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Diabetes mellitus is a common complication in the well transplant patient. Cyclosporine, tacrolimus and corticosteroids promote diabetes by several mechanisms, including the induction of insulin resistance. Patients should be frequently screened for diabetes after transplantation and patients with pre-existing diabetes should be carefully monitored for worsening control. Pharmacologic therapy for patients with diabetes must account for changes in renal and hepatic function and the diabetogenic effect of medications. Therapeutic options for transplant patients with type 2 diabetes include subcutaneous insulin, sulfonylureas, metformin, insulin secretogogues, alpha-glucosidase inhibitors, and thiazolidinediones. Complications of diabetes may potentially be avoided by early diagnosis of de novo diabetes, close monitoring of pre-existing diabetes, aggressive glycemic control, and careful attention to health maintenance.

ABBREVIATIONS:

PTDM	Post-transplant diabetes mellitus
CSA	Cyclosporine
TAC	Tacrolimus
FPG	Fasting plasma glucose
ACE	Angiotensin converting enzyme

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Introduction

Diabetes mellitus is a common complication in the well transplant patient. It arises from a relative or absolute decrease in insulin secretion along with a varying degree of peripheral insulin resistance. Many transplanted patients have pre-existing type 1 or type 2 diabetes and may have been transplanted specifically for diabetic nephropathy. Other patients develop post-transplant diabetes mellitus (PTDM), primarily as a side effect of cyclosporine (CSA), tacrolimus (TAC) and corticosteroids. The cardiovascular and peripheral vascular complications of diabetes,[1] as well as the increased susceptibility to bacterial infection,[2] are major contributors to post-transplant morbidity and mortality. Patients with diabetes may also be at higher risk of graft loss either from chronic rejection, recurrent diabetic nephropathy or accelerated cardiac allograft arteriopathy.[2,3] These risks and complications are similar for patients with pre-existing diabetes and those with PTDM.[3] Complications of diabetes may potentially be avoided by early diagnosis of de novo diabetes, close monitoring of pre-existing diabetes, and aggressive glycemic control. This review discusses the practical aspects of the diagnosis and management of diabetes after solid organ transplantation.

Risk of Post-Transplant Diabetes

In recent large studies, the incidence of PTDM varies from 2.5% to 19.1% depending on the definition of diabetes and the type of immunosuppression used.[4-7] A number of risk factors for the development of PTDM have been identified. In one large retrospective study of patients treated with CSA, patients with PTDM were significantly more likely to be black or Hispanic, older, and to have received a cadaveric renal transplant. Recipients with HLA-A 30, HLA-A A2, and HLA-Bw 42 were also significantly more likely to develop PTDM, but this requires confirmation.[2] Another study found that risk factors for PTDM included age, family history, and post-operative glucose intolerance, but did not find that sex, race, body weight, or transplant source increased the risk.[7]

Interestingly, the type of organ transplant may also be a risk factor for PTDM. Renal and pediatric lung transplant recipients may be at the highest risk, while liver and heart transplant recipients have lower rates of both de novo and pre-existing diabetes.[8-10] The risk of PTDM may be related to the degree of immunosuppression used. Cardiac and lung transplant recipients, followed by renal transplant recipients, generally require the highest doses of immunosuppression initially. Over the long-term, renal and

lung transplant recipients tend to continue treatment with corticosteroids, while many liver and cardiac transplant recipients have steroids withdrawn by the end of the first transplant year.

The calcineurin inhibitors, CSA and TAC, both increase the risk of PTDM. CSA may be diabetogenic by increasing insulin resistance,[11] decreasing insulin secretion,[12] and by decreasing the volume of pancreatic beta cells.[13] Animal studies also suggest that CSA is directly toxic to beta cells[13] and decreases the synthesis of DNA and mRNA.[14] Similarly, TAC has also been shown to reduce secretion of insulin from pancreatic beta cells[15] and increase insulin resistance.[11] Some studies have indicated that PTDM induced by TAC may be reversible as dosages of TAC and steroids are decreased.[16,17]

Several large multi-center trials have suggested that TAC is more diabetogenic than CSA. In a study of 412 patients with cadaveric renal transplants, the incidence of PTDM was 19.9% in the TAC group and 4.0% in the CSA group ($P<0.001$).[17] Similarly, a study of 244 patients with renal transplants showed that patients treated with TAC were significantly more likely to develop PTDM, and that black patients were at the highest risk (8.3% of black patients treated with CSA vs. 36.6% treated with TAC, $P<0.05$).[18] TAC-induced PTDM is not restricted to renal transplant recipients. In a study of pediatric thoracic organ transplant recipients on TAC-based immunosuppression, 17% of heart and 13% of heart-lung transplant recipients developed PTDM.[19] However, other studies have suggested that the incidence of PTDM may be less with lower doses of TAC.[20] A recent study using mycophenolate mofetil in combination with lower target serum levels of tacrolimus, showed comparable levels of PTDM with CYA-treated patients.[20]

Corticosteroids may promote the development of diabetes by several mechanisms, the most important of which is the induction of insulin resistance. Steroids may act by decreasing insulin receptor number and affinity, impairing endogenous glucose production[21] and impairing glucose uptake by muscle.[22] Reducing the dose of corticosteroids or withdrawing steroids has been shown to reduce hyperglycemia and potentially may decrease the incidence of PTDM, but it also may increase the risk of acute rejection.[23]

TYPE 1 DIABETES MELLITUS:

Hyperglycemia resulting from an absolute or relative lack of endogenous insulin. This is usually due to autoimmune destruction of the pancreatic beta cells.

Classification, Screening and Monitoring

The American Diabetes Association, in recently revised guidelines, recommends classifying patients with diabetes into type 1 and type 2. Type 1 diabetics usually have autoimmune destruction of the pancreatic beta cells and are insulin-dependent, meaning they develop diabetic ketoacidosis if exogenous insulin is not provided. Type 2 diabetics include all others who develop diabetes from other causes, and this category includes those who develop PTDM related to corticosteroids and the calcineurin inhibitors.[24]

Some type 1 diabetic patients may also develop an additional component of insulin resistance post-transplant. Insulin resistance is defined as a subnormal response to endogenous and exogenous insulin.[25] Insulin resistance may be primary (inherited defects in type 2 diabetes, auto-antibodies to the insulin receptor), or secondary (obesity, stress, infection, uremia, acromegaly, glucocorticoid excess and pregnancy).[26] Most solid organ transplant recipients develop secondary insulin resistance related to corticosteroid therapy or weight gain. Liver transplant recipients may also have insulin resistance related to increased hepatic metabolism of insulin, which may be due to denervation of the transplanted liver.[27]

The American Diabetes Association recommends diagnosing diabetes mellitus based on a fasting plasma glucose (FPG) of 126 mg/dL or higher on two separate days (Table 1). Alternative criteria include two two-hour plasma glucose values of 200 mg/dL or higher after a 75 g glucose load (the glucose tolerance test) or two random plasma glucose values of 200 mg/dL or higher along with symptoms of diabetes. Any combination of two abnormal test results can be used, but the FPG test is preferred.[24]

In the immediate post-transplant period or after treatment of acute rejection with high dose corticosteroids, many transplant recipients will have abnormal FPG tests. This should not be taken as prima facie evidence of diabetes, as the FPG levels often become normal several days later. Thus, ADA criteria should not be strictly applied to transient hyperglycemia in the setting of brief high dose corticosteroids. These patients should have a serum hemoglobin A1c level checked; values greater than 6.0% provide evidence for underlying type 2 diabetes.

Given the high risk of PTDM, the American Society of Transplantation in published practice guidelines recommends frequent screening of non-diabetic transplant recipients using FPG values. An 8-hour fasting glucose should be measured at least

Table 1 | **Criteria for Diagnosing Diabetes Mellitus**

Criteria for Diagnosing Diabetes
Fasting plasma glucose (FPG) ≥126 mg/dL two separate days
Glucose tolerance test:
Two 2-hour plasma glucose values ≥200 mg/dL after a 75 g glucose load
Two random plasma glucose values ≥200 mg/dL along with symptoms of diabetes.
Hemoglobin A1c >7 %

Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[24]

TYPE 2 DIABETES MELLITUS:

Hyperglycemia resulting from insulin resistance despite the presence of endogenous insulin. This usually covers all other cases of diabetes that do not meet criteria for type 1.

weekly for months 1 to 3, at least every other week for months 4 to 6, and at least monthly for months 6 to 12. Patients with consistently elevated fasting glucose levels should be given a glucometer and instructed to check their pre-prandial and bedtime blood glucose levels for 3-5 days. This is usually sufficient to diagnose de novo diabetes mellitus. After the first year, FPG and/or hemoglobin A1c levels should be measured at least yearly.[28] These guidelines are relatively easy to adhere to, as most patients have a metabolic profile drawn weekly for the first 3 months after transplant and often monthly after that.

In transplant recipients with known diabetes, FPG and hemoglobin A1c levels should be checked often. Patients with pre-existing diabetes should check pre-prandial and bedtime glucose levels four times daily for at least the first several post-transplant months and when treated with high dose corticosteroids for rejection episodes. This is particularly important as corticosteroids doses are reduced or discontinued, and during periods of acute renal failure, to avoid hypoglycemia. Once good glycemic control has been achieved, patients with type 2 diabetes may check glucose levels less frequently. To reduce the risk of vascular complications, the goal FSBG should be less than 126 mg/dL with a target hemoglobin A1c level of 7%.[29]

Recent literature has suggested that post-prandial glucose monitoring may be a better indicator of glycemic control than FPG in patients with type 2 diabetes.[30] Some type 2 diabetic patients with normal FPG levels have elevated post-prandial glucose levels, which correlate with elevated hemoglobin A1c levels.[31] In addition, poor post-prandial glycemic control may be an independent risk factor for peripheral vascular and cardiovascular disease.[32] Although not yet formally endorsed by the ADA as essential practice, post-prandial glycemic monitoring may be indicated for optimal glycemic control in the well transplant recipient.

Therapies

Following transplantation, treatment of patients with diabetes mellitus must take into account changes in renal and hepatic function and the diabetogenic effect of medications, particularly corticosteroids. In general, sulfonylureas, thiazolidinediones, repaglinide and metformin should be used with great caution, if at all, in liver transplant recipients in the first post-transplant year as these medications are hepatically metabolized. After the first year, however, these medications may be considered for patients with stable hepatic and renal function. In contrast, oral agents are an excellent therapeutic modality for thoracic organ transplant recipients with normal hepatic and renal function, and for renal transplant recipients with a creatinine clearance greater than 40 ml/min.

Many patients with PTDM can achieve euglycemia on oral medications alone. However, patients who were previously well controlled on oral medications may require insulin after transplantation. Occasionally patients with PTDM may become insulin dependent and will develop ketoacidosis if not given insulin. Indications that insulin therapy may be required in the post-transplant patient include severe hyperglycemia (>300 mg/dl), marked weight loss, or significant ketonuria. Many other patients with PTDM are not insulin dependent but may require subcutaneous insulin when adequate glycemic control cannot be achieved with oral agents alone. In selected patients with type 1 diabetes who have received a renal transplant, pancreas-after-kidney transplantation should be considered for diabetes therapy.

Insulin. Patients with pre-existing type 1 diabetes often require an intensification of their insulin therapy post-transplant. Diabetic patients with end stage renal disease have reduced insulin clearance and require only half the insulin of patients with normal renal function.[33] This may change dramatically

after renal transplantation, when the diabetogenic effect of corticosteroids and calcineurin inhibitors, as well as the improved clearance of insulin will increase insulin requirements. Cardiac transplant recipients may have similar increases in post-transplant insulin requirements as their renal function improves with increased cardiac output. Liver transplant recipients with type 1 diabetes may have a similar response due to improved hepatic gluconeogenesis, increased hepatic clearance of insulin, and resolution of pre-renal azotemia or the hepatorenal syndrome.[27]

Patients with consistent and severe de novo hyperglycemia (FPG >300 mg/dL) will almost certainly require initiation of insulin therapy. The choice of insulin regimen depends on the patient's degree of hyperglycemia, daily fluctuations of glucose levels, and patient and physician preferences. Possible regimens include long-acting NPH insulin at bedtime, twice daily NPH insulin, and intensive therapy with multiple injections of NPH and a pre-meal short-acting insulin. In our experience, if insulin is required, once daily insulin dosing alone is unlikely to achieve euglycemia and target hemoglobin A1c levels in the well transplant recipient. The initial starting dose of insulin depends on the patient's body weight and fasting blood glucose. Typically, patients with newly diagnosed type 2 diabetes are started on a total of 10-30 units of insulin daily. The initial insulin dose can be calculated using the mean FPG level and the patient's degree of obesity (Table 2).[34,35]

Most patients on corticosteroid therapy have higher FPG levels during the evening, and these can be difficult to control with standard twice-daily NPH insulin therapy. In our experience, administration of regular insulin or rapid acting monomeric insulin preparations (insulin lispro or insulin aspart) at each meal is often required to achieve adequate glycemic control in these patients.[36] Rapid acting monomeric insulin preparations have the advantage of being given immediately prior to meals, whereas regular insulin must be given 30 minutes prior to meals. However, post-prandial hyperglycemia (2-3 hours) may occur more frequently with these preparations due to their shorter duration of action. Thus, post-prandial glucose monitoring may be useful for patients with elevated hemoglobin A1c levels despite apparently adequate pre-prandial glucose measurements.

POST-TRANSPLANT DIABETES MELLITUS:

Diabetes occurring after solid organ transplantation (generally within 30-60 days) in a patient without a previous diagnosis of diabetes or hyperglycemia.

Intensive insulin therapy may be considered for highly motivated transplant recipients, but the weight gain associated with large doses of insulin in the setting of corticosteroid therapy may limit its use. Weight gain is a serious complication of intensive insulin therapy, and may be compounded in patients taking corticosteroids.[37] For type 1 diabetic patients, long-term studies have shown significant reductions in the development of diabetic nephropathy, retinopathy, and vascular disease with intensive therapy.[29,38,39] While intensive insulin therapy does delay the onset of microvascular complications in patients with type 2 diabetes, it does not decrease in macrovascular complications such as myocardial infarction or stroke in this group.[29,40]

Transplant recipients who cannot achieve euglycemia with high doses of insulin may benefit from the addition of metformin or a thiazolidinedione. Combination therapy should be considered in all patients on corticosteroid-based immunosuppression as both reduced insulin secretion and insulin resistance is common in this group. Intensive insulin therapy in combination with metformin may limit the weight gain associated with insulin and improve glycemic control.[40,41] The safety of metformin in the well transplant recipient is discussed below. Patients who have inadequate glycemic control despite a total insulin dose of greater than 100 units/day should be referred to a diabetologist as they may have other syndromes of primary insulin resistance and require further evaluation.

Rapid Acting Insulin Secretogogues. Repaglinide belongs to a relatively new class of hypoglycemic agents, the rapid acting insulin secretogogues.[42] These agents stimulate insulin secretion by direct action on pancreatic beta cells. They are rapidly absorbed from the GI tract and cause an acute increase of insulin secretion. Thus, repaglinide can be taken immediately before meals with good effect. It has a half-life of approximately one hour and duration of action of four hours. In contrast to sulfonylureas, patients taking repaglinide have a lower incidence of hypoglycemic episodes, which also tend to be less severe. Repaglinide is hepatically metabolized, and should not be used in patients with hepatic dysfunction. Close monitoring should be used when increasing dosages in patients with moderate to severe renal insufficiency.[43]

Table 2 | **Starting Daily Dose of Insulin in Type 2 Diabetes Based on the Mean Fasting Plasma Glucose Level and Percent of Ideal Body Weight**

		Percent Ideal Body Weight					
FPG (mg/dL)	FPG (mmol/L)	100%	120%	140%	160%	180%	200%
108	6	6 U	9 U	12 U	15 U	18 U	21 U
144	8	10 U	15 U	20 U	25 U	30 U	35 U
180	10	14 U	21 U	28 U	35 U	42 U	49 U
216	12	18 U	27 U	36 U	45 U	54 U	63 U
>252	>14	22 U	33 U	44 U	55 U	66 U	77 U

Adapted from Holman and Turner[35] and McCulloch.[34]

INTENSIVE INSULIN THERAPY:

Therapy with a combination of long- and short-acting insulin, or an insulin pump. Intensive therapy generally includes preprandial and bedtime serum glucose monitoring and four injections of insulin per day.

Sulfonylureas. Sulfonylureas act by increasing pancreatic insulin secretion and are often the initial agents for treatment of mild to moderate hyperglycemia in the well transplant recipient. They have a moderate onset of action and a long duration of effect. The choice of agent may be limited by the patient's renal function. Most sulfonylureas are renally excreted and should be avoided with any degree of renal dysfunction or the potential for renal dysfunction. Prolonged hypoglycemia may occur with the use of long-acting sulfonylurea agents in the setting of renal failure.[44] Agents with a shorter half-life, glipizide and glimepiride, may be used if renal dysfunction is not severe, but the dose should be halved for a GFR of less than 50 ml/min.[33] Both drugs should be used cautiously with hepatic dysfunction.

Metformin. Metformin acts by inhibiting hepatic glucose metabolism and is effective only in the presence of insulin. In transplant patients with diabetes, the combination of corticosteroid therapy and increased endogenous or exogenous insulin can lead to large increases in weight. Of note, metformin does not lead to an increase in insulin secretion and may facilitate weight loss, making it the preferred agent for overweight diabetic patients.[40] In addition, metformin has beneficial effects on lipid metabolism and can lower total cholesterol, LDL and serum triglycerides by up to 10%.[45] Metformin can be safely prescribed for diabetic transplant recipients with a stable creatinine (men <1.5 mg/dL; women <1.4 mg/dL) and normal hepatic function. Metformin is best used in combination with sulfonylureas, thiazolidinediones, repaglinide, or insulin therapy. For patients on metformin monotherapy whose glucose is not well controlled, a sulfonylurea, a thiazolidinediones or insulin should be added.

A rare but serious side effect of metformin is lactic acidosis, and the risk increases with hepatic dysfunction or significant renal dysfunction. Metformin is thus absolutely contraindicated in patients with failing kidney, liver or heart transplants. It should be also be discontinued when conditions that cause transient renal insufficiency occur. These include acute rejection with organ dysfunction, congestive heart failure, imaging procedures that use intravenous radiocontrast dye or major surgical procedures. In addition, it may be prudent to suspend metformin administration when initiating ACE inhibitor therapy, at least until stable renal function is achieved. Patients in whom metformin is contraindicated due to renal dysfunction may benefit from a thiazolidinedione.

Thiazolidinediones. The thiazolidinediones (rosiglitazone and pioglitazone) lower blood glucose by increasing insulin sensitivity and increasing peripheral uptake of glucose. They may be used alone or in combination with a sulfonylurea, metformin or insulin. No dosing adjustment for renal impairment is required, and therefore thiazolidinediones may be used when metformin is contraindicated. The thiazolidinediones are also hepatically metabolized, and should be avoided in patients with hepatic dysfunction. Rare cases of acute hepatic failure have been associated with rosiglitazone, and thus serum transaminase levels should be monitored weekly for a period of one month when starting therapy, and every 2 months for the first year of treatment.[46,47]

Alpha-Glucosidase Inhibitors. The alpha-glucosidase inhibitors (acarbose and miglitol) slow the intestinal absorption of glucose. A theoretical advantage of the alpha-glucosidase inhibitors is their poor systemic absorption, but given the lack of clinical data, they should be avoided in patients with moderate or

severe renal dysfunction.[33] No dosing adjustment for hepatic dysfunction is necessary. The major side effects are flatulence and diarrhea. Diarrhea can be problematic in patients taking mycophenolate mofetil for immunosuppression, as it is a common side effect leading to discontinuation of this medication. The alpha-glucosidase inhibitors may be combined with other oral medications or insulin. There are no published studies of alpha-glucosidase inhibitor use in solid organ transplant recipients.

Diet and Exercise. Dietary therapy and exercise are crucial, yet underemphasized, elements of diabetes therapy in the well transplant recipient. Adherence to the diabetic diet can greatly improve glycemic control, although reinforcement is necessary to assure continued compliance.[48] Decreasing caloric intake and weight loss are especially important in the management of type 2 diabetes, and they have independent effects on glycemic control. Exercise also aids in weight loss and improves glycemic control. Restricting caloric intake can lower FPG levels independent of the degree of patient obesity, although sustained improvements require long-term weight reduction.[49-51] Thus, nutritional counseling, preferably by a diabetes educator or registered dietician, should be the standard of care for all diabetic transplant recipients.

Unfortunately, achieving either caloric restriction or weight loss can be a daunting task for transplant recipients. Most solid organ transplant recipients have had dietary restrictions prior to their transplant. After a successful transplant, they are often liberated from their renal, heart or hepatic failure diet and can enjoy previously forbidden foods. An increase in health and the use of corticosteroids usually improves appetite. Finally, the combination of higher insulin levels with corticosteroids, at least during the first year post-transplant, generally leads to moderate weight gain.

Changing Immunosuppression Regimens. For some patients, alterations in immunosuppression agents or dosing may improve glycemic control. Minimizing corticosteroids can lower FPG levels, and should be discussed with the transplant team for individuals with difficult to control hyperglycemia. In contrast, the safety of complete steroid withdrawal depends on the type of organ transplanted. Many liver and heart transplant centers routinely withdraw steroids during the first post-transplant year with little effect on long-term organ survival.[52-54] Steroid withdrawal is less common in lung transplant recipients. In stark contrast, steroid withdrawal cannot be currently recommended for renal transplant recipients on CSA-based immunosuppression. Virtually all CSA-based steroid withdrawal regimens in renal transplantation have resulted in an increased acute or chronic rejection rates.[55] It remains to be seen if TAC or sirolimus-based steroid-free immunosuppression carry the same risks.

The efficacy of altering immunosuppression for TAC-mediated PTDM depends on the time frame of therapy. TAC-mediated PTDM usually occurs within weeks of starting therapy.[16,56] Minimizing or withdrawing TAC may be appropriate in this setting, and in some cases lead to euglycemia.[57] In contrast, changing from TAC to CSA in stable transplant patients who have been on TAC for over 1 year is not likely to have any significant effect on glycemic control.

COMBINATION THERAPY OF DIABETES:

Therapy with more than one class of hypoglycemic agent, for example insulin and an insulin sensitizing agent.

General Treatment of Diabetes After Transplantation

Glycemic Control. Treatment of hyperglycemia in the well transplant patient should be individualized based on the type of diabetes, mean serum glucose levels, renal and hepatic function and obesity.

Some guidelines for therapy are outlined in Figure 1. All patients should have a consultation with a diabetes educator, begin an exercise regimen, and see a diabetes nutritionist. After transplantation, periodic reinforcement of the diabetic diet will encourage compliance. Frequent monitoring of FPG and hemoglobin A1c levels is necessary to assess the efficacy of therapy.

Several key points should be emphasized. Insulin is the initial therapy of choice for patients within the first year post-liver transplant, with significant liver disease, with pre-existing type 1 diabetes, or with multiple FPG levels >300 mg/dl. Metformin should be considered as a second agent in patients that are not able to achieve euglycemia with monotherapy using insulin, insulin secretogogues, thiazolidinediones, or sulfonylureas. Patients on metformin should have normal renal and hepatic function. In patients with normal liver function, the insulin sensitizing thiazolidinediones are a good choice for either primary therapy when FPG levels are <300 mg/dl, or as a second agent if euglycemia

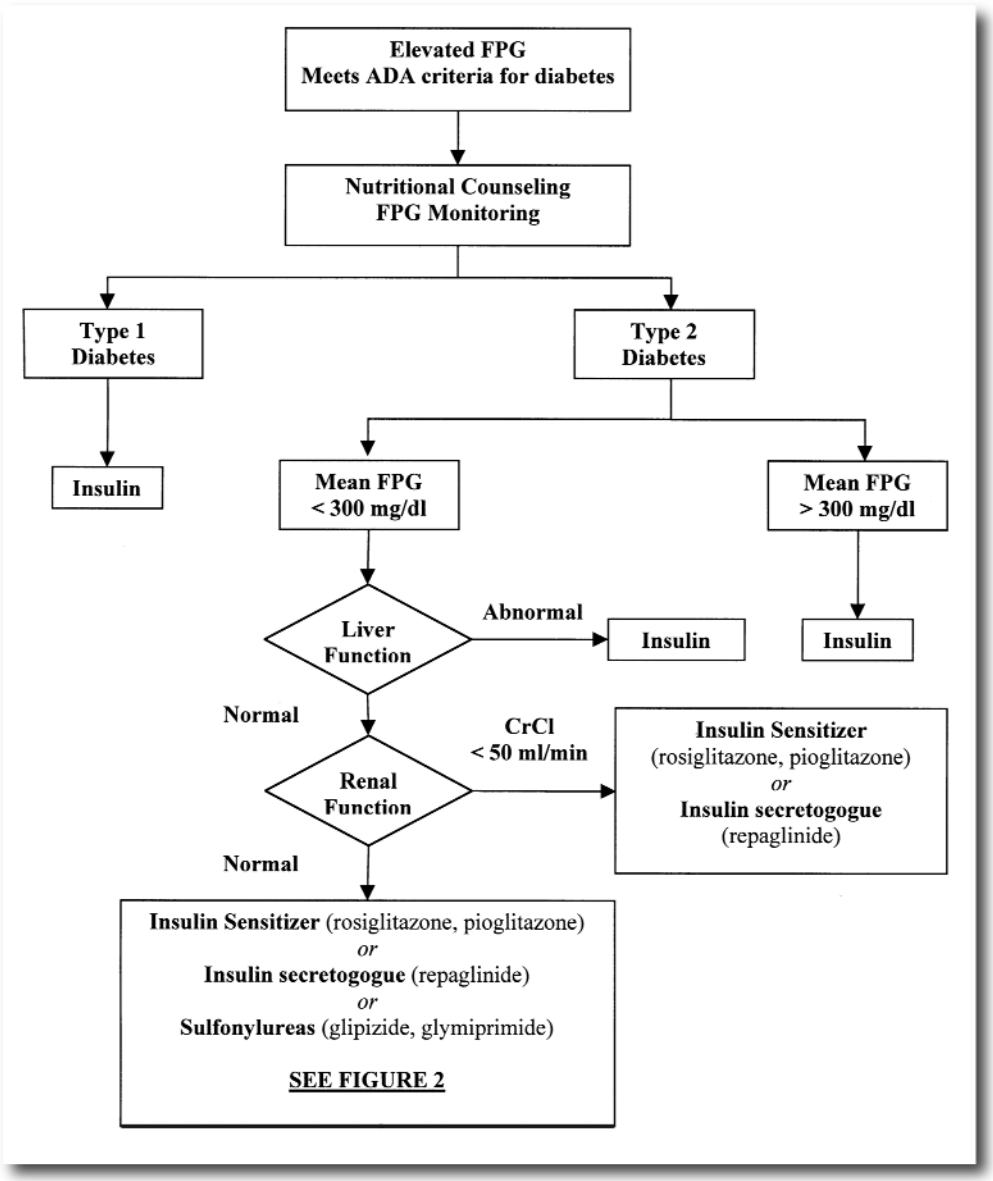

Figure 1. Suggested algorithm for initial diabetes therapy in the well transplant patient.

cannot be achieved with insulin, repaglinide, or sulfonylurea monotherapy. Sulfonylureas and repaglinide are not used in combination as they have similar mechanisms of action. Finally, sulfonylurea agents and repaglinide should be discontinued in any type 2 diabetic patient that starts insulin therapy.

Assessing the adequacy of therapy and adjusting the medical regimen can be challenging, especially in type 2 diabetic patients. Figure 2 suggests a treatment algorithm that may be useful in gauging therapeutic efficacy and deciding when to add additional agents or switch to insulin. The hemoglobin A1c level, a reflection of long-term glycemic control, is used as the primary marker of adequate therapy. Additional agents can be added in a stepwise fashion if target levels are not achieved.

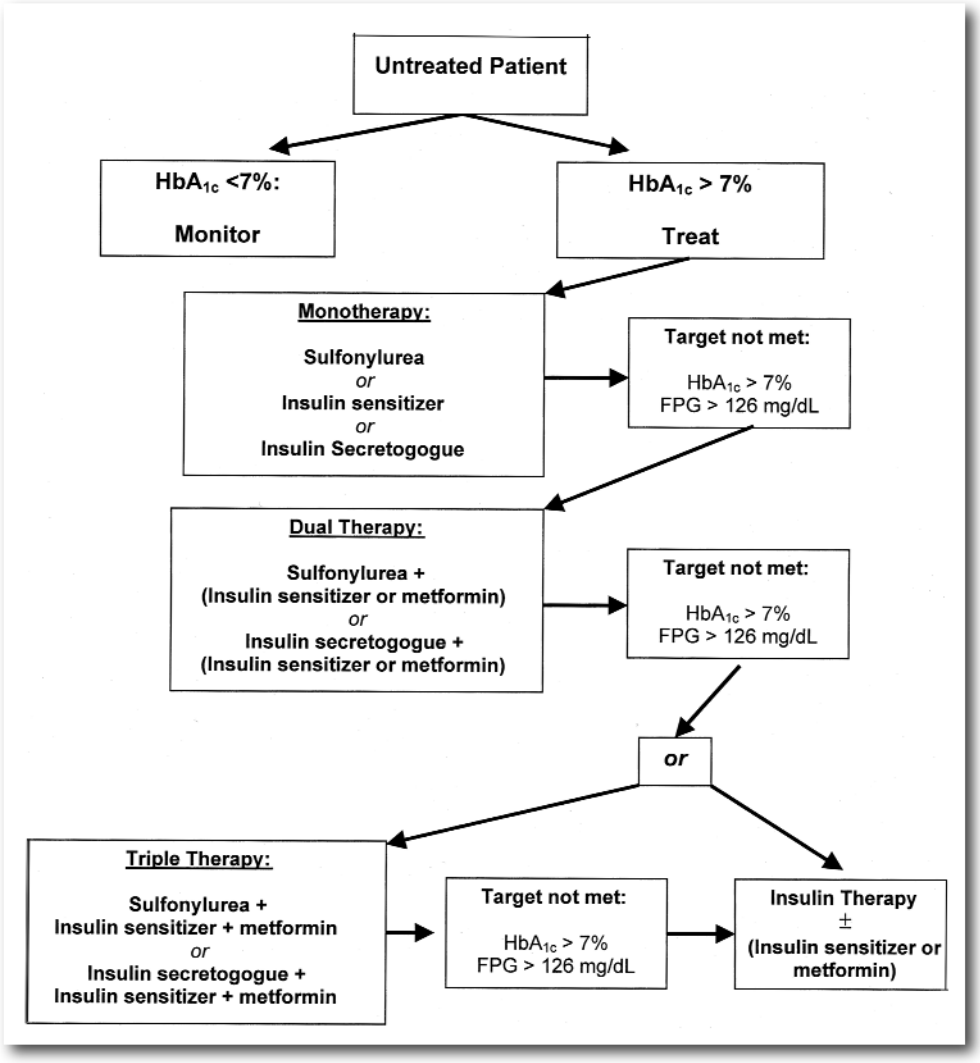

Figure 2. Suggested algorithm for oral agent therapy in transplant recipients with type 2 diabetes, normal liver function and CrCl >50ml/min. Adequacy of therapy is assessed by the FPG and hemaglobin A1c levels.

During episodes of transplant rejection, acute renal failure, critical illness, infection, or myocardial infarction, careful monitoring of PPG levels is necessary. Patients well controlled on oral medications may require insulin. Patients on metformin should have the medication immediately discontinued. Changes in renal function can lead initially to prolonged hypoglycemia or euglycemia, followed later by an increased need for glycemic therapy as renal function recovers.

Routine Diabetic Health Maintenance. All transplant recipients with diabetes should have routine preventive care and screening for diabetes-related end-organ damage. A routine ophthalmologic examination for diabetic retinopathy should occur at least yearly. Patients should be educated regarding diabetic foot care, especially with the increased risk of infection while on immunosuppression medication. Hyperlipidemia should be aggressively treated and is discussed elsewhere in this issue. Yearly screening

for microalbuminuria should be undertaken, even in renal transplant recipients, as diabetic nephropathy can reoccur in the renal transplant.[58]

Angiotensin converting enzyme (ACE) inhibitor therapy should be strongly considered to delay or prevent the onset of diabetic nephropathy in all diabetic solid organ transplant recipients. Therapy with ACE inhibitors and aggressive control of hypertension can prevent or even reverse microalbuminuria in diabetic patients.[59] In addition to the renal-protective effects, therapy with ACE inhibitors may dramatically lower the cardiovascular mortality for high risk patients.[60] Care must be taken, however, to monitor for possible complications of ACE inhibitor or angiotensin II receptor blocker therapy. Hyperkalemia is a common side effect of CSA and TAC therapy in transplant recipients and can be exacerbated by ACE inhibitors. In addition, ACE inhibitors may precipitate acute renal failure in the patient with native or transplant renal artery stenosis or with underlying renal insufficiency. With appropriate monitoring, these reversible adverse effects can be caught early, and concerns regarding their occurrence should not prevent ACE inhibitor therapy in the diabetic transplant recipient.

Conclusion

In summary, patients with solid organ transplants are at high risk for developing PTDM. CSA, TAC and corticosteroids promote diabetes by inducing insulin resistance. The calcineurin inhibitors are, in some patients, directly toxic to pancreatic beta cells. Patients should be frequently screened for diabetes after transplantation and patients with pre-existing diabetes should be carefully monitored for worsening control. Pharmacologic therapy for patients with diabetes must account for changes in renal and hepatic function and the diabetogenic effect of medications. Early diagnosis of diabetes, aggressive glycemic management and careful attention to health maintenance can potentially reduce the incidence of cardiovascular and infectious complications, as well as graft loss.

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