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SYMPOSIUM

Glycemic Control and Organ Transplantation

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Abstract

A discussion of hyperglycemia during organ transplantation is a broad topic that includes patients with a known history of diabetes pretransplant, those at risk for post-transplant diabetes, those with stress-induced hyperglycemia, those with hyperglycemia related to immunosuppressive therapy, and hyperglycemia in the deceased organ donor. In contrast to the plethora of articles and studies describing perioperative and critical care management of hyperglycemia in cardiac, trauma, and medical/surgical intensive care unit patients, relatively few published articles in the field of organ transplantation can be found. This article consists of a review of available literature in the form of publications and abstracts, and a preliminary report of the authors' work with liver transplantation and deceased organ donors.

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Introduction

The topic of hyperglycemia and organ transplantation is broad and includes patients with a known history of diabetes pretransplant, those at risk for post-transplant diabetes, those with stress-induced hyperglycemia related to the transplant procedure itself and associated induction immunosuppressive therapy, and finally those with post-transplant or new onset diabetes secondary to chronic immunosuppressive medications. An entirely separate issue is the management of hyperglycemia associated with the deceased organ donor.

In contrast to the plethora of articles and studies describing perioperative and critical care management of hyperglycemia in cardiac, trauma, and medical/surgical intensive care unit patients, relatively few published articles in the field of organ transplantation can be found. While transplant patients may constitute a small population within some of the published studies, focused articles in this specific patient population are difficult to find. Certainly, there are no prospective, randomized trials performed in transplant patients that describe key management issues. Many transplant-related perioperative hyperglycemia publications/presentations are in the form of abstracts/posters presented at meetings of particular societies (e.g., American Transplant Congress, American Diabetes Association, and Society of Critical Care Medicine).

This article consists of a review of available literature in the form of publications and abstracts and a preliminary report of the authors' work with liver transplantation and deceased organ donors. Hyperglycemia in patients with pre-existing diabetes awaiting pancreas transplantation is beyond the scope of this article.

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Abbreviations: (BS) blood sugar, (IL) interleukin, (NODM) new onset diabetes mellitus, (PTDM) post-transplant diabetes mellitus, (UNOS) United Network for Organ Sharing

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It is important to emphasize, before discussing the limited data that is available regarding hyperglycemia and organ transplantation, that correlation between hyperglycemia and poor outcomes does not necessarily mean that there is a cause and effect relationship between them. As the majority of randomized studies (discussed at length in other articles featured in this symposium) have not been able to demonstrate a survival benefit associated with intensive glycemic control of 80–110 mg/dl, the studies discussed here may simply be revealing the causal relationship between severity of illness or stress response and hyperglycemia. The only prospective randomized trial that was able to demonstrate a survival advantage with control between 80–110 mg/dl versus a higher target was the original study of Van den Berghe and colleagues in 2001.[1] All subsequent studies[2–11] have failed to show a benefit, and more importantly, the largest and latest study[3] suggested a decreased survival in the study group that received tight glycemic control.

It is likely that the 80–110 mg/dl target is simply "too tight" and difficult to achieve without unacceptably high rates of dangerous hypoglycemia (<40 mg/dl). In addition, these studies have often mixed, potentially dramatically different patient types (e.g., cardiac surgical, trauma, neurological, or medical) in a single study. It is conceivable that some of these groups might benefit while others might not, thus combining them all in order to achieve sufficient "numbers" for the study may be counter-productive. Focused studies in specific groups of patients targeting a more reasonable glucose level (e.g., 100–140 mg/dl) may reveal the benefits of intensive glycemic control without the risks of severe hypoglycemia.

Perioperative Hyperglycemia and Its Relation to Post-Transplant Rejection

No prospective studies have been performed that address the relationship between hyperglycemia and transplant outcomes. There are, however, a few retrospective reports since 2000 comprised of relatively small numbers of patients. Unfortunately, these articles have yielded conflicting results. An abstract from 2000 by Thomas and associates from Australia reported a correlation between hyperglycemia in diabetic patients and renal transplant rejection.[12] A follow-up study of 230 nondiabetic patients undergoing first renal transplantation from deceased donors[13] revealed that 73% of patients experienced a blood sugar (BS) >8.0 mmol/liter (168 mg/dl) and 31% >11.2 mmol/liter (246 mg/dl) immediately after surgery, and 51% of patients had BS >8.0 mmol/liter (168 mg/dl) both immediately after surgery and on the following morning. All patients received 1 g of intravenous methylprednisolone intraoperatively and 500 mg the following morning. Only those with a high panel reactive antibody received additional steroid administration after day 1. Some 42% of patients with BS <168 mg/dl developed rejection compared to 71% with BS >168 mg/dl. Glucose levels immediately following transplantation were independently associated with acute rejection (odds ratio = 1.015, 95% confidence interval 1.008 to 1.022, $p < .001$).

A small study (100 nondiabetic patients) in 2007 again demonstrated the relationship between hyperglycemia and kidney allograft rejection.[14] The investigators reported that mean BS immediately after surgery was 250 mg/dl in patients who developed acute rejection and 185 mg/dl in those who did not. In contrast, a report from the Netherlands[15] failed to demonstrate any relationship between hyperglycemia within the first 48 h and rejection. The immunosuppressive protocols in this last study were very different from the earlier studies in that in the latter study, relatively small doses of steroids were administered (100 mg/day of methylprednisolone for 2 days), a CD25 antibody was given for induction, and the rejection rates were much lower (30% versus >60%). In addition, the authors concede that their institution was more "aware" of the benefits of tight glycemic control, and it was possible that both groups may have received more insulin therapy, which may have influenced the results.

There are many explanations as to why hyperglycemia may lead to organ allograft damage. Hyperglycemia augments antigen presentation and costimulation,[16,17] increases ischemic damage and the inflammatory response from ischemia/reperfusion,[13] activates dendritic cells,[18] and increases the expression of adhesion molecules and the production of cytokines.[19,20] Together, all of these factors may lead to an increased incidence of rejection.

Intensive Glycemic Control in Organ Transplant Recipients: Abstracts Presented at the American/World Transplant Congresses

There is a paucity of data available regarding the benefits of intensive glycemic control in organ transplant recipients. Lead author Dr. Marvin presented data on the effective implementation of tight glycemic control in 32 liver transplant recipients utilizing an automated computerized insulin dosing calculator[21] based on a published protocol developed at Yale University to target BS levels between 100 and 139 mg/dl[22] The mean glucose level achieved in the first 48 h after liver transplantation was 139 mg/dl

with no significant hypoglycemia (defined as less than 70 mg/dl). In this study, point-of-care glucose meters were utilized to determine glucose levels. The study was designed to compare an intensively controlled group with a retrospective comparison group with higher glucose targets and was, therefore, not designed to evaluate for outcome differences between the groups. It did demonstrate, however, that intensive glycemic control is achievable with an effective protocol, despite the hemodynamic milieu of perioperative liver transplantation.

Hsaiky and coworkers presented their experience with intensive glycemic control in 100 liver transplant patients,[23,24] where they retrospectively compared the results of a sliding scale regimen with a target of <180 mg/dl to an intensive group targeting 80–110 mg/dl. Despite being able to reach the target in only 24% of the intensively controlled patients, they were able to statistically demonstrate a 15% reduction in infection ($p = .01$), a 9% absolute reduction in rejection rates (14% versus 25%, $p = .02$), and lower blood transfusion requirements (5.0 versus 2.0, $p < .05$). Mortality during hospital stay was reduced from 4% in the conventional group to 2% in the intensively treated group ($p = .56$). These results, however, must be viewed with caution given the small numbers of patients (50/group) and the nature of the publication (abstract). No complete manuscript from this group has been published to date.

Full Manuscripts

Ammori and colleagues reported a statistically significant association between glucose levels >150 mg/dl intraoperatively during liver transplantation and increased infection rates at 30 days (48% versus 30%, $p = .02$) and 1 year mortality (21.9% versus 8.8%, $p = .05$) when compared to intensive control of <150 mg/dl.[25] These results were obtained despite a significantly larger dose of insulin administered to the poorly controlled group (24 ± 2 versus 13 ± 3 U, $p < .01$). In addition, no significant differences, other than a mean age of 47 versus 53 in the intensively versus poorly controlled group, respectively, could explain the mortality difference between the groups.

In April 2009, Park and associates reported that, in 680 patients undergoing liver transplantation, severe intraoperative hyperglycemia was associated, upon multivariate analysis, with a 2.25 odds ratio of postoperative infection ($p = .006$) when compared to a normoglycemic group.[26] In this study, the authors divided patients into 3 groups based on mean levels of hyperglycemia: mild (150–180 mg/dl), moderate (180–200 mg/dl), and severe (>200 mg/dl). Only the group experiencing severe hyperglycemia was found to have a significantly increased incidence of surgical site infection.

The mechanism whereby hyperglycemia results in increased infection rates may be related to its ability to impair neutrophil and macrophage function, impair phagocytic activity and bacteriocidal capabilities, and inhibit the formation of healthy collagen.[25,27–32] In addition, glucose transporter-2-mediated glucose uptake in the liver is independent of insulin and proportional to the amount of glucose in the blood. This may lead to toxic levels of glucose within hepatocytes.[25,33]

Unfortunately, after an exhaustive search of literature, we were unable to find studies that address these issues in other solid organ transplants.

Hyperglycemia-Inducing Medications Utilized for Induction and Maintenance Immunosuppression: New-Onset (or Drug-Induced) Diabetes Mellitus

Post-transplant diabetes mellitus (PTDM) or new-onset diabetes mellitus (NODM) is a multifactorial disease caused by a combination of decreased insulin secretion and increased insulin resistance[34] that occurs in a large number of transplant patients within the first year, depending on the patient population studied: 7%–26% for heart recipients, 24.3% for lung transplantation patients, 15.4% for those undergoing combined heart and lung transplantation, and 0%–32% for liver recipients.[35–38] Even in functioning pancreas allografts, the incidence has been reported to be approximately 20% after 39 months of follow-up.[39] In kidney transplant patients, when using the guidelines established by the American Diabetes Association, Cosio and coworkers found that there was a 13% prevalence of NODM and a 33% incidence of impaired fasting glucose or impaired glucose tolerance by 1 year post-transplant.[40]

It is believed that NODM is not a novel disorder but one that develops in patients with preexisting risk factors for the development of the disease, which is then unmasked by a combination of the transplant procedure and post-transplant immunosuppressive medications.[34] Patients with renal failure have been demonstrated to have impaired glucose tolerance thought to be secondary to circulating "uremic toxins" that create insulin resistance and impair insulin release.[41] In addition, patients with baseline deficits in B-cell function prior

to transplantation are at increased risk of developing NODM after transplantation.[42,43] Most cases of NODM develop within the first 3 months after transplantation.

The most significant factor in the development of NODM is the use of immunosuppressive medications. Immunosuppressive regimens have dramatically changed since 2000. The increased use of induction therapy, including anti-T or B-cell antibody preparations and steroid-free or steroid-avoidance protocols, have reduced the duration and magnitude of steroid administration. In addition, the recognition that the backbone of immunosuppression, calcineurin inhibitors (tacrolimus and cyclosporine), have significant side effects, including diabetes, metabolic syndrome, and renal dysfunction, have led to reduction in overall dosages with reduced complications.

Steroids, however, remain an important part of the armamentarium to prevent and treat rejection in transplant recipients. Most protocols call for administration of the equivalent of 500–1000 mg of methylprednisolone intraoperatively, followed by varying rates of tapering over the subsequent 3 months. These high doses invariably lead to perioperative hyperglycemia, and over the ensuing weeks to months, the incidence of hyperglycemia/diabetes developing ranges from 10%–20%.[44–47] A study of hospitalized patients treated with steroids demonstrated a >50% incidence of hyperglycemia, defined as a blood glucose >200 mg/dl, in patients without a known history of diabetes and an incidence of 64% in the total patient population receiving high-dose steroids.[48]

Steroids cause increased BS predominantly by increasing insulin resistance secondary to increased hepatic gluconeogenesis and decreased glucose uptake and glycogen synthesis in skeletal muscle.[49,50] Midtvedt and colleagues studied the effect of weaning steroids on insulin resistance after renal transplantation utilizing hyperglycemic euglycemic glucose clamp procedures.[51] They found that there was a marked improvement in insulin sensitivity as steroids were weaned down to a dose of 5 mg/day of prednisone. No additional benefit was achieved below the 5 mg daily dose.

Tacrolimus and cyclosporine are calcineurin inhibitors, which provide the anchor for most modern immunosuppression protocols. Both are capable of inducing diabetes through direct B-cell toxicity, diminished insulin synthesis or release, and decreased insulin sensitivity.[41,52,53] However, multiple studies have demonstrated that the incidence of PTDM is higher with tacrolimus when compared to cyclosporine.[54,55] A study by Sato and associates concluded that tacrolimus-associated PTDM is induced by decreased insulin secretion by the pancreas, in contrast to cyclosporine administration, which leads to increased insulin secretion.[41] In addition, the level of pretransplant insulin secretion was a significant predictor for the development of PTDM. Most studies of cyclosporine use fail to clearly demonstrate an independent diabetogenic effect of the drug in the absence of corticosteroid administration.[34] In contrast, reducing the dosage of tacrolimus has been demonstrated to improve or eliminate NODM.[56] A study by Boots and coworkers examined the effects of lowering both steroids and tacrolimus in kidney transplant patients in order to determine the relative roles of each agent in the development of NODM.[35] They found that reducing the steroids improved insulin sensitivity while reducing the tacrolimus improved B-cell function.

Data from multiple trials have demonstrated that those patients who develop NODM after renal transplantation have a reduced graft and patient survival, which is similar to patients with known preexisting diabetes. The poorer results are secondary to a combination of infectious complications and development of accelerated cardiovascular disease.[57–63] It has also been demonstrated that even those patients with impaired fasting glucose or impaired glucose tolerance, in the absence of diagnosed diabetes, have worse outcomes compared to a normoglycemic group.[40,62]

It would be helpful to better understand and predict the increases in glucose levels produced by a given dose of corticosteroids so that preemptive or simultaneous insulin dosing can be performed. Unfortunately, few data exist to guide clinicians as to how to preemptively prevent expected elevations of glucose levels after steroid administration.

Hyperglycemia in Potential Deceased Organ Donors

Deceased organ donors provide the vast majority of solid organs for transplantation within the United States. The "stress" to the cardiovascular system that occurs as a result of brain death is dramatic and leads to marked activation of the sympathomimetic axis with the associated release of epinephrine, corticosteroids, and glucagon,[64–66] as well as cytokines such as interleukin (IL)-6 and IL-8.[67,68] Working together, these agents serve to dramatically increase gluconeogenesis and insulin resistance, impair release of insulin from the pancreas,

and result in marked hyperglycemia.[69] In addition, the diabetes insipidus that occurs as the result of brain swelling results in significant free-water loss and leads to hypernatremia.[66,70–72] Severe hypernatremia has been associated with worse outcomes after liver transplantation.[73–75] Management of hypernatremia requires large boluses of free water, most often in the form of dextrose-containing solutions. Combined with the stress-induced insulin resistance and gluconeogenesis associated with brain death, the administration of high sugar-containing solutions results in marked hyperglycemia.

Aggressive management of hyperglycemia in the organ donor is now part of standard donor management algorithms developed by the United Network for Organ Sharing (UNOS), the private agency contracted to direct the Organ Procurement and Transplantation Network. The goals set forth by UNOS target BS between 120 and 180 mg/dl (UNOS Web site, www.unos.org). No direct evidence exists, however, to suggest that these targets are any better or worse than lower or higher targets.

It has been suggested for years that hyperglycemia is correlated with poor outcomes in terms of infection, sepsis, and death in specific populations (e.g., cardiac and trauma). Until 2009, no studies were published addressing this issue in deceased organ donors. A study by Blasi-Ibanez and colleagues provided the first hint that a correlation exists between hyperglycemia and organ function in deceased organ donors.[76] The researchers retrospectively examined terminal renal function in 458 potential organ donors and correlated the terminal creatinine and calculated glomerular filtration rates with glucose levels. They found that only 28% of donors had prerecovery glucose levels < 200 mg/dl and that 39% had levels >250 mg/dl. Thus hyperglycemia was found to be extremely prevalent in deceased organ donors and was statistically correlated with worse prerecovery renal function. In addition, increased variability of the glucose levels was also correlated with poorer renal function. The authors suggested that better control of glucose in this population might lead to enhanced function of the allograft in the recipient. An accompanying editorial to the manuscript commented, "It is tempting to speculate that even modest decrements in glucose levels might produce better outcomes. This intervention is the type of low-cost/high-benefit one that the proponents of tight glycemic control have hoped for. … Instead of looking at broad application across heterogeneous populations, they have created a model to tease out what matters and how."[77]

After retrospectively determining the correlation between hyperglycemia in organ donors and worse renal function, the authors of the aforementioned study received a grant from the Health Resources Service Administration entitled "Intensive Insulin Therapy in Deceased Donors to Improve Renal Allograft Function and Transplanted Allograft Outcomes." This is a prospective, randomized study that evaluates the effect of intensive insulin therapy on renal function in deceased organ donors. So far, 35 patients have been entered into the study.[78] We await the results of this promising trial.

We are currently implementing tight glycemic control in organ donors throughout the states of Minnesota, South Dakota, and North Dakota through the LifeSource Organ and Tissue Donation organ procurement organization, which coordinates the care of deceased organ donors and facilitates placement of the retrieved organs and tissue. LifeSource recently began utilizing a Food and Drug Administration-approved insulin dosing software system (GlucoCare™ IGC System, Pronia Medical Systems, LLC, Louisville, KY) to target glucose levels in donors between 100 and 140 mg/dl.[11] To date, a total of 23 patients have been enrolled using the system, and 34% of patients were able to reach the target level with the baseline protocol. The remainder of the patients have demonstrated remarkable rates of insulin resistance. Insulin boluses as high as 30–40 U and insulin infusion rates of 40–50 U/h are not uncommon. Usually, this is in response to standard hormonal resuscitation that includes T4, steroids, and D50. Often, once the glucose levels are markedly out of range, it is extremely difficult to effectively reduce the levels to within the target range. We are actively working to modify the baseline protocol in a systematic way to develop a novel organ-donor-specific protocol for the management of hyperglycemia.

Conclusion

Transplant allograft recipients are a unique group of patients with major risk factors for hyperglycemia, which include preoperative risk factors, the degree of surgical stress related to the transplant procedure, and the hyperglycemia-inducing medications required to maintain a healthy graft. Studies that specifically explore the myriad variables inherent in the prevention and management of hyperglycemia in the transplant recipient are needed. In addition, the management of hyperglycemia in the deceased organ donor is a relatively new area of research that warrants further study.

Disclosures:

Michael Marvin is the chief medical officer/cofounder of Pronia Medical Systems, LLC. The company is the developer of the GlucoCare IGC System used for management of continuous insulin infusions in critically ill patients.

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