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ORIGINAL ARTICLE

Complications associated with hyperglycemia in liver transplant patients[☆]



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KEYWORDS

Liver transplant;
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Abstract

Background: Hyperglycemia is a frequent phenomenon in hospitalized patients that is associated with negative outcomes. It is common in liver transplant patients as a result of stress and is related to immunosuppressant drugs. Although studies are few, a history of diabetes and the presentation of hyperglycemia during liver transplantation have been associated with a higher risk for rejection.

Aims: To analyze whether hyperglycemia during the first 48 hours after liver transplantation was associated with a higher risk for infection, rejection, or longer hospital stay.

Methods: A retrospective cohort study was conducted on patients above the age of 15 years that received a liver transplant. Hyperglycemia was defined as a value above 140 mg/dl and it was measured in three different manners (as an isolated value, as a mean value, and as a weighted value over time). The relation of hyperglycemia to a risk for acute rejection, infection, or longer hospital stay was evaluated.

Results: Some form of hyperglycemia was present in 94% of the patients during the first 48 post-transplantation hours, regardless of its definition. There was no increased risk for rejection (OR: 1.49; 95% CI: 0.55-4.05), infection (OR: 0.62; 95% CI: 0.16-2.25), or longer hospital stay between the patients that presented with hyperglycemia and those that did not.

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Conclusions: Hyperglycemia during the first 48 hours after transplantation appeared to be an expected phenomenon in the majority of patients and was not associated with a greater risk for rejection or infection and it had no impact on the duration of hospital stay.

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PALABRAS CLAVE

Trasplante hepático;
Rechazo del injerto;
Hiperglucemia

Complicaciones asociadas a la hiperglucemia en pacientes trasplantados de hígado

Resumen

Antecedentes: La hiperglucemia es un fenómeno frecuente en los pacientes hospitalizados asociado a desenlaces negativos, y es frecuente en los pacientes trasplantados de hígado como un fenómeno de estrés y asociada a medicamentos inmunosupresores. Aunque los estudios son escasos, el antecedente de diabetes, así como la hiperglucemia durante el trasplante hepático, se han asociado con mayor riesgo de rechazo.

Objetivo: Estudiar si la hiperglucemia durante las primeras 48 h después de un trasplante hepático se asocia a un mayor riesgo de infección, rechazo o estancia hospitalaria.

Métodos: Estudio de cohorte de tipo retrospectivo en pacientes mayores de 15 años que recibieron un trasplante hepático. Se definió la hiperglucemia como un valor superior a 140 mg/dl y se midió de 3 maneras diferentes (como un valor aislado, como la media de los valores y como un valor ponderado en el tiempo) y se analizó su relación con el riesgo de rechazo agudo, infección y tiempo de estancia hospitalaria.

Resultados: Un 94% de los pacientes presentó alguna forma de hiperglucemia durante las primeras 48 h postrasplante independientemente de cómo esta fue definida, y no hubo un mayor riesgo de rechazo (OR: 1.49; IC 95%: 0.55-4.05), infección (OR: 0.62; IC 95%: 0.16-2.25) o tiempo de estancia hospitalaria entre los pacientes que la presentaron y los que no.

Conclusión: La hiperglucemia durante las primeras 48 h después de un trasplante pareciera ser un fenómeno esperable en la mayoría de pacientes y no se asocia a un mayor riesgo de rechazo, infección y no impacta en el tiempo de estancia hospitalaria.

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Introduction

Hyperglycemia is defined as any glucose value > 140 mg/dl.¹ It occurs in 32 to 38% of all hospitalized patients, 41% of all the critically ill, 44% of patients with heart failure, and up to 80% of patients after cardiac surgery; between 30 and 80% of those individuals have no history of diabetes.² Stress hyperglycemia is that which presents in patients with no history of diabetes and is usually transitory. It is caused by counterregulatory hormones (such as cortisol and adrenaline) and by the increase in insulin resistance,^{3,4} but the most important factor appears to be hepatic gluconeogenesis.⁵ Hyperglycemia in the hospitalized patient, especially those that have undergone transplantation, can also be the consequence of the use of different types of medication, such as glucocorticoids and other immunosuppressant drugs.^{6,7}

The long-term deleterious effects of hyperglycemia are well-known, especially those related to micro and macrovascular damage.^{8,9} In the context of the acute patient, hyperglycemia produces changes in the immune system¹⁰ and coagulation.¹¹ In addition, fluctuations in glucose levels induce apoptosis in the endothelial cells, causing endothelial dysfunction.¹²

In the patient with no history of diabetes, hyperglycemia is a mortality marker, especially in those patients in intensive care units (ICUs). It is also associated with longer periods of hospital stay and a greater risk for postoperative infection.¹³⁻¹⁵ Hyperglycemia has additionally been associated with adverse events in patients with acute myocardial infarction¹⁶⁻¹⁹ and with cerebrovascular disease (CVD).^{20,21}

On the other hand, diabetes is a frequent comorbidity in patients on the liver transplantation waiting list, presenting in 65% of them.²² Despite this fact, there is scant evidence that hyperglycemia is a risk factor for negative outcomes in patients that have undergone transplantations, even though, in general, diabetes is associated with a worse outcome in liver transplantation patients. The prevalence of post-transplantation diabetes is as high as 31-38%,²³ and these patients are at a higher risk for cardiovascular complications, such as high blood pressure and coronary disease, as well as a higher mortality rate, compared with those patients that do not develop diabetes.^{24,25} Likewise, patients that develop post-transplantation diabetes have a higher number of acute rejection episodes, and infectious and neurologic complications.²⁶⁻²⁸

Different mechanisms have been proposed by which hyperglycemia could produce graft damage and increase

the risk for rejection. Hyperglycemia increases the co-stimulation and presentation of antigens, and increases ischemic damage²⁹ and the inflammatory reaction associated with reperfusion;³⁰ it increases cytokine production and adhesion molecule expression, as well as dendritic cell activation.^{31,32}

Some observational studies have evaluated the impact of diabetes on patient survival and the risk for complications in the immediate post-transplantation period,^{26,33} whereas others have reported an association between hyperglycemia during the intraoperative period and the risk for postoperative infection and mortality at the first year follow-up.^{34,35} However, none of the studies took metabolic control into account during the immediate post-transplantation period; that has only been evaluated in patients that underwent bone marrow or kidney transplantation.^{36–39}

Based on the above, we decided to conduct an observational study to determine whether there was an association between the increased glucose values during the first 48 h after liver transplantation and the risk for early rejection, bacterial infection, or longer hospital stay. Our hypothesis was that the presence of sustained hyperglycemia during that period of time was associated with a greater risk for early rejection, a higher risk for nosocomial infection, and longer hospital stay.

Methods

Study design and population

A retrospective cohort study was designed analyzing all the records of the patients that underwent liver transplantation within the time frame of 2006 and 2011 at the *Hospital Pablo Tobón Uribe*, a highly specialized university hospital and transplantation center in the city of Medellín, Colombia. We included patients above the age of 15 years that had at least one glucose measurement within the first 48 h after transplantation and excluded all the patients that died as a consequence of surgical complications within the first 24 h, posttransplantation.

Measurements

All the glucose measurements recorded within the first 48 h after transplantation from the time of the patient's admittance into the ICU were documented. Three different measurements were used for determining hyperglycemia: a) at least one value > 140 mg/dl, b) the mean or median of all measurements > 140 mg/dl, and c) the time-weighted (equivalent of an area under the curve of all the measurements) glucose value > 140 mg/dl. A linear relation between the measurement values was assumed for the latter, with intervals of 2 hours or more, and the result was the percentage of time during the first 48 h posttransplantation in which the patient had glucose values > 140 mg/dl.⁴⁰ The patients were differentiated according to a history of diabetes mellitus. Infection was established as confirmed or probable within the first 30 posttransplantation days in accordance with the Center for Diseases Control (CDC) definitions⁴¹ and with the medical history records. Early acute cellular rejection of the liver allograft was defined by the medical team

in charge of the treatment of those patients in whom biochemical abnormalities accompanied by histologic rejection changes were detected in the first 90 days after transplantation. Nosocomial mortality was defined as the death of a patient during hospitalization that was not related to complications inherent in the surgical procedure.

Among the confounding variables of risk for graft rejection were the prior sensitization according to the presence of preformed antibodies directed at the anti-HLA major histocompatibility complex (MHC) recorded in the medical history, the commencement of treatment with calcineurin inhibitors 72 h after liver transplantation, and the condition that led the patient to require a transplant; alcoholic, cryptogenic, viral, or autoimmune cirrhosis, or other causes. The confounding variables regarded as risk for infection were the use of parenteral nutrition, ICU stay, the need for transfusion after transplantation,⁴² age, and female sex.⁴³

Analysis plan

The continuous variables were presented as medians with interquartile ranges or as means with standard deviation. The nominal variables were presented as proportions with confidence intervals. The association between the dichotomous variables was explored through the chi-square test or the Fisher exact test in accordance with the expected value of the cells, and the association magnitude was established through an indirect relative risk (odds ratio) obtained by means of the Woolf approximation with a 95% confidence interval. The association between the continuous variables was explored using the Student's t test, assuming unequal variances.

Results

The data of 316 patients that underwent liver transplantation were collected; 152 patients were excluded from the analysis due to a lack of glucose results at 48 h after transplantation ($n = 142$) and to death during the procedure or in the immediate postoperative period ($n = 10$). The proportion of rejections in the excluded patients was 10.5% ($n = 16$). Of the 164 patients analyzed, 108 (66%) were men and the mean age was 51 ± 12.3 years. [Table 1](#) shows the general population information.

According to the established definitions, 94% of the patients analyzed presented with at least one form of hyperglycemia: a minimum of one value above 140 mg/dl in 154 patients and the mean of all the measurements > 140 mg/dl in 140 patients. The mean glucose level at the time of ICU admission was 182 ± 55 mg/dl and the patients analyzed had glucose levels above 140 mg/dl for an average 30% of the first 48 h. In the bivariate analysis, hyperglycemia was not associated with a greater risk for rejection, infection, or longer hospital stay, regardless of its definition ([table 2](#)). The results did not vary in the analysis of those patients with no history of diabetes or those that had more than one glucose measurement in the first 48 h ([tables 3 and 4](#)). None of the factors regarded as potential confounding variables (late commencement of calcineurin inhibitors, HLA histocompatibility, the reason for transplantation, sex, age, the need for transfusion, the use of total

Table 1 General population characteristics.

Variable	n = 164
Age (range)	51 ± 12.3 (15-70)
Sex, n (%)	
Men	108 (65.8%)
<i>Diabetes mellitus</i>	
History of diabetes mellitus, n (%)	48 (28%)
Development of posttransplantation diabetes, n (%)	35 (30%)
Hospital stay in days (range)	20 ± 19.9 (4-139)
ICU stay in days (range)	5.5 ± 9.1 (1-100)
TPN use (percentage), n (%)	13 (8%)
Red blood cell transfusion (percentage), n (%)	120 (74%)
Late calcineurin inhibitor commencement, n (%)	12 (7.3%)
Cause of transplantation, n (%)	
Alcoholic cirrhosis	33 (20%)
Cryptogenic cirrhosis	23 (14%)
Viral hepatitis (B and C viruses)	33 (20%)
Autoimmune hepatitis	33 (20%)
Others	42 (25.6%)
MELD (range)	18.6 ± 5.5 (8-39)
Immunosuppression	
Steroids	164 (100%)
Azathioprine	152 (92.6%)
Ciclosporin	158 (96.3%)
Early acute cellular rejection, n (%)	33 (20%)
Infection, n (%)	12 (7.3%)
Urinary infection	4
Pneumonia	4
Abdominal infection	2
Phlebitis	1
Fungemia	1
Death, n (%)	26 (16%)

ICU: intensive care unit; MELD: model for end-stage liver disease; TPN: total parenteral nutrition.

parenteral nutrition [TPN], or length of stay in the ICU) were associated with the risk for rejection or infection (data not shown).

No greater risk for infection (OR 2.3; 95% CI = 0.48-10.9) or difference in the length of hospital stay (20.7 days vs 19 days) was found in the diabetic patients when compared with the non-diabetic ones. The proportion of diabetic patients on the transplantation waiting list was high (28%), and the quantity of patients that developed diabetes after transplantation was considerable (30%).

Discussion

In our study, we attempted to clarify whether hyperglycemia, defined either as an isolated, mean, or time-weighted value, was associated with a greater risk for rejection, infection, or longer hospital stay. Our results showed that a large proportion of patients that underwent liver transplantation presented with some degree of hyperglycemia during the first 48 h after transplantation and that an important number of those patients had elevated glucose values for the majority of that period. However, those high glucose values, whether isolated, mean, or weighted, were not associated with a higher risk for infection, rejection, or longer hospital stay. In addition, when a history of diabetes was taken into consideration, no greater risk for infection during the postoperative period was found.

According to previous studies on animal models and some clinical observations, hyperglycemia is associated with immune and non-immune alterations that could increase the risk for rejection or infection in transplantation patients. These include a greater inflammatory response associated with reperfusion-related ischemia, which appears to be mediated by an exaggerated adhesion of leukocytes to the endothelium.^{30,44} Furthermore, hyperglycemia in the postoperative period reflects an insulin-resistant state, which is associated with higher alpha tumor necrosis factor and interleukin 1, 6, and 12 values; all of this favors a state of systemic inflammation that could increase the immunologic response against the graft.⁴⁵ Finally, the elevated glucose levels increase the expression of the major histocompatibility complex class I and class II molecules, with the subsequent potential increase of the innate immune response activation mechanisms.⁴⁶ From the clinical viewpoint, in an analysis carried out on 184 patients that evaluated intraoperative glucose levels,³⁴ the authors reported that values above 150 mg/dl were associated with a greater risk for infection at 30 days following surgery, as well as with a higher mortality rate at one year.

Multiple studies have also been conducted evaluating the impact that hyperglycemia has on hospitalized patients. In a published study by Umpierrez et al.¹³ in which hyperglycemia was defined according to its isolated values, it was associated with longer hospital stay. In another study¹⁴ that also considered the isolated values in the immediate postoperative period, hyperglycemia was associated with a 5-fold greater risk for presenting with nosocomial infections. When the outcomes of critically ill hospitalized patients have been evaluated, taking into account the length of time glucose levels remained high, it was found that there could be a benefit in relation to mortality if the values stayed within a 144-200 mg/dl range.⁴⁰ The proportion of diabetic patients on the transplantation waiting list was high in our study, a result that has also been described in other case series.²² Our results showed that a considerable number of nondiabetic patients developed diabetes mellitus after transplantation, which was also similar to data described in other studies.²³

The majority of studies that have evaluated glycemia in hospitalized patients usually define it as one or several values that are altered at one period of time. However, it is important to consider not only isolated or mean values, but also the length of time during which the patient

Table 2 Association between acute rejection, nosocomial infection, or length of hospital stay and the different definitions of hyperglycemia (n = 164).

Variable	Definition 1	Definition 2
Rejection	OR 0.56 (95% CI 0.14-2.11)	OR 0.55 (95% CI 0.21-1.43)
Infection	OR 0.71 (95% CI 0.10-4.99)	OR 0.85 (95% CI 0.20-3.67)
Mean hospital stay ^a	3.56 (95% CI -7.77-14.90)	3.90 (95% CI -4.16-11.96)
		Definition 3
Rejection		8.05 (95% CI -0.31-16.42)
Infection		6.57 (95% CI -13.30-26.46)
Mean hospital stay ^a		-4.42 (95% CI -1.71-2.32)

Hyperglycemia definitions: 1) at least one value > 140 mg/dl, 2) mean of all the measurements > 140 mg/dl, and 3) time-weighted value.
^a Expressed as difference of means.

Table 3 Association between acute rejection, nosocomial infection, or length of hospital stay and the different definitions of hyperglycemia in non-diabetic patients (n = 116).

Variable	Definition 1	Definition 2
Rejection	OR 0.70 (95% CI 0.12-3.86)	OR 0.56 (95% CI 0.19-1.66)
Infection	OR 0.54 (95% CI 0.05-4.9)	OR 0.76 (95% CI 0.14-3.9)
Mean hospital stay ^a	4.80 (95% CI -12.4-21.9)	5.12 (95% CI -5.1-15.3)
		Definition 3
Rejection		6.27 (95% CI -1.6-14.16)
Infection		16.6 (95% CI 10.95-22.2)
Mean hospital stay ^a		-6.4 (95% CI -16.0-3.4)

Hyperglycemia definitions: 1) at least one value > 140 mg/dl, 2) mean of all the measurements > 140 mg/dl, and 3) time-weighted value
^a Expressed as difference of means.

presents with the elevated glucose levels; such differences in the type of measurement could partially explain the contradictory results of studies that have included glycemic control.^{40,47-51}

One of the important limitations of our study was the high number of patients that were excluded for not having an adequate register of glucose measurement during the first 48 h after transplantation and the subsequent reduction in the sample size necessary for detecting differences. Nevertheless, all the hyperglycemia measurements appeared

to favor it as a «protective factor» in relation to adverse events and the proportion of rejections was even lower in the patients not included in the analysis (10% vs 20%). An important strength of our study was the detailed exploration of the exposure variable, with the different manners in which hyperglycemia was defined; not only did we look for an association with isolated values, but we also took into account the length of time the glucose values remained high.

Despite the limitations that correspond to an observational study in terms of residual confounding and population

Table 4 Association between acute rejection, nosocomial infection, or length of hospital stay and the different definitions of hyperglycemia in those patients with more than one glucose measurement in the first 48 hours (n = 153).

Variable	Definition 1	Definition 2
Rejection	OR 0.31 (95% CI 0.06-1.49)	OR 0.44 (95% CI 0.16-1.21)
Infection	OR 0.48 (95% CI 0.05-4.43)	OR 0.77 (95% CI 0.15-3.83)
Mean hospital stay ^a	5.1 (95% CI -12.2-22.5)	4.5 (95% CI -4.5-13.7)
		Definition 3
Rejection		8.9 (95% CI 0.26-17.5)
Infection		8.6 (95% CI -11.2-28.5)
Mean hospital stay ^a		-4.9 (95% CI -11.7-1.79)

Hyperglycemia definitions 1) at least one value > 140 mg/dl, 2) mean of all the measurements > 140 mg/dl and 3) time-weighted value
^a Expressed as difference of means.

type, this analysis showed that hyperglycemia is most likely a frequent phenomenon in the immediate postoperative period of patients that undergo liver transplantation, and that complications like those of rejection and infection essentially depend on other factors, such as the use of immunosuppressant drugs, histocompatibility, and age, among others. A clinical trial could confirm whether carrying out some form of metabolic control in liver transplantation patients would provide any benefit in relation to rejection or infection. However, in patients that underwent kidney transplantation and had strict glycemic control, the risks appear to be greater than the benefits,³⁹ and in critically ill patients in the ICU, kidney transplantation appears to bring about a high risk for hypoglycemia and a higher mortality rate.⁵¹ Previous findings and the results of our study suggest that glycemic control contributes very little in relation to complications in liver transplantation patients.

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Conflict of interest

The authors declare that there is no conflict of interest.

Annex 1. Immunosuppression regimen used at the institution

a) Corticosteroids

Methylprednisolone 500 mg i.v. in the anhepatic stage, and continued in the postoperative period as follows:

- Day 1: methylprednisolone 200 mg, i.v., at 4 doses of 50 mg/6 h.
- Day 2: methylprednisolone 160 mg, i.v., at 4 doses of 40 mg/6 h.
- Day 3: methylprednisolone 120 mg, i.v., at 4 doses of 30 mg/6 h.
- Day 4: methylprednisolone 80 mg, i.v., at 2 doses of 40 mg/12 h.
- Day 5: methylprednisolone 40 mg, i.v., at one dose.
- Starting at day 6: oral prednisone at a dose of 20 mg/day in the mornings.

b) Azathioprine

1-2 mg/kg from the immediate posttransplantation period through a nasogastric tube and then orally. In the case of renal dysfunction or any other contraindication for the use of a calcineurin inhibitor, mycophenolate 1.5 g v.o. every 12 h is indicated.

c) Calcineurin inhibitors

Ciclosporin or tacrolimus: they are begun once the patient is hemodynamically stable with good diuresis and no renal dysfunction.

The medication of choice is ciclosporin v.o. or via gastric tube at increasing doses until reaching therapeutic levels (see below) or presenting with side effects.

d) Induction therapy

Only basiliximab or daclizumab are used in patients with preoperative renal dysfunction or in patients that undergo liver or kidney transplantation. Two doses are placed, one in the first 6 h posttransplantation, and the other on post-transplantation day 3.

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