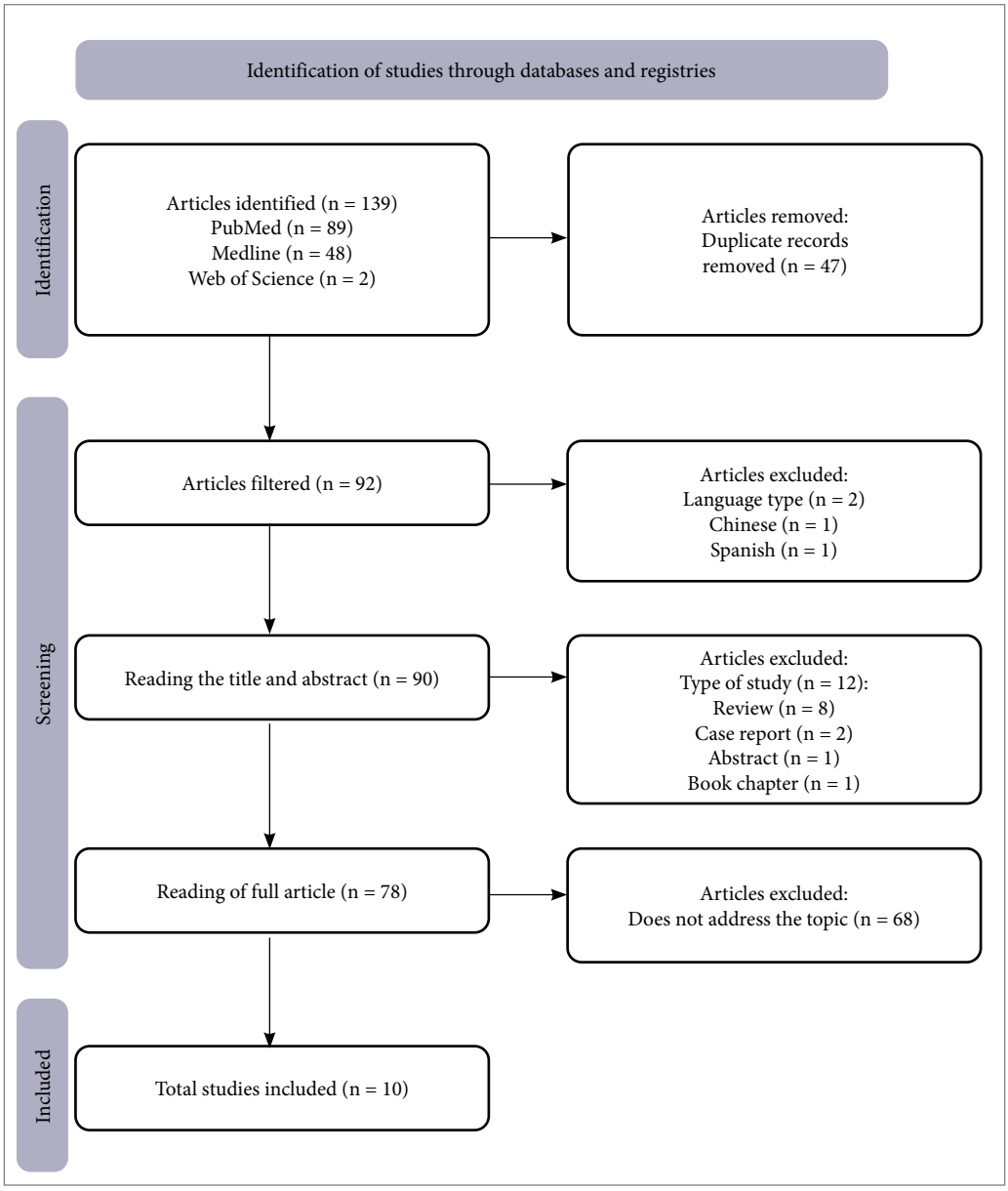

Figure 1. Screening of articles using the PRISMA Statement 2020 flowchart for systematic reviews.

Source: Elaborated by the authors.

The articles were screened using inclusion and exclusion criteria. Duplicate articles, articles in Chinese or Spanish, with a low level of evidence, such as reviews, case reports, abstracts, and book chapters were excluded, as were those that did not address the research topic of hyperglycemia in the perioperative period of LT. For this reason, the search priority was to consider only scientific articles that described insulin resistance in liver disease, the correlation of DM with LT, glycemic changes during liver resection and LT, and the association of glycemic changes with postsurgical complications.

In the end, the articles that fit the theme were analyzed and included in a data extraction table with information that contributed to answering the research question and objectives. The results are described in Table 1.

Table 1. Extraction table of the articles included in the scoping review.

Authors	Journal/Year	Objectives	Type of Study	Results
Ammori JB et al.[11]	Journal of Surgical Research, 2007	To examine the effect of intraoperative glycemic control in LT recipients.	Retrospective study	During the study period, a total of 184 patients met the criteria for analysis. Recipients with strict glycemic control had an average glucose of 135 mg/dL compared to 184 mg/dL in the inadequate control group. Although the incidence of most postoperative complications was similar, inadequate glycemic control was associated with a significantly increased rejection rate at 30 days after transplantation, with an incidence of around 48% versus 30% and with an increased mortality rate at 1 year of 21.9% versus 8.8% between the inadequate control groups and the group with strict control, respectively.
Wallia A et al.[12]	Transplantation, 2010	To analyze the association between perioperative hyperglycemia and outcomes within one year after LT.	Retrospective study	A total of 113 LT recipients were included. The rejection rate was significantly lower for patients with postoperative glucose levels < 200 mg/dL versus > 200 mg/dL. The need for prolonged ventilation was more common in patients with glucose < 200 mg/dL versus > 200 mg/dL. While other outcomes such as infection, rehospitalization, and patient/graft survival were not different between the glucose control groups, rejection was associated with an increase in rehospitalizations and infections.
Builes Montaño CE et al.[13]	Revista de Gastroenterología de México, 2014	To determine whether there is an association between the increase in blood glucose levels during the 48 h after LT and the risk of early rejection, bacterial infections, or longer hospital stays.	Retrospective study	Some form of hyperglycemia was present in 94% of patients during the first 48 h post-transplant, regardless of its definition. There were no increased risk of rejection, infection, or longer hospital stays among patients who had hyperglycemia and those who did not.
Blasi A et al.[14]	Annals of Hepatology, 2015	To describe the hyperglycemic pattern of LT in three different types of donors and its predictive factors and to investigate the relationship between transient hyperglycemia after reperfusion and liver graft function.	Prospective study	The greatest increase in glucose levels after reperfusion was observed in LT recipients with PAF donors and the lowest in LT recipients with donors after cardiac death. The glucose level during the anhepatic phase was the only modifiable predictive variable of hyperglycemia after reperfusion. No relationship was found between hyperglycemia after reperfusion and EAD. However, the recipients with the highest glucose levels after reperfusion tended to achieve the best glucose control at the end of the surgery and those who were unable to control their glucose levels after reperfusion showed EAD more frequently. The highest levels of caspase-3 were found in recipients with the lowest glucose values after reperfusion.
Katsura E et al.[15]	Medical Science Monitor, 2016	To assess whether glucose levels in pre-LT patients with a living donor were a prognostic factor for post-LT survival.	Prospective study	Fasting plasma glucose (FPG) of at least 100 mg/dL significantly decreased survival after transplantation, while postprandial hyperglycemia had no effect on survival. In addition, overall mortality and the incidence of vascular disease were significantly higher among patients with uncontrolled FPG.
Ramos-Prol A et al.[16]	Journal of Endocrinological Investigation, 2017	To assess whether intensive glycemic control in hospitalized patients without diabetes undergoing LT is associated with a lower rate of graft rejection at 3 months and 5 years post-transplant.	Comparative cross-sectional study	A statistically significant interaction was shown between the treatment group and the presence of diabetes for the rejection rate 3 months and 5 years after transplantation. At both time points, the intensive insulin treatment group had lower rejection rates in patients with diabetes, which did not occur in patients without diabetes.

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Table 1. Continuation...

Authors	Journal/Year	Objectives	Type of Study	Results
Ke QH et al.[17]	Hepatobiliary & Pancreatic Diseases International, 2018	To assess the impact of new-onset hyperglycemia on the prognosis of post-LT patients, the need for strict glycemic control immediately after LT and to determine the etiology of new-onset hyperglycemia.	Retrospective study	Of the 3,339 liver recipients, 42.4% developed hyperglycemia of n onset. Recipients with new-onset hyperglycemia had a higher incidence of post-transplant complications such as graft and kidney failure, infection, biliary stenosis, cholangitis, and tumor recurrence in a glucose concentration-dependent manner compared to recipients without new-onset hyperglycemia. Independent risk factors for new-onset hyperglycemia were donor warm ischemia time > 10 min, cold ischemia time > 10 h, anhepatic time > 60 min, recipient model for end-stage liver disease score > 30, moderate ascites and corticosteroid use. Liver enzymes (alanine aminotransferase and gamma-glutamyl transpeptidase) on day 7 post-transplant correlated significantly with new-onset hyperglycemia.
Giráldez E et al.[18]	Diabetology & Metabolic Syndrome, 2018	To investigate the ability of postoperative glycemic profiles measured over 7 days to predict mortality in patients undergoing LT, differentiating between those with and without preexisting DM.	Observational study	Patients had a survival rate of 85% at 1 year and 65% at 10 years, with no difference in mortality between patients with and without diabetes. In the glucose profiles, however, differences were observed between patients with and without diabetes: patients with diabetes recorded lower baseline glucose values, which gradually increased until reaching a peak on days 2 and 3 and then declined thereafter; individuals with diabetes started with higher values that gradually decreased over the course of the first week. Glucose profiles were found to be statistically associated with mortality among patients without diabetes, but not among patients who had diabetes before transplantation.
Chae S et al.[3]	PLoS ONE, 2020	To investigate the impact of PRS itself on the occurrence of hyperglycemia and the release of C-peptide, treating PRS as a surrogate marker for insulin resistance during the intraoperative period after graft reperfusion in patients undergoing LT.	Retrospective study	There were no significant differences in pre- and intraoperative recipients and graft findings between the groups. Although glucose and C-peptide levels increased continuously during the surgical phases in both groups, glucose, and C-peptide levels during the neohepatic phase were significantly higher in the SPR group than in the non-SPR group, and greater changes in levels were observed between the preanhepatic and neohepatic phases. There was a higher incidence of C-peptide levels > 2.0 ng/mL and maximum glucose levels > 200 mg/dL in the neohepatic phase in patients with PRS than in those without PRS. The infusion of exogenous insulin was significantly associated with the occurrence of hyperglycemia during the neohepatic phase.
Kumar S et al.[2]	BMC Anesthesiology, 2020	To analyze whether strict control of intraoperative glycemia improves survival at 1 year and reduces surgical complications, including infections, after LT.	Prospective study	There was no statistically significant difference in patient survival between conventional and strict control, respectively: 1 year, 88% versus 88%; 3 years, 86% versus 84%; 5 years, 82% versus 78%. Graft survival between the conventional and strict control groups at 1 year was 88% versus 84%; 3 years, 82% versus 76%; and 5 years, 78% versus 70%, respectively.

LT: liver transplantation; EAD: early graft dysfunction; FPG: fasting plasma glucose; PRS: postreperfusion syndrome; DM: diabetes mellitus; FAP: familial amyloidotic polyneuropathy. Source: Elaborated by the authors.

RESULTS

Ten studies were analyzed in this scoping review, including three prospective studies, five retrospective studies, one comparative cross-sectional study, and one observational study. These studies provided a diverse and comprehensive base of data, allowing for a more in-depth understanding of the subject under investigation.

Comparison between intensive and conventional glycemic control

In a prospective randomized study comparing patients undergoing LT, the conventional group had an average intraoperative blood glucose of 143.3 mg/dL, while the strict control group had 130.7 mg/dL. The strict group received more insulin. In the conventional group, seven patients had at least one episode of hypoglycemia, while in the strict group thirteen patients had one episode. Patient survival did not differ between the conventional and restricted groups: at 1 year it was around 88%; at 3 years,

86% versus 84%; and at 5 years, 82% versus 78%, respectively. Graft survival also showed no significant difference between the conventional and rigorous groups, with an average of 88% versus 84% at 1 year, 82% versus 76% at 3 years and 78% versus 70% at 5 years, respectively. The postoperative stay in the intensive care unit was similar in both groups, with an average of 3 days. There was no significant difference in postsurgical complications, including biliary fistula, reoperation for bleeding, kidney failure, need for dialysis, bacterial, fungal, and wound infections. However, survival improved significantly in patients with average intraoperative glycemia ≤ 120 mg/dL.[2]

In a comparative cross-sectional study, 176 LT patients were included in the intensive treatment group and 178 in the conventional treatment group. The rejection rate after 3 months was significantly lower in patients with diabetes treated with the intensive protocol compared to the conventional protocol, with no differences observed between the protocols in patients without diabetes. The rejection rate fell from 26.5% to 5.5% in patients with diabetes, while it increased in those without diabetes from 3.5% to 4.2%. Graft survival at 3 months revealed a significant interaction between treatment and the presence of diabetes. During conventional control, the degree of rejection was: 31.8% mild, 45.5% moderate, and 22.7% severe. During the period of intensive glycemic control, the degree of rejection was around 10% moderate and 90% severe. After 5 years, the rejection rate was also lower in patients with diabetes in the intensive protocol, representing around 39.7% compared to 21.8% in the conventional protocol, with no change in those without diabetes, who had 12.2% in the intensive protocol and 15.8% in the conventional protocol.[16]

The risk of mortality was assessed at 3 months and 5 years after transplantation. Mortality at 3 months was 1.7% in the intensive glycemic control group and 3.9% in the conventional group. At 5 years, mortality was 2.9% in the intensive group and 5.6% in the conventional group. When analyzing patients with diabetes, the 5-year mortality rate was 1.8% in the intensive group and 7.9% in the conventional group. Among patients without diabetes, there was no difference between the groups, with a 1.7% mortality rate in both.[16]

The number of mild hypoglycemic events was significantly higher in the intensive treatment group compared to the conventional group, with an average of 0.76 cases per patient without diabetes in the intensive treatment and 0.05 in the nonconventional group. For patients with diabetes, the average was 1.17 in the intensive group and 0.15 in the conventional group. With regard to severe hypoglycemic events, the differences between the groups were also significant, with an average of 0.13 cases per patient without diabetes in the intensive treatment and 0.01 in the conventional treatment, and 0.37 for patients with diabetes in the nonintensive treatment versus 0.03 in the nonconventional treatment.[16]

In a retrospective study of 184 patients undergoing LT, 60 patients had strict intraoperative glycemic control, while 124 patients were poorly controlled. The strict control group had lower average glucose concentrations, around 135 mg/dL versus 183 mg/dL for the inadequate control group, despite receiving less insulin, 13 versus 24 units, respectively. The group with strict control had fewer infections in the first 30 postoperative days than the group with inadequate control, representing 30% versus 48%, respectively. There were no significant differences in acute cellular rejection (18% versus 12%), hepatic artery thrombosis (0% versus 2%), biliary complications (15% versus 19%), and the need for retransplantation (3% versus 2%) between the strictly controlled and poorly controlled groups, respectively. Survival was better in the strict control group than in the poorly controlled group, with 91.2% versus 78.1% at 1 year and 85.9% versus 72.7% at 2 years, respectively.[11]

Implications of PRS on glycemia

With regard to the repercussions of PRS on glycemia, in a retrospective study, patients undergoing LT were divided into a group with PRS and a group without PRS. Glucose and C-peptide levels increased during the surgical phases in both groups, but in the neohepatic phase they were significantly higher in the SPR group. Patients with PRS required insulin infusion more frequently. The incidence of C-peptide levels > 2.0 ng/mL and glucose peaks > 200 mg/dL in the neohepatic phase was higher in the PRS group than in the group without PRS, at around 70.1% versus 54.6% and 84.5% versus 59.8%, respectively. Between the 2nd and 7th postoperative days, the incidence of glucose peaks > 200 mg/dL was also higher in the group with PRS. New-onset DM and early bacteremia were more frequent in the PRS group.[3]

Effects of preexisting diabetes on LT

In a study of 91 patients with liver cirrhosis undergoing LT, patients with fasting plasma glucose (FPG) and postprandial glucose ≥ 250 mg/dL were treated with insulin. Thirty patients diagnosed with DM before LT had a lower 5-year survival rate compared to the control group of 61 patients. Twenty-five patients were treated with insulin and also showed significantly worse borderline survival compared to the control group of 66 patients. The survival rate of 32 patients with glycemia ≥ 200 mg/dL in 120 min of glucose tolerance testing did not differ significantly from 21 patients with impaired glucose tolerance and 7 patients with normal glycemia, with 5-year survival rates of 65%, 63% and 70%, respectively. The survival rate of the 41 patients with FPG ≤ 90 mg/dL did not differ significantly from the control group of 50 patients, with 5-year survival rates of 65% and 69%, respectively. The survival rate of 32 patients with HbA1c ≥ 5% also did not differ significantly from the control group of 59 patients, with 5-year survival rates of 64% and 70% respectively.[15]

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The 41 patients with elevated FPG ≥ 100 mg/dL had lower 5-year survival rates than the control group, around 52% versus 78%, respectively. A comparative analysis of 32 patients with very high FPG ≥ 111 mg/dL, 19 with moderate FPG 100–110 mg/dL and 50 with normal FPG < 100 mg/dL showed significant differences in post-LT prognosis, with 5-year survival rates of 75%, 59%, and 42%, respectively. The prevalence of vascular diseases, including thrombotic microangiopathy, portal vein thrombosis, nonocclusive mesenteric ischemia, and stroke, was higher among patients with elevated FPG.[15]

In a retrospective study of 133 patients undergoing LT, 35% had a history of diabetes, 44% had episodes of rejection, 58% had infections, 28% needed prolonged ventilation, and 64% required rehospitalization. Patient and graft survival at one year was 90% and 88%, respectively. Patients with postoperative glucose < 200 mg/dL had a lower rejection rate compared to those with > 200 mg/dL, with 60% of patients with preexisting diabetes being in the > 200 mg/dL group, than 28% in the < 200 mg/dL group. Prolonged ventilation occurred more frequently in patients with glucose < 200 mg/dL. Patients with post-transplant rejection had more infections (around 1.89 versus 1.19) and more days of rehospitalization (an average of 11.12 versus 5.75) compared to those without rejection, respectively.[12]

In an observational study of 632 patients undergoing LT, 20% had a history of diabetes. The survival rate was 85% at 1 year and 65% at 10 years. Patients with diabetes had higher preoperative glucose levels compared to those without diabetes. After LT, glucose levels gradually decreased in patients with diabetes, while they increased to a peak on days 2 and 3 in those without diabetes, before returning to baseline levels. Patients with diabetes were older, had less need for transfusions and lower Model of End-Stage Liver Disease (MELD) receptor scores. Survival rates at 1 and 10 years were similar among patients with diabetes, at around 89% and 68%, and around 86% and 65% among those without diabetes. Among patients without diabetes, mortality increased significantly in older individuals, with malignant etiology, greater need for transfusion, and longer parenteral nutrition. Elevated glucose levels 48 to 72 h post-LT were associated with higher mortality and worse response to insulin treatment in the first week.[18]

Glycemic changes in LT recipients according to donor type

In a prospective study of 436 patients undergoing LT, the grafts came from three types of donors: 381 after brain death, 29 after cardiac death, and 26 with familial amyloid polyneuropathy (FAP). There was a significant increase in glucose levels after reperfusion in all groups, with the highest levels and percentages of increase in recipients of donors with PAF, and the lowest in recipients of donors after cardiac death. The glucose level by the end of surgery decreased in all groups, with a significant drop from 220 to 197 mg/dL only in recipients of donors after brain death. Glucose levels in the anhepatic phase and after reperfusion were independent predictors of its reduction, with higher levels associated with better glycemic control at the end of surgery.[14]

The overall incidence of early graft dysfunction (EAD) was 26%, with 114 cases of EAD among the 436 LT. By type of donor, the incidence was 24% for donors after brain death, 58% for donors after cardiac death, and 23% for donors with FAP. The increase in glucose levels after reperfusion was similar between recipients with and without EAD in all donor groups. In donor recipients after brain death, inadequate glycemic control (final glucose higher than that after reperfusion) was associated with a higher incidence of EAD, at around 31%, than those with good glycemic control, at around 19%. In recipients with EAD, glucose levels did not decrease after reperfusion, while they decreased by 11% in those without EAD.[14]

A joint analysis of the liver tissue samples before and after refusion showed a significant increase in all immunological markers such as interferon-gamma (IFN-γ), interleukin 1 beta (IL-1β) and IL-6. However, when separating the samples based on glucose levels after reperfusion into < or > 180 mg/dL, grafts with glycemia > 180 mg/dL did not show a significant increase in IL-1β. There was a tendency for IFN-γ and IL-6 to increase with lower glucose levels after reperfusion. The expression of the caspase-3 gene showed no changes after reperfusion, but recipients with lower glucose levels showed higher levels of caspase-3 in the donor tissue samples.[14]

New-onset hyperglycemia in post-LT patients

In a retrospective cohort study of 164 patients undergoing LT, 94% had post-LT hyperglycemia: 154 with at least one value above 140 mg/dL and 140 with average glycemia > 140 mg/dL. The average blood glucose on admission to the intensive care unit was 182 mg/dL, with 30% of the time in the first 48 h above 140 mg/dL. Hyperglycemia was not associated with a higher risk of rejection, infection, or longer hospitalization. In patients with diabetes, there was no greater risk of infection or difference in length of stay, which was around 20.7 days versus 19 days compared to those without diabetes.[13]

However, in a retrospective study with a cohort of 3,339 patients undergoing LT, 42.4% had new-onset hyperglycemia and different results compared to the previous study. These recipients showed a significantly higher incidence of post-transplant complications, including liver and kidney graft complications, acute rejection, biliary stenosis, and cholangitis, compared to patients without new-onset hyperglycemia. Among the 21.1% of recipients with extremely high FPG levels (above 0 ≥ 11.1 mmol/L), there was a higher incidence of serious complications, especially infection, with around 38.7% versus 11.3%,

and recurrence of hepatocellular carcinoma, on average 19.3% versus 11.4%, compared to recipients without hyperglycemia, respectively. In addition, these patients had a significantly lower overall and tumor-free survival.[17]

The group with new-onset hyperglycemia had specific donor and recipient characteristics compared to the group without hyperglycemia, including greater ABO incompatibility, longer ischemia time, higher MELD score, and greater use of maintenance corticosteroid therapy. Acute hepatitis using steroid pulse treatment in the first month after transplantation occurred in only eight patients and was not considered a relevant risk factor. Independent risk factors for new-onset hyperglycemia were identified as donor warm ischemia time > 10 min, cold ischemia time > 10 h, anhepatic time > 60 min, recipient MELD classification > 30, moderate ascites and increased use of corticosteroids. The intraoperative corticosteroid bolus was an independent protective factor against new-onset hyperglycemia.[17]

During the first week post-transplant, initial function was considered poor in 16.6% of patients, which significantly increased the risk of new-onset hyperglycemia. Independent risk factors, such as prolonged cold ischemia time and high MELD score, increased independently of the risk of poor initial function. Fasting plasma glucose correlated significantly with serum levels of alanine aminotransferase (ALT) and gamma-glutamyltranspeptidase (GGT) on the 7th day post-transplant. Patients with new-onset hyperglycemia had significantly higher ALT and GGT levels compared to patients without new-onset hyperglycemia. To predict the prevalence of new-onset hyperglycemia, ALT showed a sensitivity of 64% and specificity of 61% with a cut-off point of 280 U/L. There was no significant difference in total bilirubin and AST levels between the groups with and without new-onset hyperglycemia.[17]

DISCUSSION

Diabetes mellitus and LT

One study observed that the use of DM medication and high FPG levels in pre-LT patients negatively influenced the post-transplant survival rate. Fasting plasma glucose ≥ 100 mg/dL significantly reduced survival, regardless of previous treatment for DM. The study recommends maintaining FPG between 90 and 100 mg/dL in patients with pre-LT cirrhosis.[15]

In the study, mortality was similar between patients with high and normal FPG, but vascular disease was a more prominent cause of death among those with high FPG[15]. Another study indicated that the risk of vascular events, including cardiovascular disease, increases in patients with DM[19], and coronary artery calcification in patients with cirrhosis was associated with high FPG levels[20]. In patients with cystic fibrosis and diabetes, microvascular complications occur with fasting hyperglycemia[21]. In addition, thrombotic angiopathy has been associated with oxidative modification of von Willebrand factor in patients with diabetes.[22]

Elevated FPG indicates a greater abnormality in glycemic control compared to postprandial hyperglycemia in DM2. Beta-cell dysfunction begins in prediabetes and LT does not improve it but can reduce insulin resistance[23]. High glycemia in pre-LT patients significantly reduces post-transplant survival compared to patients with normal glycemia. Regardless of diabetes criteria, high FPG pre-LT may indicate advanced stage DM, with a higher prevalence of severe vascular disease compared to patients with normal glycemia after LT.[15]

An observational study found that plasma glucose profiles in the first week post-LT differed between patients with and without previous DM. High glucose levels are associated with a higher risk of mortality in patients without diabetes, but not in patients with diabetes. This is because patients with diabetes tolerate higher glycemic values with no impact on mortality, possibly due to unknown protective factors against stress hyperglycemia. In the first week after LT, patients with diabetes have different glucose profiles to those without diabetes: those with diabetes start with high plasma glucose on the first day, which decreases after 48 h. Those without diabetes start with lower glucose, rising for up to 48 to 72 h before decreasing. This difference occurs under continuous insulin infusion. Thus, high glycemia in patients with diabetes does not affect mortality, possibly due to chronic adaptation to hyperglycemia, which attenuates the harmful effects in stressful situations[18]. Another study showed that patients without diabetes with higher levels of glycated hemoglobin, indicating poorer control of the disease, also tolerated hyperglycemia better.[24]

Glycemic changes during LT

During LT, blood glucose concentrations rise sharply from 110 to 204 mg/dL in the preanhepatic phase and to 384 mg/dL in the neohepatic phase. Despite the concomitant increase in insulin concentrations, hyperinsulinemia does not effectively control hyperglycemia in the neohepatic phase, possibly due to peripheral insulin resistance exacerbated by hepatectomy. In patients with renal insufficiency, the risk of hypoglycemia increases due to suppression of renal glucose release and decreased glycogen storage[25]. The hyperinsulinemia observed in these patients is due to reduced renal clearance and the effects of the uremic toxin

on the liver. Malnutrition and muscle loss can aggravate the decrease in hepatic glycogen stores and gluconeogenic capacity. In addition, acidosis limits the liver's ability to compensate for normoglycemia.[6]

In one study, patients with diabetes before transplantation had more hyperglycemic events during hospitalization. Intensive insulin treatment provided superior glycemic control compared to the use of insulin on a sliding scale. Despite the beneficial glycemic targets during management, the number of severe levels of hypoglycemia was relatively low. Lower rates of graft rejection were observed in the group undergoing intensive insulin treatment. Several mechanisms explain the increased risk of rejection related to hyperglycemia, such as increased production of cytokines like tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, IL-12, adhesion molecules, dendritic cells, and altered expression of major histocompatibility complex (MHC) class I and II molecules, which intensifies the immune response against the graft. In addition, hyperglycemia aggravates ischemic damage and postreperfusion inflammation, apparently mediated by exaggerated leukocyte adhesion to the endothelium.[16]

The administration of corticosteroids can aggravate preexisting insulin resistance and increase the release of counterregulatory hormones such as glucagon, adrenaline, noradrenaline, growth hormone, and cortisol. The infusion of vasoactive drugs, such as epinephrine, norepinephrine, and dopamine, also contributes to an increase in blood glucose levels. Other sources of glucose include blood transfusions and hepatic glucose released by the graft, especially during rewarming and after perfusion. The abrupt increase in hyperglycemia in the neohepatic phase is mainly caused by the influx of glucose from the grafted liver.[6]

In PRS, the increase in stress factors aggravates insulin resistance, as measured by C-peptide, resulting in glycemic levels above 200 mg/dL in the neohepatic phase and in the first postoperative week. Hyperglycemia in the neohepatic phase was approximately three times more frequent in patients with PRS than in patients without PRS. The stress associated with PRS compromises glycemic control, increasing the need for exogenous insulin infusion during surgery.[6]

In a retrospective study, PRS was identified as an independent factor that compromises intraoperative glycemic control, resulting in significant insulin insensitivity and pancreatic hypersecretion of insulin. Although the exact mechanism of hyperglycemia-related PRS is uncertain, ischemia-reperfusion in grafts and patients causes biochemical and cellular changes that generate proinflammatory cytokines and free radicals, as well as activating the complement system. These changes lead to an inflammatory response mediated by interactions between neutrophils and platelets, resulting in endothelial swelling, vasoconstriction, leukocyte sedimentation, and hemoconcentration. The production of inflammatory mediators can exacerbate PRS, provoking an intense local inflammatory response that contributes to the activation of hepatic gluconeogenesis and peripheral insulin resistance.[3]

The increase in glucose levels after reperfusion varied significantly between grafts from donors after cardiac death, accounting for around 12%, and donors due to PAF, accounting for around 96%. Grafts from donors after cardiac death, which have lower glucose levels, suffer from warm ischemia before recovery, which leads to a more marked depletion of glycogen compared to cold ischemia (approximately 0.15% and 5.5%, respectively). This intense depletion of glycogen during warm ischemia may explain the lower levels of glucose after reperfusion in these receptors. In contrast, PAF receptors, which do not undergo warm ischemia, retain more glycogen, resulting in higher glucose levels after reperfusion. Given that the rate of graft dysfunction is higher in donors after cardiac death, reaching an average of 58% compared to PAF with 23%, a possible relationship between postreperfusion glucose levels and liver function is suggested. Reinforcing this idea, glucose levels were lower in recipients of brain-dead donors with EAD compared to donors without EAD.[14]

Inflammatory markers increased after graft reperfusion, with a greater increase observed in grafts with lower glucose levels, indicating that transient hyperglycemia does not exacerbate the inflammatory lesion. Higher levels of caspase-3 in the first biopsies of these grafts indicate a more compromised condition. Post-ischemia-reperfusion apoptotic damage is known to play a crucial role in organ failure, making caspase-3 a reliable marker of cellular condition.[14]

Glycemic changes and postsurgical complications

In a study of 184 patients undergoing LT, the overall infection rate in the first 30 days post-transplant was significantly higher in the group with poorly controlled hyperglycemia at 48% compared to the group with well-controlled glycemia < 150 mg/dL at 30%[11]. In another study with 680 patients, severe hyperglycemia ≥ 200 mg/dL more than doubled the risk of surgical site infection in the immediate post-transplant period.[26]

Hyperglycemia negatively affects the main components of the immune system. It suppresses early inflammatory responses, alters the expression of adhesion molecules, impairs complement activation, deregulates endothelial nitric oxide production, and increases proinflammatory levels, such as the cytokines IL-1β, IL-18, and TNF-α. In addition, hyperglycemia weakens macrophage phagocytosis and reduces adhesion, chemotaxis, and the production of reactive oxygen species by neutrophils, as well as interfering with the glycosylation of immunological proteins and collagen.[6]

Hyperglycemia after LT is associated with an increase in the inflammatory response related to ischemia-reperfusion, mediated by the exacerbated adhesion of leukocytes to the endothelium. In addition, postoperative hyperglycemia reflects insulin resistance, associated with high levels of TNF-α and IL-1, IL-6, and IL-12, which promote systemic inflammation and can intensify the

immune response against the graft. High levels of glycemia also increase the expression of MHCs I and II, potentiating the activation of the innate immune response[4]. Glucose values > 150 mg/dL were associated with a higher risk of infection 30 days after surgery and higher mortality at one year.[13]

Hyperglycemia increases the production of reactive oxygen species in endothelial cells, with superoxide generated by the mitochondrial electron transport chain linking high glucose to endothelial damage. In addition, hyperglycemia is associated with impaired vasodilation, a reduction in the inducible nitric oxide synthase enzyme and a decrease in circulating nitric oxide levels. High blood glucose concentrations also eliminate ischemic preconditioning and amplify reperfusion lesions in the liver, potentiating ischemia-reperfusion injury and contributing to reduced graft and patient survival. Furthermore, since non-insulin-dependent glucose uptake in the liver is directly proportional to blood glucose concentrations, intracellular glucose overload can induce direct toxic effects on the transplanted liver or intraoperative hyperglycemia can reflect a dysfunctional liver graft, resulting in poorly controlled hyperglycemia despite insulin therapy.[11]

New-onset hyperglycemia can significantly increase the risk of post-transplant complications, such as graft failure, acute rejection, and biliary stenosis. The results indicated that high levels of FPG are associated with a higher risk of complications, probably in a concentration-dependent manner. Extremely high FPG levels ≥ 11.1 mmol/L in the first month post-transplant not only increased the risk of complications but also reduced overall and tumor-free survival rates. Although the underlying mechanism remains unclear, strict glycemic control with immediate intensive insulin therapy is essential in the initial period after LT.[17]

All phases of ischemia during LT, cold ischemia time, anhepatic time, and especially warm ischemia time of the graft were identified as independent factors for the development of new-onset hyperglycemia. These results highlight the role of ischemic graft injury, which induces hepatic insulin resistance by activating proinflammatory pathways. In addition to prolonged ischemic time, other independent risk factors include high MELD score, moderate ascites, and continuous use of post-transplant corticosteroids. Given the adverse effects of corticosteroids, a corticosteroid-free protocol, including only an intraoperative bolus dose, is strongly recommended[27]. A high MELD score, combined with prolonged ischemia time, has also recently been associated with graft dysfunction, a risk factor for post-transplant hyperglycemia.[17]

This retrospective study showed a close relationship between markers of liver damage and new-onset hyperglycemia in the initial phase after LT. High levels of ALT and GGT were correlated with FPG in liver recipients. These markers are used as potential biomarkers for glucose metabolism, reflecting systemic and hepatic insulin resistance, as well as insulin secretion. This finding highlights the central role and predictive value of graft function in glucose homeostasis after LT. Thus, poorer graft quality and compromised initial function can contribute to the occurrence of new-onset hyperglycemia, which in turn can act as a surrogate marker for graft quality or an indication of the poor condition of the recipient.[17]

FINAL CONSIDERATIONS

Strict glycemic control in patients undergoing LT resulted in lower average intraoperative glycemia and significantly better survival for those with glycemia ≤ 120 mg/dL. Patients with PRS had higher insulin requirements and a higher incidence of metabolic complications. Postoperative hyperglycemia was associated with high rates of surgical site infection, rejection, and mortality, especially in patients without diabetes. Effective glycemic management in the perioperative period is crucial to improving clinical outcomes in these patients.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantial scientific and intellectual contributions to the study: Lima MI, Cavalcanti Filho DS, Silva GHG, Silva JH, Ferreira JVL, Freire MIM, Almeida REC, Macedo VPO, Silva HRS, Fonseca Neto OCL. **Conception and design:** Lima MIM, Fonseca Neto OCL. **Data analysis and interpretation:** Cavalcanti Filho DS, Silva GHG, Silva JH, Ferreira JVL, Freire MIM, Almeida REC, Macedo VPO. **Article writing:** Lima MI, Cavalcanti Filho DS, Silva GHG, Silva JH, Ferreira JVL, Freire MIM, Almeida REC, Macedo VPO. **Critical review:** Lima MI, Fonseca Neto OCL. **Final approval:** Fonseca Neto OCL.

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DATA AVAILABILITY STATEMENT

All data sets were generated or analyzed in the current study.

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