Reperfusion injury is a biphasic process which causes cell damage in its ischemia and reperfusion phase. While the tissue damage in the ischemia phase is mainly caused by the energy deprivation and the subsequent disruption of the cellular hemostasis, the reperfusion phase damage (more severe damage) is secondary to the inflammatory reactions involving the oxygen free radicals, endothelial cells as well as the leukocytes.[3] This process is an early inflammatory response which follows the perfusion of warm blood into the previously ischemic and cold organ following transplantation. Reperfusion injury has detrimental effects on the tissue hemostasis of the ischemic organs, and may have a pivotal short and long-term impact on the renal allograft function.[14]

As GSPE seems to antagonize a number of steps in the ischemia-reperfusion process, and due to its anti-inflammatory properties, we hypothesize that GPSE could have a potential protective effect on the transplanted kidney when added to the machine Perfusion Fluid and Cold Static Storage System.

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Re: Hyperglycemia After Kidney Transplantation: Frequency and Risk Factors

Dear Editor,

In the past issue of the *Iranian Journal of Kidney Disease*, Khalili and colleagues have reported the association of hyperglycemia posttransplantation with higher doses of cyclosporine, cytomegalovirus infection, higher serum creatinine levels, and dyslipidemia in 22.5% of the Iranian patients.[1] As expected this association was compatible as of other reports. As mentioned in the limitations of the study, a history of pretransplant diabete

mellitus (DM), effect of hyperglycemia and acute rejection, family history, long-term graft survival, cardiovascular disease risk with mortality, and body mass index could not be evaluated in this study.

Definition to classify DM and hyperglycemia that develops after transplantation have been inconsistent and include widely variant definitions ranging from "insulin dependence" and "a fasting blood glucose greater than 160 mg/dL" to the more stringent contemporary criteria set by the American Diabetes Association. Other terms such as transplant-associated hyperglycemia, new onset DM after transplantation could be mentioned. The term new-onset DM is preferred to distinguish the newly acquired condition, which includes new-onset DM, impaired fasting glucose, and impaired glucose tolerance, and prediabetic states that pose a cardiovascular disease threat similar to that seen with overt DM.[2] Posttransplant DM (PTDM) or new-onset DM is a multifactorial disease caused by a combination of decreased insulin secretion and increased insulin resistance that occurs in a large numbers of transplant patients within the first year. Cosio and coworkers found that there was a 13% prevalence of new-onset DM and a 33% incidence of impaired fasting glucose or impaired glucose tolerance by 1 year posttransplant.[3]

The literature is unclear about the effects of new-onset DM on graft failure. A study that analyzed the changing causes of graft loss in the general transplant population over the past 3 decades found that patient death has gradually superseded rejection as the major cause of graft loss.[4] Although new-onset DM clearly contributes to overall graft failure rates as a result of increased mortality, after adjustment for this increase in the risk of death the direct effect of new-onset DM on allograft survival is difficult to ascertain. It is believed that new-onset DM 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. 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. In addition, patients with baseline deficits in B-cell function prior to transplantation are at increased risk of developing new-onset DM after transplantation. Most cases of new-onset DM develop within the first 3 months after transplantation.[5]

Both acute rejection and new-onset DM were associated with similar risk of transplant failure from any cause, but the mechanism of graft loss was different. Acute rejection was associated with death-censored graft loss, and weakly associated with death with a functioning graft. By contrast, new-onset DM was associated with death with a functioning graft but had a borderline association with death-censored graft loss. Patients who developed both acute rejection and new-onset DM had the greatest risk of early transplant failure. New-onset DM might influence the structure and function of the allograft, and result in accelerated deterioration of graft function via a mechanism that is still poorly understood. Alternatively, the association between new-onset DM and death-censored graft loss might be the result of a previous episode of acute rejection; prior episodes of acute rejection are hypothesized to result in augmented immunosuppression, which subsequently leads to new-onset DM and an increased risk of death-censored graft failure.[6] Data on peri-operative hyperglycemia and its relation to posttransplant rejection have conflicting results. There are a few retrospective reports since 2000 including relatively small numbers of patients. Thomas and coworkers reported a correlation between hyperglycemia in diabetic patients and renal transplant rejection.[7] A small study (100 nondiabetic patients) in 2007 again demonstrated the relationship between hyperglycemia and kidney allograft rejection.[8] In contrast, a report from the Netherlands[9] failed to demonstrate any relationship between hyperglycemia within the first 48 hours and rejection. The immunosuppressive protocols in this last study were very different from the earlier studies. There is an association between hyperglycemia and delayed graft function. Both creatinine and neutrophil gelatinase-associated lipocalin, a marker of ischemic injury and kidney function, fall less rapidly in patients with elevated blood glucose.[10] Hyperglycemic patients have an increased risk for delayed graft function and should be treated by more potent immune therapy and strict control of blood glucose in peritransplant period.[11] Immunosuppressive drugs have an important role in pathogenesis of new-onset DM.

Steroid is the most responsible agent to prevent and treat rejection in transplant recipients. Most protocols used equivalent of 500 mg to 1000 mg of methylprednisolone intra-operatively, 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/DM developing ranges from 10% to 20%.[12] A study of hospitalized patients treated with steroids demonstrated a more than 50% incidence of hyperglycemia, defined as a blood glucose greater than 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.[13]

Steroids cause increased blood glucose predominantly by increasing insulin resistance secondary to increased hepatic gluconeogenesis and decreased glucose uptake and glycogen synthesis in skeletal muscle. It is found that there was a marked improvement in insulin sensitivity as steroids were weaned down to a dose of 5 mg/d of prednisone. No additional benefit was achieved below the 5 mg daily dose.[14] Tacrolimus and cyclosporine are calcineurin inhibitors, and included in the most modern immunosuppression protocols. Both are capable of inducing diabetes through direct B-cell toxicity, diminished insulin synthesis or release, and decreased insulin sensitivity.[15] However, multiple studies have demonstrated that the incidence of PTDM is higher with tacrolimus when compared to cyclosporine. Tacrolimus-associated PTDM is induced by decreased insulin secretion by the pancreas, in contrast to cyclosporine administration, which leads to increased insulin secretion.[16] Most studies of cyclosporine use fail to clearly demonstrate an independent diabetogenic effect of the drug in the absence of corticosteroid administration. Data from multiple trials have demonstrated that those patients who develop new-onset DM 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. 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.[17] Cardiovascular disease is the leading cause of death in renal transplant recipients, and accounts for approximately half of all deaths in these patients, as they are burdened with both traditional and transplant-specific risk factors. On univariable analysis, new-onset DM was associated with an increased risk of developing ischemic heart disease, but this link was not independent of other variables, such as serum cholesterol and triglyceride levels, included in the multivariate analysis.[18] Several factors were associated with cardiac events in a multivariate model: a prior cardiovascular event; pretransplant or post-transplant diabetes; a history of tobacco use; obesity at the time of transplant; multiple rejection episodes; and pretransplantation dialysis for more than 1 year. Increasing levels of fasting glucose posttransplantation were associated with a raised incidence of cardiovascular events. This increase in the cardiovascular event rate predominantly resulted from cardiac and peripheral vascular disease rather than cerebrovascular events. The overall incidence of cardiovascular events was significantly higher in patients with either impaired fasting glucose or new-onset DM than in those who were euglycemic.[3]

The link between cytomegalovirus infection and the development of new-onset DM was first reported in 1985 in a renal transplant recipient. Limited studies suggested that both asymptomatic cytomegalovirus infection and cytomegalovirus disease are independent risk factors for the development of new-onset DM.[19] In a study consisting of 160 nondiabetic renal transplant recipients who were prospectively monitored for cytomegalovirus infection during the first three months after transplantation, showed that asymptomatic cytomegalovirus infection was associated with a four-fold increased risk of new-onset diabetes suggesting that impaired pancreatic cell insulin release may be involved in the pathogenic mechanism of cytomegalovirus -associated new-onset DM. It is speculated that cytomegalovirus -induced release of proinflammatory cytokines may lead to apoptosis and functional disturbances of pancreatic cells.[20] The relative risk of new-onset DM associated with a positive hepatitis C virus serology ranges from 1.3 to 1.4 . While no prospective study has evaluated the impact of pretransplant clearance of hepatitis

C virus on the incidence of new-onset DM, two retrospective reports suggest that this strategy could be beneficial.[21,22] For definitive screening of new-onset DM 2-hour plasma glucose after an oral glucose tolerance test 10 weeks after kidney transplantation was associated with increased risk of long-term overall graft loss. There was no significant association between fasting blood glucose and overall graft loss and no associations between any level of hyperglycemia and death-censored graft survival.[23] There is no collecting data on longer follow up of Iranian postransplant recipient with hyperglycemia. Indeed a large multicenter prospective study needed to answer questions about patient and graft survival.

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