Complications associated with hyperglycemia in liver transplant patients

Carlos Esteban Builes Montaño\textsuperscript{a,\ast}, Julián Felipe Montoya\textsuperscript{b}, Carolina Aguilar Londoño\textsuperscript{b}, Karen Lorena Palacios Bayona\textsuperscript{b}, Juan Carlos Restrepo Gutiérrez\textsuperscript{c}, Johnayro Gutiérrez Restrepo\textsuperscript{a}, Clara María Arango Toro\textsuperscript{a}, Fabián Alberto Jaimes Barragan\textsuperscript{c}

\textsuperscript{a} Hospital Pablo Tobón Uribe, Medellín, Colombia
\textsuperscript{b} Universidad de Antioquia, Medellín, Colombia
\textsuperscript{c} Hospital Pablo Tobón Uribe, Universidad de Antioquia, Medellín, Colombia

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\textbf{KEYWORDS}
Liver transplant; Graft rejection; Hyperglycemia

\textbf{Abstract}
\textbf{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.

\textbf{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.

\textbf{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.

\textbf{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.


\textasteriskcentered * Corresponding author: Hospital Pablo Tobón Uribe, Calle 78B # 69 – 240, Medellín, Colombia. Phone: +57 4 4459100.
\textit{E-mail address:} cbuiles@hptu.org.co (C.E. Builes Montaño).

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Introduction

Hyperglycemia is defined as any glucose value > 140 mg/dl. 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. 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, but the most important factor appears to be hepatic gluconeogenesis.

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.

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

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. Hyperglycemia has additionally been associated with adverse events in patients with acute myocardial infarction and with cerebrovascular disease (CVD).

On the other hand, diabetes is a frequent comorbidity in patients on the liver transplantation waiting list, presenting in 65% of them. 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%, 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. Likewise, patients that develop post-transplantation diabetes have a higher number of acute rejection episodes, and infectious and neurologic complications.

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 damage \(^ {29} \) and the inflammatory reaction associ-
ated 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, \(^ {36-39} \) whereas
others have reported an association between hyperglycemia
during the intraoperative period and the risk for postopera-
tive 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 observa-
tional 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 Medellin, Colom-
bia. 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 measure-
ments) 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 percent-
age 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 mel-
itus. Infection was established as confirmed or probable
within the first 30 posttransplantation days in accordance
with the Center for Diseases Control (CDC) definitions \(^ {41} \)
and with the medical history records. Early acute cellular re-
jection of the liver allograft was defined by the medical team
in charge of the treatment of those patients in whom bio-
chemical abnormalities accompanied by histologic rejection
changes were detected in the first 90 days after transplan-
tation. 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 rejec-
tion 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, cryp-
togenic, 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 dichoto-
mous 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 transplanta-
tion were collected; 152 patients were excluded from the
analysis due to a lack of glucose results at 48 h after trans-
plantation (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 hyper-
glycemia: 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, hyper-
glycemia was not associated with a greater risk for rejection,
infection, or longer hospital stay, regardless of its defini-
tion (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 transplan-
tation, sex, age, the need for transfusion, the use of total
Furthermore, hyperglycemia in the postoperative period reflects an insulin-resistant state, which was also similar to data described in other studies. 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. 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. 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. From the clinical viewpoint, in an analysis carried out on 184 patients that evaluated intraoperative glucose levels, 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., in which hyperglycemia was defined according to its isolated values, it was associated with longer hospital stay. In another study 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. The proportion of diabetic patients on the transplantation waiting list was high in 2004, and the quantity of patients that developed diabetes after transplantation was considerable.

### 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. 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. 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. From the clinical viewpoint, in an analysis carried out on 184 patients that evaluated intraoperative glucose levels, 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.

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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 1 General population characteristics.

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

ICU: intensive care unit; MELD: model for end-stage liver disease; TPN: total parenteral nutrition.
Table 2  Association between acute rejection, nosocomial infection, or length of hospital stay and the different definitions of hyperglycemia (n = 164).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition 1</th>
<th>Definition 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>OR 0.56 (95% CI 0.14-2.11)</td>
<td>OR 0.55 (95% CI 0.21-1.43)</td>
</tr>
<tr>
<td>Infection</td>
<td>OR 0.71 (95% CI 0.10-4.99)</td>
<td>OR 0.85 (95% CI 0.20-3.67)</td>
</tr>
<tr>
<td>Mean hospital stay</td>
<td>3.56 (95% CI -7.77-14.90)</td>
<td>3.90 (95% CI -4.16-11.96)</td>
</tr>
</tbody>
</table>

Definition 3

| Rejection         | 8.05 (95% CI -0.31-16.42)  |
| Infection         | 6.57 (95% CI -13.30-26.46) |
| Mean hospital stay | -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.

*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).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition 1</th>
<th>Definition 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>OR 0.70 (95% CI 0.12-3.86)</td>
<td>OR 0.56 (95% CI 0.19-1.66)</td>
</tr>
<tr>
<td>Infection</td>
<td>OR 0.54 (95% CI 0.05-4.99)</td>
<td>OR 0.76 (95% CI 0.04-3.9)</td>
</tr>
<tr>
<td>Mean hospital stay</td>
<td>4.80 (95% CI -12.4-21.9)</td>
<td>5.12 (95% CI -5.1-15.3)</td>
</tr>
</tbody>
</table>

Definition 3

| Rejection         | 6.27 (95% CI -1.6-14.16)  |
| Infection         | 16.6 (95% CI 10.95-22.2)  |
| Mean hospital stay | -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

*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).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition 1</th>
<th>Definition 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>OR 0.31 (95% CI 0.06-1.49)</td>
<td>OR 0.44 (95% CI 0.16-1.21)</td>
</tr>
<tr>
<td>Infection</td>
<td>OR 0.48 (95% CI 0.05-4.43)</td>
<td>OR 0.77 (95% CI 0.15-3.83)</td>
</tr>
<tr>
<td>Mean hospital stay</td>
<td>5.1 (95% CI -12.2-22.5)</td>
<td>4.5 (95% CI -4.5-13.7)</td>
</tr>
</tbody>
</table>

Definition 3

| Rejection         | 8.9 (95% CI 0.26-17.5)  |
| Infection         | 8.6 (95% CI -11.2-28.5) |
| Mean hospital stay | -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

*Expressed as difference of means.
type, this analysis showed that hyperglycemia is most likely a frequent phenomenon in the immediate postoperative period of patients who 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, and in critically ill patients in the ICU, kidney transplantation appears to bring about a high risk for hypoglycemia and a higher mortality rate. Previous findings and the results of our study suggest that glycemic control contributes very little in relation to complications in liver transplantation patients.

Financial disclosure

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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 posttransplantation day 3.

References


