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Immunosuppressive Agents: Effects on Glucose and Lipid Metabolism

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Since the first successful kidney transplant in 1959, transplantation medicine has evolved into mainstream medical therapy. Such solid organ transplantation, however, would not have been possible without the development of compounds that can suppress the immune system safely. Agents commonly employed for immunosuppression include glucocorticoids, calcineurin inhibitors, such as cyclosporine and tacrolimus (FK506), and azathioprine. The recent availability of potent immunosuppressive drugs such as mycophenolate mofetil (MMF) and mammalian target of rapamycin (mTOR) inhibitors such as sirolimus (rapamycin) has allowed protocols to be designed to minimize use of calcineurin inhibitors or steroids. Despite their desired action on the immune system, however, immunosuppressive therapies are associated with adverse effects that have deleterious effects on recipient quality of life and survival. Glucocorticoids, cyclosporine, and tacrolimus have been the major offending players affecting glucose homeostasis after solid organ transplantation. Post-transplant diabetes mellitus has been documented in up to 40% of renal and liver transplant recipients [1]. Glucocorticoids, cyclosporine, and sirolimus commonly are associated with hyperlipidemia. Hyperlipidemia is associated not only with an increased risk of cardiovascular disease in renal transplant recipients, but also correlates with allograft survival [2]. Thus, dysregulated glucose and lipid metabolism are well-recognized complications of organ transplantation and immunosuppression. This article focuses on the effects

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of immunosuppressive therapies on glucose and lipid metabolism. Adrenal effects of these drugs, where known, also are discussed.

Drugs used for immunosuppression in solid organ transplantation

Glucocorticoids

Effects of glucocorticoids on glucose metabolism

The first description of hyperglycemia associated with glucocorticoid use has been attributed to Ingle in 1941 [3]. The immunosuppressive benefits of glucocorticoid therapy, however, have continued to support its use in maintenance immunosuppressive medication regimens, despite the increased risk of new-onset diabetes mellitus, hyperlipidemia, and other pleiotropic effects of exogenous glucocorticoid use. A review of over 12,000 Medicare beneficiary records of patients receiving kidney transplants between 1996 and 2000 found that glucocorticoids were used as part of the immune regimen in over 97% of individuals [4]. The incidence of post-transplant diabetes mellitus (PTDM) was 9% at 3 months, 16% at 12 months, and 24% at 36 months after transplant. Contributing factors to the development of PTDM with glucocorticoid use are increasing dose used (irrespective of adjustment for weight), older age [2], positive family history of diabetes mellitus, and ethnicity [4,5]. A protective factor is early steroid withdrawal, but this does not affect all ethnicities equally [6].

The mechanisms through which glucocorticoids can induce hyperglycemia are many. Glucocorticoids promote hepatic gluconeogenesis, degradation of proteins to free amino acids in muscle, and lipolysis [7]. In addition, they decrease peripheral insulin sensitivity and inhibit pancreatic insulin production and secretion [8,9]. Glucocorticoids decrease insulin-mediated glucose uptake by mechanisms that are not understood clearly. Although glucocorticoids are the most common cause of drug-induced diabetes mellitus [10], patients who have decreased insulin secretory reserve are much more likely to develop diabetes [11]. Less consistent associations for risk for development of PTDM are human leukocyte antigen types A30, B27, and Bw42, and transplantation using deceased donor kidneys [12].

Effects of glucocorticoids on lipid metabolism

Hyperlipidemia incidence is variable postsolid organ transplant, with overall rates for kidney transplant reported between 16% and 60%, postcardiac transplant between 60% and 80%, and postliver transplant 45%, in settings of immunosuppressive regimens that included glucocorticoid use [13]. Several studies have shown in renal transplant patients that immunosuppressive regimens excluding prednisone, using alternate day, or using lower doses of prednisone are associated with lower cholesterol levels [14–16]. In liver transplant recipients, higher glucocorticoid dose has been associated with

hyperlipidemia [17], while in heart transplant recipients, those able to discontinue glucocorticoid from their immunosuppressive regimen had up to 26% lower fasting cholesterol levels than those continuing on glucocorticoid [18].

Glucocorticoids can alter activity of several key enzymes. These include increased activity of acyl coenzyme A carboxylase, fatty acid synthase and HMG CoA reductase, and decreased activity of lipoprotein lipase (LPL). Increased hepatic very low density lipoprotein (VLDL) synthesis and down-regulation of low density lipoprotein (LDL) receptor activity result in increased VLDL, cholesterol, and triglyceride levels and decreased high density lipoprotein (HDL) levels [13,19]. These effects can contribute to risk of cardiovascular disease in post-transplant recipients, and regimens minimizing glucocorticoid dose have engendered increased interest. In a randomized, double-blind study of renal transplant recipients, the effects and feasibility of lower, tapering doses versus regular continued doses of prednisone were studied [20]. All transplant recipients received MMF and cyclosporine also. At baseline, the control group, who were treated with higher prednisone doses ranging from 15 mg to 30 mg daily, had lower cholesterol levels than the intervention group, who received the lower prednisone dosing. At 6 months and 12 months, however, cholesterol and triglyceride levels were significantly higher in the control group, who received higher doses of prednisone, compared to the intervention group, who received low-dose prednisone. Unfortunately, the organ rejection rate for the lower or no prednisone group was 23%, compared with 14% for the control group, suggesting a higher rejection rate, and supported by other steroid withdrawal trials in renal transplantation [21].

Adrenal effects of glucocorticoids

Suppression of the pituitary–adrenal axis occurs rapidly with exogenous glucocorticoid therapy. Fifty milligrams of prednisone daily for 5 days has been associated with decreased responsiveness to insulin-induced hypoglycemia and corticotropin (ACTH) stimulation [22]. Shorter-acting steroids such as prednisone, cortisol, or prednisolone suppress the pituitary axis less than dexamethasone [23], although all have been used either in immunosuppressive maintenance or rescue protocols. Protocols for steroid taper typically should entail small, graduated dose decreases over increments of 1 to 2 weeks for those on long-term glucocorticoid therapy, primarily to prevent precipitating an exacerbation of the immune responses being treated by the glucocorticoid. If steroid withdrawal is considered, assessment of adrenal reserve should be considered when a dose of 5 mg of prednisone or its equivalent is reached. Sequential (monthly) basal morning cortisols have been reported as helpful in guiding rate discontinuation of glucocorticoid therapy [24]. More often, rapid ACTH testing (250 μg of synthetic ACTH given by intravenous bolus followed by a cortisol level drawn 30 to 60 minutes later should yield a cortisol value greater than 20 μg/dL) is a useful test of the pituitary–adrenal axis performed easily in an outpatient setting [25].

Calcineurin inhibitors

Calcineurin inhibitors have played a major role in immunosuppressive regimens since their introduction in 1980. Cyclosporine and tacrolimus, the two drugs under this class, are used in most transplant patients. These agents act against the T cell activator protein, calcineurin, inhibiting T cell activation and cytokine gene expression. Both drugs also inhibit the actions of prolactin, an immune activator, thereby providing a synergistic effect on immunomodulation [26]. Both agents commonly are associated with hyperglycemia and hyperlipidemia as adverse effects. The individual effects of these agents in clinical studies are difficult to interpret, because concomitant administration of steroids almost always occurs as a confounding factor. Although the two drugs in this class are believed to act similarly, cyclosporine does not cause impaired glucose metabolism to the same extent as tacrolimus. In some patients, hyperlipidemia occurs secondary to an underlying genetic predisposition and/or environmental factors [27].

Cyclosporine

Effects of cyclosporine on glucose metabolism. Cyclosporine (Sandimmune, Neoral) is associated with impaired glucose metabolism and post-transplant diabetes mellitus in 5% to 35% of renal transplant recipients. While glucocorticoids increase insulin resistance, cyclosporine appears to decrease insulin secretion.

Studies in animals receiving cyclosporine have demonstrated functional and morphological abnormalities in pancreatic islet cells. Specifically, reduction in insulin secretion, diminished β cell density, and decreased insulin synthesis have been reported. Several in vitro studies have shown that cyclosporine has a direct inhibitory effect on insulin release from human pancreatic islet cells [28]. Alterations in islet cell morphology, including cytoplasmic swelling and vacuolization, and immunohistochemical and ultrastructural loss of secretory granules have been noted in pancreatic islet transplants on biopsy [29]. A recent report suggests altered mitochondrial function of islet β cells exposed to cyclosporine [30]. Some early rat studies also have suggested worsened peripheral insulin resistance, although this has not been demonstrated in human studies.

Some investigators have reported the lack of effects of cyclosporine on glucose in the absence of concomitant administration of steroids [31]. Cyclosporine is believed to decrease metabolism of prednisolone by interfering with the cytochrome P-450 system in renal transplant recipients, thereby worsening potential for hyperglycemia [32]. Hyperglycemic clamp studies in nontransplanted hemodialysis subjects after treatment with cyclosporine have shown a decrease in insulin and C peptide secretion [33]. These subjects showed a decrease in second-phase insulin secretion but no change in first-phase secretion. No differences in insulin sensitivity or glucose clearance were shown. However, the exact mechanism by which cyclosporine causes

a reduction in islet insulin secretion is understood poorly. No significant relationship between cyclosporine dosing or cyclosporine blood trough concentration and impaired insulin secretion has been documented. Robertson and colleagues [34] found no abnormalities in pancreatic β cell function as assessed by intravenous glucose tolerance testing before and during a 2-year course of cyclosporine therapy in a small group of patients who had multiple sclerosis.

Effects of cyclosporine on lipid metabolism. After glucocorticoids, cyclosporine is a common offending agent causing post-transplant hyperlipidemia. The exact mechanisms underlying cyclosporine-induced hyperlipidemia have not been elucidated completely, but they appear to be dose- and duration-related. Studies in nontransplant subjects who received cyclosporine show increases in plasma cholesterol with elevation of LDL levels [35]. It has been suggested that cyclosporine inhibits steroid 26-hydroxylase, an important mitochondrial enzyme that enables bile acid synthesis from cholesterol [19]. Inhibition of bile acid synthesis, elevated hepatic cholesterol, and down-regulation of the LDL receptor then results in hypercholesterolemia. Cyclosporine is carried by LDL particles and can bind to the LDL receptor [36]. LDL receptor blockade by cyclosporine can lead to elevated LDL levels and cause hyperlipidemia. Low cholesterol levels therefore can increase toxicity by increasing drug delivery to target tissues. Cyclosporine increases hepatic lipase activity and decreases LPL activity, resulting in impaired VLDL and LDL clearance [37]. Cyclosporine can inhibit prednisone metabolism and thereby worsen lipid abnormalities induced by glucocorticoids. Increased susceptibility of LDL to oxidation has been suggested in a study of renal transplant recipients treated with cyclosporine [38]. The pro-oxidant effect of cyclosporine could increase cardiovascular risk, and could, in part, explain accelerated atherosclerosis seen in transplant recipients. Inhibition of calcineurin by cyclosporine can increase vascular tone and systemic vascular resistance, leading to hypertension. Cyclosporine also elevates lipoprotein (a) levels in renal transplant recipients [39]. Discontinuation of cyclosporine is associated with improvement in hyperlipidemia; this effect could be related to improvement in kidney function and concomitant reduction of steroid doses.

Tacrolimus

The other important calcineurin inhibitor, tacrolimus (Prograf), is a macrolide antibiotic with more potent immunosuppressant activity than cyclosporine. It appears to have significant effects on glucose metabolism and less deleterious effects on lipids.

Effects of tacrolimus on glucose metabolism. Tacrolimus appears to cause significant alterations in blood glucose compared with cyclosporine. In vitro studies have demonstrated that tacrolimus can decrease insulin secretion

from islet cells, similar to the effects of cyclosporine. In a human islet cell line, tacrolimus has been shown to decrease insulin mRNA, insulin synthesis, and insulin secretion in a dose-dependent manner [40]. In rats, vacuolation of islet cells and reduction in insulin content and secretion that reverse within 2 weeks of discontinuation of the drug have been demonstrated [41,42]. Consistent with these in vitro and animal data, similar reversible histopathologic changes, including cytoplasmic swelling and vacuolation, apoptosis and loss of secretory granules, have been noted in patients receiving simultaneous kidney–pancreas transplants on tacrolimus regimens [29].

In a cohort of 18 individuals, glucose metabolism was assessed by intravenous glucose tolerance testing before and after renal transplantation. The transplanted patients received only tacrolimus for immunosuppression, but no steroids. After receiving tacrolimus, a significant increase in plasma glucose and decrease in the insulin sensitivity index were found compared with pretransplant measurements [43]. This decrease was noted to be caused by decreased insulin secretion as opposed to worsening insulin resistance, and was worsened when the trough levels of tacrolimus were the highest. In a prospective randomized longitudinal study in renal allograft recipients, tacrolimus caused a reduction in C peptide and insulin secretion 3 weeks after transplantation [44]. At the end of the study in 3 years, however, there were no differences in any parameters of glucose metabolism studied in the groups receiving tacrolimus or cyclosporine. This suggests that there is no chronic cumulative toxicity on the pancreatic beta cell caused by tacrolimus. Similarly, no differences were found in glucose metabolism or pancreatic secretory capacity in islet transplant patients receiving tacrolimus at 3 months or 3 years compared with patients on cyclosporine [45].

A retrospective analysis suggested that conversion of renal transplant recipients from tacrolimus to cyclosporine resulted in significant lowering of blood glucose, reduction in HbA1c, reduction in insulin dosage, or reversal of diabetes without altering graft function [46]. Although some reports have shown that tacrolimus and cyclosporine induced a similar glucose intolerance and hyperinsulinemia after successful allogeneic liver transplantation, other studies show a higher incidence of hyperglycemia or diabetes in tacrolimus-treated patients. In contrast, two studies in patients who received liver transplants did not show any significant diabetogenic adverse effect or dose dependency of tacrolimus treatment [47].

Thus the effect of tacrolimus on glucose metabolism appears to be a reversible, dose-dependent cytotoxicity to the beta cell in animal models and in human clinical studies. Administration of pulse steroids potentially could worsen tacrolimus-induced hyperglycemia.

Effects of tacrolimus on lipid metabolism. Tacrolimus appears to have less adverse effects on lipids than cyclosporine, not explained by concomitant steroid administration [48,49]. In the absence of lipid-lowering therapy, tacrolimus has been associated with lower LDL cholesterol, apolipoprotein B,

and triglyceride levels with no differences in HDL cholesterol [50,51]. Combination therapy with glucocorticoids results in increased cholesterol and triglyceride levels in plasma. Cross-over studies in renal and liver transplant patients have shown improvement in lipid profiles after switching to tacrolimus from cyclosporine [52,53]. A retrospective analysis of 150 pancreas–kidney transplantation recipients showed no differences in plasma cholesterol or triglyceride levels 5 years after transplant in patients receiving tacrolimus versus those who did not [54].

Azathioprine

Azathioprine (Imuran) served as a mainstay of immunosuppression along with glucocorticoids until the advent of the calcineurin inhibitors. Azathioprine inhibits purine synthesis and DNA replication. There are no data to suggest that azathioprine disrupts glucose or lipid metabolism.

Mycophenolate mofetil

Mycophenolate (MMF, Cellcept) has found an important role in immunosuppressant therapies, enabling the use of steroid-sparing or low-dose calcineurin inhibitor regimens. The immunosuppressive activity of MMF is thought to derive mainly from inhibition of de novo purine synthesis in T and B lymphocytes and therefore cell proliferation [55].

Effects of mycophenolate on glucose metabolism

In vitro studies in rat islets have shown MMF to inhibit insulin secretion, predominantly through effects on voltage-dependent calcium channels [56] and through induction of beta cell apoptosis [57]. One in vitro study in human islets showed that MMF had no deleterious effects on human islet insulin secretion or insulin gene expression [58]. No effects on glucose metabolism have been noted in clinical trials, although studies are scarce. In liver transplant recipients, addition of MMF to tacrolimus did not decrease the occurrence of glucose intolerance or post-transplant hyperglycemia compared with patients treated with tacrolimus alone [59]. Some studies have shown lower incidence of post-transplant diabetes in patients receiving MMF as part of their immunosuppression, although studies using intravenous glucose tolerance tests and glucose clamp studies are lacking.

Effects of mycophenolate on lipid metabolism

There is an association between hyperlipidemia and mycophenolate mofetil, although, once again, the data are limited. There is no direct evidence that MMF affects lipoprotein metabolism or causes hyperlipidemia. No evidence of significant differences in serum cholesterol or triglycerides have been noted in rabbits fed high-cholesterol diets without or with MMF,

but evidence of reduced atherosclerosis has been noted in the latter group [60]. In renal transplant recipients, MMF did not worsen lipid profiles of patients treated with cyclosporine and glucocorticoids [61]. The product information for Cellcept (http://www.rocheusa.com/products/cellcept/pi.pdf), however, states that hypercholesterolemia was noted in 41% of cardiac transplant recipients receiving 3 g/d of MMF. Treatment with other immunosuppressive medications and other risk factors are unknown for this group of patients. An interesting aspect of this drug is that MMF is being studied in animal models as an immune modulator of inflammatory activation in atherosclerosis.

Therefore, in contrast to other available immunosuppressants, MMF appears to lack cardiovascular toxicity or diabetogenic potential, thus making it an excellent candidate for combination regimens.

Mammalian target of rapamycin inhibitors

Sirolimus

Sirolimus or rapamycin (Rapamune) is a macrolide that prevents T cell activation through inhibitory effects on the protein kinase, mTOR. mTOR plays an important role in cell growth and proliferation and has been termed a nutrient sensor regulated by insulin, glucagon, and certain amino acids. Inhibition of mTOR by sirolimus could result in various effects on intermediary metabolism.

Effects of sirolimus on glucose metabolism. The effects of sirolimus on insulin action and secretion are being debated, and data are conflicting. In skeletal muscle cells, long-term exposure to rapamycin has been shown to decrease insulin-dependent glucose uptake and glycogen synthesis and increase fatty acid oxidation [62]. Rapamycin has been shown to modulate glucose transport in 3T3-L1 adipocyte cells, preventing long-term insulin-induced increases in glucose transporter 1 (GLUT 1) protein synthesis and to decrease insulin-mediated glucose uptake and insulin signaling in adipocytes [63,64]. There are also studies showing rapamycin to decrease insulin resistance and partially improve insulin-dependent glucose transport [65].

In vitro effects of sirolimus on islet cells are also conflicting. Some studies have shown deleterious effects of rapamycin on rodent [66] and human islets [67], resulting in reduced insulin secretion and impaired beta cell function at doses higher than used in clinical settings. There is also evidence that sirolimus has no deleterious effects on human islet insulin secretion at levels used for immunosuppression in people. In vivo rodent studies have suggested that sirolimus causes insulin resistance [68]. Studies in mini-pigs treated with sirolimus demonstrated improved basal and glucose-stimulated insulin levels and decreased apoptosis [69]. Therefore, the effects of sirolimus on islets and insulin secretion seem to depend upon the cell lines or animal models used and plasma drug concentrations. In a small cohort of renal

transplant recipients, sirolimus caused worsening of glucose intolerance and insulin resistance and insulin secretion even after discontinuation of tacrolimus [70].

Therefore, based on existing evidence, effects of sirolimus on glucose metabolism appear to be cell-, species- and dose-dependent. Overall, it appears to have beneficial effects on islet cells, which could explain its successful use in islet cell transplantation partially. Sirolimus potentially can worsen insulin resistance, but more studies are required, because data are conflicting.

Effects of sirolimus on lipid metabolism. Hyperlipidemia is a well-known consequence of sirolimus therapy in kidney, liver, and pancreas transplant recipients [71,72]. Hyperlipidemia is a serious adverse effect, because it may exacerbate the lipid disturbances associated with cyclosporine, glucocorticoids, and renal disease [73]. The incidence of sirolimus-associated dyslipidemia is as high as 49% in liver transplantation [74,75] and 40% in renal transplantation. In a study in guinea pigs treated with rapamycin, animals that received the drug had higher triglyceride levels, increased VLDL and small dense LDL, and higher glucose and circulating free fatty acid levels [76].

Reversible hypertriglyceridemia that improved after dose reduction or resolved 1 to 2 months after discontinuation of the drug has been noted in patients who received renal transplants in several studies [77,78] . Increased free fatty acid pool has been noted in patients who had sirolimus-related hypertriglyceridemia, possibly due to increased hormone sensitive lipase and decreased lipoprotein lipase activity secondary to elevated apolipoprotein C-III levels. Increased hepatic synthesis and delayed clearance of triglyceride-rich lipoproteins have been implicated as potential mechanisms of sirolimus-induced hypertriglyceridemia [71].

In a cohort of patients with renal allografts who were taking cyclosporine and glucocorticoids, the addition of sirolimus increased the mean fasting serum cholesterol and triglyceride levels as compared with placebo [79]. These levels were significantly higher in patients receiving higher doses, suggesting a dose relationship. These effects however, were reversible with discontinuation of sirolimus. In a retrospective analysis of 55 stable liver transplant recipients who received sirolimus along with tacrolimus and/or MMF, hypercholesterolemia was noted in 15% and hypertriglyceridemia in 10% of patients who received sirolimus. This was not significantly different from the control group of patients who received tacrolimus with MMF. No differences in LDL or HDL were noted [80]. Trotter and colleagues [81] studied a cohort of 57 liver transplant subjects and found worsened hypercholesterolemia and hypertriglyceridemia in subjects treated with the combination of cyclosporine and sirolimus as opposed to tacrolimus and sirolimus.

Overall, the benefits of sirolimus supersede its dyslipidemic effects, because it leads to use of calcineurin inhibitor-sparing regimens, and therefore a lower

incidence of nephrotoxicity. It is also interesting to note that sirolimus inhibits smooth muscle cell proliferation and migration and decreases the vascular response to injury in rats. These beneficial effects have led to the development of sirolimus-coated coronary stents used for percutaneous coronary intervention, in an effort to prevent stent restenosis [82].

Everolimus

Everolimus is a semisynthetic derivative of sirolimus that acts by inhibition of mTOR. Safety and efficacy have been established in a few trials involving liver and kidney transplantation. Everolimus also is plagued by dyslipidemic adverse effects, including elevations in cholesterol and triglycerides. Early in vitro data in macrophages suggest disruption of cellular lipid homeostasis, increased cholesterol efflux, and decreased triglyceride synthesis [83]. Everolimus has shown beneficial effects in patients who receive cardiac transplant, however, by reducing allograft vasculopathy [84].

Newer agents

Polyclonal antibodies such as antithymocyte globulin and antilymphocyte globulin are used as part of induction therapy and/or acute rejection treatments. Monoclonal antibodies such as basiliximab, daclizumab, and muromonab (OKT3) are use as antirejection therapies or in treatment of steroid-resistant acute rejection. No known adverse effects on glucose or lipid metabolism are known for any of these preparations.

Summary

Immunosuppression medications contribute to the morbidity of organ transplantation. Adverse effects including dyslipidemia and glucose intolerance are extremely common after transplantation and contribute significantly to cardiovascular morbidity and mortality. Tables 1 and 2 summarize the effects of various immunosuppressants on blood glucose

Table 1
Effects of immunosuppressive drugs on glucose

Drug	Effect on glucose
Glucocorticoids	↑↑↑
Calcineurin inhibitors:	
Cyclosporine	↔ or ↑
Tacrolimus (FK506)	↑↑
Azathioprine	↔
mTOR inhibitors:	
Sirolimus	↔ or ↑
Everolimus	? ↔
Mycophenolate mofetil	↔

Abbreviations: ↑, increased; ↓, decreased; ↔, unchanged.

Table 2
Effects of immunosuppressants on lipids

Drug	Effect on lipids
Glucocorticoids	↑ TG, ↑ cholesterol, ↓ HDL
Calcineurin inhibitors:	
Cyclosporine	↑ TG, ↑ cholesterol, ↑ Apo B
Tacrolimus (FK506)	↓ cholesterol, ↓ TG, ↔ HDL
Azathioprine	↔
mTOR inhibitors:	
Sirolimus	↑ ↑ TG, ↑ cholesterol
Everolimus	↑ TG, ↑ cholesterol
Mycophenolate mofetil	? ↑ cholesterol

Abbreviations: Apo B, apolipoprotein B; HDL, high-density lipoprotein; TG, triglycerides; ↑, increased; ↓, decreased; ↔, unchanged.

and lipids. Immunosuppressive regimens should be chosen carefully to minimize these risks. Until the ideal immunosuppression regimen is developed, individualization of immunosuppression for each patient is necessary. Metabolic alterations induced by glucocorticoids should be identified and treated. Calcineurin inhibitors at lower doses, in conjunction with the newer immunosuppressive agents such as mycophenolate mofetil, appear to have less detrimental effects on glucose metabolism. Dyslipidemia itself should not be a deterrent to use of any of the agents, because therapies for effective lipid lowering are available.

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