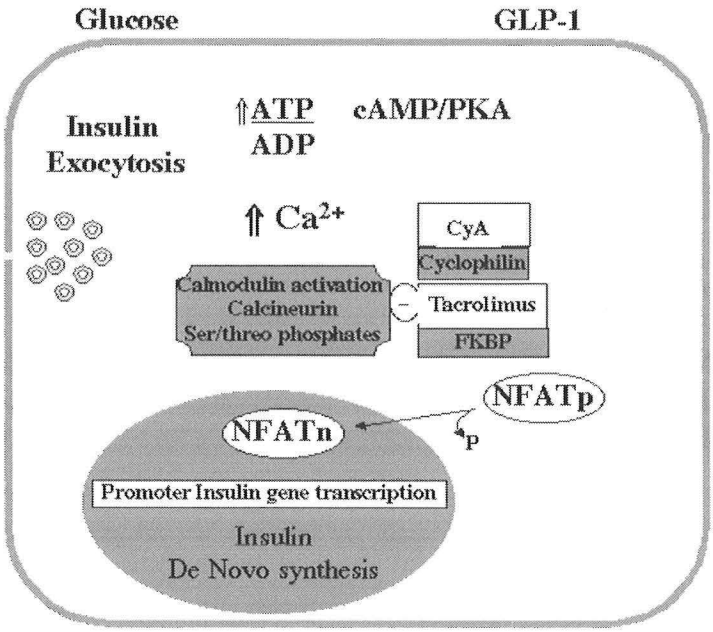
Post Transplantation Diabetes Mellitus



Internal Medicine Grand Rounds
University of Texas
Southwestern Medical Center at Dallas
May 22, 2003

This is to acknowledge that Dr. Pablo Mora has not disclosed any financial interest or other relationships with commercial concerns related directly to this program. Dr. Mora will not be discussing off label use in his presentation.

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May 22, 2003

Areas of interest:

Diabetes Mellitus in the underserved populations
Insulin Delivery systems
Post renal transplantation Diabetes Mellitus

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Introduction

Transplantation Medicine has grown to be a daily part of today's medical practice and with the introduction of modern immunosuppresion agents and protocols, improvements in graft survival has been achieved.
The metabolic consequences of therapy with these agents are many and among them, post transplantation Diabetes Mellitus has become extremely common and is the focus of this discussion.

The purpose of this Grand Rounds are:

1-To review the principles of diagnosis and classification of diabetes mellitus developing after solid organ transplantation

2-To examine the effects of chronic organ failure and immunosupression protocols on glucose homeostasis

3-To formulate therapeutic strategies for diabetes in the post-transplant recipient

Definitions:

Diabetes Mellitus

In 1997, the Expert Committee on the Classification and Diagnosis of Diabetes Mellitus of the American Diabetes Association (ADA) recommended a new set of diagnostic criteria for diabetes. One major change in the diagnostic criteria was the category of diabetes, which ADA defined as a fasting plasma glucose (FPG) level of 126 mg/dl or more. The same committee also recommended the use of FPG over an oral glucose tolerance test (OGTT).(8)
On the other hand, the 1998 Provisional Report of a World Health Organization (WHO) consultation suggested using the levels 126 mg/dl fasting and 200 mg/dl at 2-hour post glucose load as diagnostic criteria for Diabetes Mellitus.(5)

Post Transplantation Diabetes Mellitus(PTDM)

It can be defined as Diabetes Mellitus developing in any patient without history of diabetes before transplantation, who has sustained hyperglycemia that meets the current diagnostic criteria by the American Diabetes Association or the World Health Organization.
PTDM can then be assigned to the same category as Type 2 Diabetes Mellitus since it has both a component of insulin resistance and an insulin secretion defect.
It may not be possible to extrapolate from data for type 2 diabetes for the development of future diabetes-related complications of Post Transplantation Diabetes because of difference in the natural history of these disorders. (134,135)

Incidence and risk factors for PTDM

Posttransplantation diabetes has been associated with the following risk factors;

- Age
- Non-white ethnicity
- Inmunosuppression
    - Glucocorticoid therapy for rejection
    - Inmunosuppresion with High dose of cyclosporine
    - Inmunosuppresion with tacrolimus

There is conflicting evidence regarding the importance of:

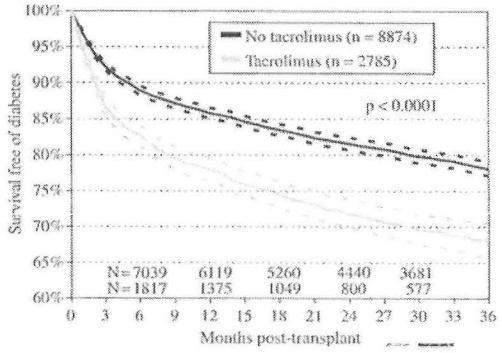
- Family history of diabetes
- Impaired glucose tolerance before transplantation
- BMI
- Vital status of the organ donor

Nonwhite transplant recipients are at higher risk of PTD because of a greater risk of diabetes and the differential diabetogenic effect of immunosuppressive agents.(38,134,135) Glucocorticoids, cyclosporine, and tacrolimus have been shown to impair insulin secretion and insulin action through dose-dependent, complex, and imperfectly understood mechanisms.(1,4,25,34,53,61,77,78,86,105,132,147,161,171,177,185,207,209,220) There has been several attempts to develop indexes to predict post transplantation diabetes or to recognize high risk individuals but no randomized control trial using any intervention categorizing the recipients into low and high risk individuals has been reported. (35,68,143,145)

Kasiske et al, using data from the United Renal Data System identified 11659 Medicare beneficiaries who received their first kidney transplant in 1996-2000, confirming the observation that immunosupression using tacrolimus versus cyclosporine-based protocols is one of the most important single risk factor for the development of PTDM for this population. (92)

Increased incidence of PTDM with Tacrolimus vs Cyclosporin immunosupression

United Renal Data System



Kasiske, B et al Am J Transplant 3:178-185,2003

Several series of patients who developed Diabetes Mellitus after liver or heart transplantation has been reported. The incidence tends to be lower for the liver recipients and very frequently Diabetes Mellitus resolves before the first year after surgery. (35,134, 135, 143,145,165)

Dallas's experience:

Meyer, Sherri et al (personal communication) studied one hundred and sixteen medical records from six renal transplant centers (five in Dallas one from San Antonio) . The purpose of this study was to establish a predictive model using univariate and multivariate analyses to evaluate risk factors in the development of PTDM. Pre-transplant factors such as age, gender, race, pre-transplant body mass index (BMI), reported family history of DM, history of gestational DM, duration of dialysis, and use of steroids pre-transplantation, were evaluated to determine if an association exists between any identified factors and an increased risk of development of PTDM. Post-transplant factors included one year post-operative BMI, hyperglycemia during the immediate post-transplant phase, immunosuppressive regimens, organ donor source, recipient HLA types, hospitalizations/duration, number of rejection episodes, occurrence of acute tubular necrosis(ATN) and CMV (cytomegalovirus infections) were evaluated to determine their potential relationship to the development of PTDM. Bimonthly blood glucose levels and use of pharmaceuticals agents for glycemic control were used to categorize patients with and without PTDM. Methodology was a 12 month retrospectively review since the peak onset of PTDM is reported to occur within the first year post-transplant.

The first patients entering the study were transplanted in January 1999 and the final entrants were transplanted in February 2000. A predictive model was developed using both univariate and multivariate logistic regression. Significant univariate predictors of outcome were submitted to a stepwise reduction technique and resulted in a final model involving the significant variables. The significant univariate variables (elevation of one pre-transplant BG, pre transplant BMI, presence or absence of reported family history of DM, family history severity score, HLA types DR1 and B49 were submitted to a forward stepwise procedure in logistic regression. Although the first tacrolimus dose was significant with the diagnostic group for PTDM, this immunosuppressive medication was used in only 63.2% of subjects, and therefore could not be included in the logistic regression analysis. The final model was composed of those variables having the strongest relationship with the outcome. These consisted of chi-square: -8.913+ 0.033 (pre transplant BG) + 0.112 (pre transplant BMI) + 0.221 (family history score) + 1.555 (DR1). This equation accounts for < 38% of the variability of the outcome measure. Using this equation, 97.7% (specificity) of the non-diagnostic group, and 47% of the diagnostic group were correctly classified.

Is PTDM a result of chronic organ failure?

Methodology of assessment of insulin secretion and insulin resistance

The euglycemic insulin clamp and the intravenous glucose tolerance test (IVGTT) are standard methods for the measurement of insulin resistance in research, but they are impractical in clinical practice and are difficult to perform in population based studies. The hyperinsulinemic-euglycemic clamp measures insulin resistance (IR) directly and is considered the "gold standard"; the homeostasis model assessment (HOMA) requires only fasting glucose and insulin concentrations. (12,15,50,69,110,125,126,202) This mathematical model is based on the theory of a negative feedback loop between the liver and beta cells that regulates both fasting glucose and insulin concentrations and can be used to estimate

pancreatic beta-cell function an degree of IR. This method has been studied in several clinical scenarios including non diabetic population, different age groups and ethnic minorities. This methodology has also been investigated as a index to predict cardiovascular event risk both in normal and impaired glucose tolerance individuals.(14,15,43,50,67,85,93, 98,117,120,140,153,192,201,218,222)
Several other individual variables, such as family history of diabetes, BMI, blood pressure (BP), waist and hip circumference, fasting triglycerides, HDL, glucose, insulin, and hepatic enzymes, are known to correlate with insulin resistance . Combinations of variables used to predict insulin resistance have been assessed in a small number of studies, and most studies have assessed prediction in individuals with impaired glucose tolerance (IGT) and diabetes.(187)
The majority of these methods have been replicated and validated in transplant recipients but there is no consensus about the best method to use.(32,26,77,78) By far, the most frequently used is the HOMA model probably because of simplicity when studying populations like this in whom vascular access may be a problem.

Chronic renal failure as an insulin resistant state

Uremia is typically associated with impaired glucose metabolism. Some patients manifest fasting hyperglycemia in response to oral and intravenous glucose loads, while other are able to maintain normoglycemia by raising plasma insulin levels. Tissue insensitivity to insulin is of primary importance, but alterations in insulin degradation and insulin secretion also may contribute.(2,6,29,124,150,159,160)
The variable severity of these changes in individual patients explains the variable plasma levels of insulin and glucose that may be seen, both fasting and following a glucose load. Impaired tissue sensitivity to insulin occurs in almost all uremic subjects and is largely responsible for the abnormal glucose metabolism seen in this condition.(29,30,31,66,94,113)
Accumulation of a uremic toxin or toxins and excess of parathyroid hormone (PTH) resulting in abnormalities in phosphate and vitamin D metabolism are thought to be responsible for the insulin resistance. As an example, the observation that tissue sensitivity to insulin can be substantially improved by dialysis is consistent with a role for uremic toxins.
The skeletal muscle seems to be the primary site of insulin resistance.(29)
Impaired insulin sensitivity has also been demonstrated in patients with only mild to moderate reductions in renal function.(51,52)
The degree of tissue insensitivity to insulin directly correlates with maximal aerobic work capacity, indicating that physical training may ameliorate insulin resistance in patient with renal failure.(41)
An analysis of the insulin resistance data from the NHANES III survey suggested that insulin resistance and hyperinsulinemia are present in Chronic Kidney Disease without clinical diabetes and that further studies into the causality between insulin resistance and chronic kidney disease are needed.(21)
There is been a suggestion that the association between end stage renal disease and insulin resistance is the observation of increased liver iron deposition in these individuals, that explains in part the hepatic insensitivity to insulin action .
Emerging evidence has disclosed unsuspected influences between iron metabolism and type 2 diabetes . The relationship is bi-directional-iron affects glucose metabolism and viceversa. Oxidative stress and inflammatory cytokines influence these relationships, amplifying and potentiating the initiated events,(49)
Anemia is an almost universal finding in patients with ESRD. Intravenous administration of iron to dialysis patients may have an association with higher mortality in the setting of cardiac disease. Other potential risk of high dose of IV iron include malignancies and infections. Moreover, improvements in the hematocrit with high doses of intravenous iron

may lead to a diagnosis of" functional iron deficiency" without addressing multiple other conditions which are associated with insulin resistance and which may require specific therapy.

Role of chronic hepatitis C infection/cirrhosis as a risk factor for the development of T2DM.

A higher prevalence of type 2 diabetes mellitus has been reported with hepatitis C virus infection.(199)

This is a report of the prevalence of T2DM reported in the Third National Health and Nutrition Examination Survey -NHANES III (1988-1994) . Of the 9841 persons evaluated, 8.4% had T2DM and 2.1 % were anti-HCV positive. T2DM occurred more often in persons who were older, were nonwhite, had a high BMI and had low socioeconomic status. T2DM was less common in persons who acknowledged previous illicit drug use. After adjustment for these factors, persons 40 years of age or older with HCV infection were more than three times more likely than those without HCV infection to have T2DM (adjusted odds ratio, 3.77 (95% CI, 1.80 to 7.87). No increase in the prevalence of T2DM was found among persons with hepatitis B virus infection, even after adjustment for variables associated with both T2DM and hepatitis B virus infection.(130)

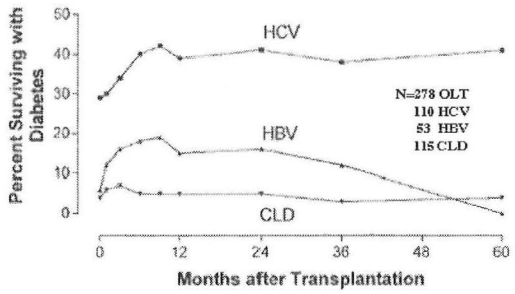
Several studies have been reported trying to establish a potential relationship between HCV infection and diabetes: (17,123,154)

Association of HCV and development of PTDM after transplantation

A high prevalence of DM has been reported in patients with chronic hepatitis C virus infection in the renal and liver transplant recipients (58,173,219)

BIGAM et al studied 278 liver transplant recipients in Toronto, Canada, whose original cause of liver failure was HCV infection (110 patients), hepatitis B virus infection HBV 53 patients) and cholestatic liver disease CLD(115 patients) . The pre transplantation prevalence of diabetes was higher in the HCV group (29%) compare with the HBV (6%) and CLD (4%) groups ($p<0.001$). The prevalence of diabetes remained higher in the HCV group, 1 year after transplantation : 37%, 10% and 5% in the HCV, HBV and CLD groups, respectively ($p<0.001$). The cumulative steroid dose during the first year of transplantation was significantly lower in the HCV group compared with the CLD group. Multivariate analysis revealed that HCV-related liver failure ($p=0.002$) pre transplantation diabetes ($p<0.0001$) and male sex ($p=0.019$) were independent predictors of the presence of diabetes 1 year after transplantation. The high prevalence of diabetes persisted in the HCV group, with 41% diabetic at 5 years. The majority of patients with diabetes mellitus (89%) required insulin therapy after transplantation.(12)

Hepatitis C related cirrhosis as a predictor of PTDM

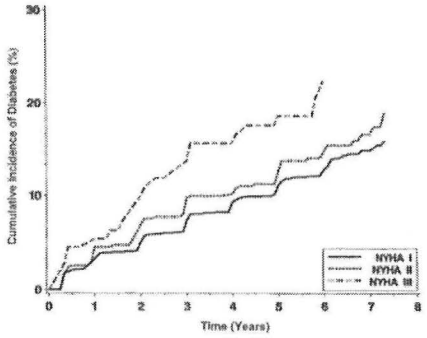


Bigani, D et al Hepatology 32: 87-90,2002

Insulin resistance in Chronic Heart Failure

Chronic heart failure describes a condition of progressive deterioration of myocardial function seen in a variety of diseases affecting the heart. Ten patients with CHF and 10 normal controls were studied using the intravenous glucose tolerance test. The data showed that patients with chronic stable heart failure are insulin resistant with both fasting hyperinsulinemia and a hyperinsulinemic response to a glucose load.(190)

Heart Failure Functional Class and development of DM



Tenenbaum, A et al Am J Med 114:271-275,2003

Tenenbaum et al followed patients with a history of myocardial infarction who had been screened for the development of of categorical hyperglycemia(diabetes). Patients, according to the New York Heart Association criteria for heart failure, who had NHYA class III were twice as likely to develop fasting hyperglycemia or >126 mg/dl compared with those in classes I or II. (194) Several studies that sought to determine whether patients with heart failure are in fact more insulin resistant that those without it, have left little doubt that heart failure is an "insulin resistant state".(63)

Role of current immunosupression protocols in the pathophysiology of PTDM

Immunosuppresion agents:

The immunosuppressive agents that are available can be classified into two broad categories according to origin: xenobiotic agents and biologic agents.(206)
The immunosuppressive drugs available for renal transplant recipients will be classified as:
a- Xenobiotics:

Inhibitors of cytokine transcription (cyclosporine, tacrolimus)
Inhibitors of growth factor signal transduction (sirolimus, leflunomide)
Inhibitors of nucleotide synthesis (mycophenolate mofetil, azathioprine, brequinar, mizoribine, leflunomide)
Inhibitors of cell differentiation/maturation (deoxyspergualin)

b- Biological agents:

Polyclonal antilymphocyte preparations
Monoclonal antibodies

Mechanism of action of xenobiotic immunosuppressive agents:

a) Inhibitors of cytokine transcription.

Cyclosporine, tacrolimus and sirolimus bind a group of cytosolic proteins called immunophilins. Cyclosporine binds to the immunophilin cyclophilin, and tacrolimus and sirolimus bind to the immunophilin FKB12. The drug-immunophilin complex is the active intracellular inhibitor. Cyclosporine and tacrolimus are inhibitors of T-cell cytokine transcription, whereas sirolimus inhibits the transduction of signals derived by cytokines. T-cell activation is initiated when the T-cell receptor binds alloantigen that is presented in the the context of MHC (major histocompatibility complex) by an APC (Antigen presenting cell) and the T cell also receives an accessory signal from a cell surface molecule on an APC (second signal). The CD4 or CD8 molecule also bind to the MHC molecule. Conformation changes occur in the CD3 complex and others structures, which result in phosphorylation and activation of a a series of protein tyrosine kinases. Two principal effector pathways are activated: phospholipase C and Ras-map kinase. Phospholipase C lyses the membrane lipid phophatidyl inositol to release inositol triphosphate and diacylglycerol. Diacylglycerol activates protein kinase C, which stimulates synthesis of the transcription factors jun and fos, which form activator protein 1. Inositol triphosphate increases levels of cytoplasmic calcium, which activates the calcium calmodulin-dependent phosphatase calcineurin. The removal of phosphate groups from the nuclear factor of activated T cells (NFATp) allows the NFATp to undergo translocation into the nucleus and to bind to promoter regions in the gene for interleukin (IL)-2, ultimately leading to IL-2 secretion.
The complex of cyclosporine-cyclophilin or of tacrolimus-FK506 binding protein (FKBP) binds to calcineurin and inhibits its phosphatase action. As a consequence, activation of IL-2 gene transcription does not occur, and there is no T-cell division or differentiation. The NFAT is found in T-cells, accounting for the specificity of cyclosporine and tacrolimus to inhibit T-cell activation. Cyclosporine A may exert part of its immunosuppressive action by stimulating production of transforming growth factor beta. Among the properties of TGFB are inhibition of IL-2 stimulated T-cell proliferation, inhibition of generation of cytotoxic T cells, and stimulation of tissue fibrosis. TGFB may be the mediator of immunosuppression and fibrosis associated with the use of cyclosporine.
Cyclosporine A is a cyclic endecapeptide derived from Fungi imperfecti (Deuteromycoya) and its immunosuppressive properties were discovered in 1972. Cyclosporine has been one of the most important landmarks in the field of transplantation of modern medicine.

Tacrolimus (formely known as FK506) is a cyclic macrolide that originally was isolated from a soil actinomycete, and its immunosuppressive were discovered in 1985. Tacrolimus exerts immunosuppression by binding intracellularly to immunophilins, termed FKBPs. The complex of tacrolimus-FKBP12 bind and inhibits the activity of calcineurin in a manner analogous to the blocking of dephosphorylation of NFAT and T-cell activation from cyclosporine-cyclophilin.

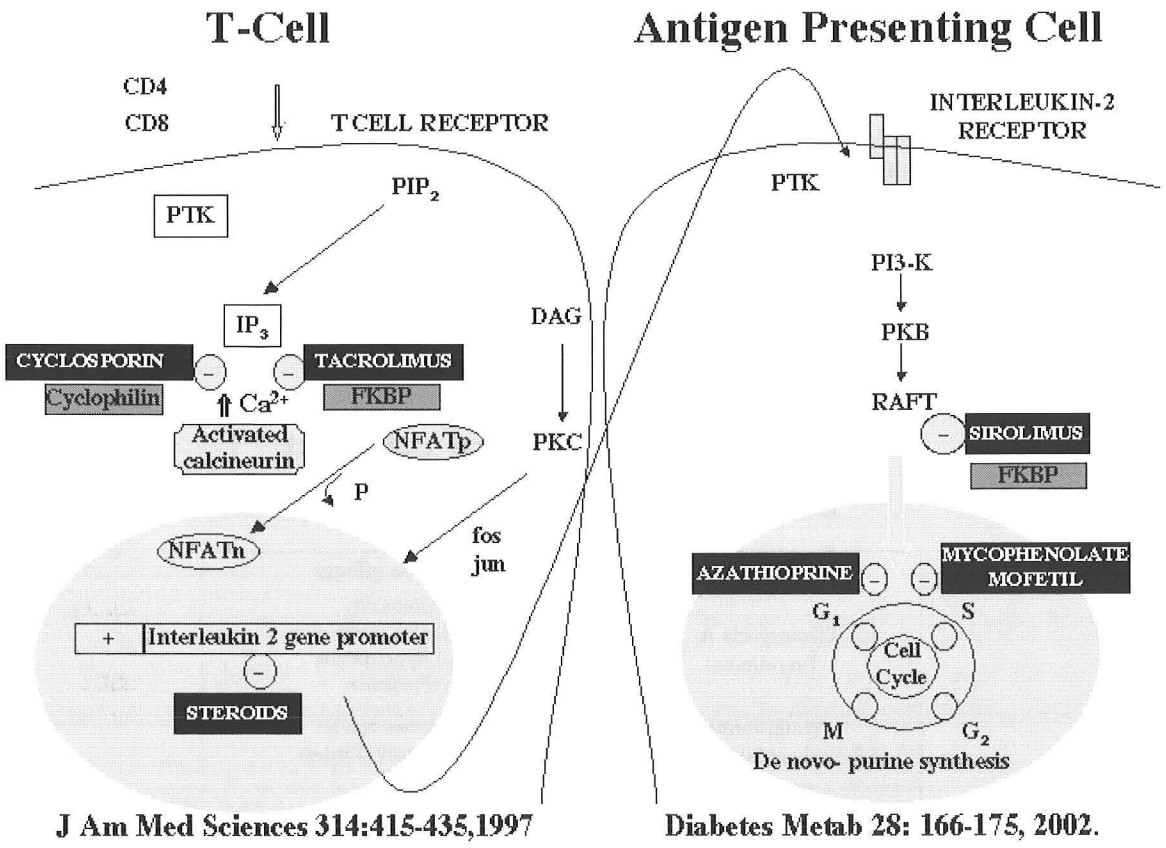
b) Inhibitors of Growth Factor Signal Transduction.

Sirolimus (formerly known as rapamycin) is a cyclic macrolide antibiotic produced by the Streptomyces hygroscopicus; its immunosuppressive properties were discovered in 1977. Sirolimus also binds to to FKBPs, but differently from tacrolimus and cyclosporine, sirolimus does not inhibit calcineurin. The sirolimus-FKBP complex exerts immunosuppressive action by interaction with an effector protein. Sirolimus prevents cell cycle progression from G1 phase to S phase, even after T-cell stimulation by cytokines. Sirolimus binds to a different immunophilin than Cyclosporin A (CsA), and the combination of the two immunosuppressive agents offers the potential advantage of synergism, resulting in lower doses of CsA or a reduction/discontinuation of steroids has been possible in some renal transplant recipients treated with sirolimus. Sirolimus has a different side effect profile, characterized more by thrombocytopenia, leucopenia and hyperlipidemia.

c) Inhibitors of Nucleotide Synthesis.

Proliferation of lymphocytes necessitates purine and pyrimidine nucleotides for DNA synthesis. Several immunosuppressive agents exert action by inhibition of nucleotide synthesis and by preventing lymphocytes from entering the S phase. Azathioprine was the first immunosuppressive agent widely used in transplantation, and it interferes with purine synthesis. The new agents, mycophenolate mofetil and mizoribine, also interfere with purine synthesis. Brequinar sodium and leflunomide are inhibitors of pyrimidine biosynthesis. Mycophenolate mofetil has been approved by the FDA for prevention of acute rejection and is part of the standard immunosuppression regimen in many centers. The most common side effects are gastrointestinal, including nausea, vomiting and diarrhea. There has been higher incidence of CMV tissue invasive disease(GI tract). Other reported side effects included leucopenia, thrombocytopenia, anemia and lymphoproliferative disorder post-transplantation. The introduction of azathioprine in the early 1960's allowed for transplantation of kidneys from donors who were not genetically identical. Most of the early immunosuppressive regimens in renal transplantation incorporated azathioprine. Before the introduction of CsA, the addition of azathioprine to steroids resulted in higher rates of renal graft survival. Azathioprine still is used in some patients who received transplants many years ago. The addition of azathioprine to a CsA-based immunosuppressive regimen does not appear to result in significant improvement in long term graft survival for the majority of patients.

To review the specific impact of the Cyclosporine A, tacrolimus, sirulimus , mycophenolate mofetil as well as biological agents for short and long term graft survival (including treatment of acute and chronic rejection) for solid organ transplantation, is beyond the scope of this Grand Rounds.



Modern immunosupression protocols

In general, choices of immunosuppressive therapy have to be made in three different stages: induction, antirejection and maintenance therapy. Induction therapy is applied early after transplantation and aims to reduce early episodes of rejection and to optimize the opportunities for log-term graft survival. Antirejection therapy is intense and concentrated in a limited period of time; emphasis is on reversing a state of heightened immunologic activity. Maintenance therapy is necessary for long periods, and its aim is to prevent rejection and damage of the allograft.

Most transplant recipients receive steroids and cyclosporine immediately before or after transplantation . Some center substitute tacrolimus for cyclosporine. Induction therapy using polyclonal antibodies or monoclonal antibodies is effective but carries a higher risk of complications and is very expensive. Usually is reserved for patients at risk for delayed function and for recipients at high immunologic risk, such as recipients of a repeat transplant or patients who are highly sensitized.

Steroids have been the first-line agent for the treatment of acute rejection for many years and are still considered the first choice in most centers. Polyclonal and monoclonal antibodies can be more effective for a first episode of acute rejection, but because of the concern about their toxicity, they are reserved usually for the steroid-resistant episodes of rejection. Mycophenolate mofetil and tacrolimus have been effective in refractory episodes of rejection and are considered adequate alternatives in refractory rejection.

CsA or tacrolimus are the foundation of the maintenance regimen for most renal transplant recipients. Mycophenolate mofetil rapidly has gained acceptance in the transplant community and is now used as maintenance therapy for most new renal transplant recipients in the USA. Steroids still are used by most transplant centers in the USA, although many

centers in Europe avoid steroids as part the their immunosuppression or discontinue them early after transplantation. There are studies underway to determine how to best identify which patients can be treated safely without steroids. Azathioprine is part of the maintenance therapy of patients who received renal transplants in the past, but mycophenolate mofetil has taken its place as maintenance therapy for new transplant recipients. Sirolimus has been very effective in early clinical trials, and the absence of nephrotoxicity makes it a very attractive agent for long-term use in renal transplantation.(152,206)

Metabolic effects of current immunosupression drugs

The use of cyclosporine and tacrolimus in transplantation has markedly reduced the risk of side effects of immunosupression, and dramatically prolonged graft survival and recipients' life expectancy (11,116,204,205)

Side effect profile of current immunosuppressive agents

Drug	Main side effects
Cyclosporin A Tacrolimus	Nephrotoxicity Altered glucose metabolism Arterial Hypertension Dyslipidemia
Azathioprine Mycophenolate mofetil	Bone marrow aplasia Gastrointestinal/Diarrhea
Sirolimus	Dyslipidemia Thrombocytopenia
Corticosteroids	Altered glucose metabolism Arterial Hypertension Dyslipidemia Osteoporosis

Diabetes Metab 28: 166-175, 2002.

Association between the steroids and diabetes mellitus

The first description of a diabetic state induced by steroid was done by Ingle (82) in 1941. One of the first description in man is the report by Bookman (16) in 1953 of five cases of diabetes induced by treatment of rheumatological disorders (two patients), sarcoidosis and phemphigus . Many other reports followed after this one (128)

The effects of steroid on glucose metabolism have been extensively reviewed and decreased glucose utilization and increased hepatic glucose production have been well documented as the primary defects (24,146). This concept was used to improve the yield of glucose challenge to diagnose diabetes in a more sensitive way.(44)

These concepts have been used to propose an animal model of insulin resistance in the rat using low dose dexametasone. (178)

In the early transplant era, steroid were cleared identified as a pathogenic (risk) factor for diabetes in renal transplant recipients.(27,212)

After the introduction of cyclosporine, steroid still remained a risk factor for the development of hyperglycemia after transplantation, particularly at high doses. (7,56)

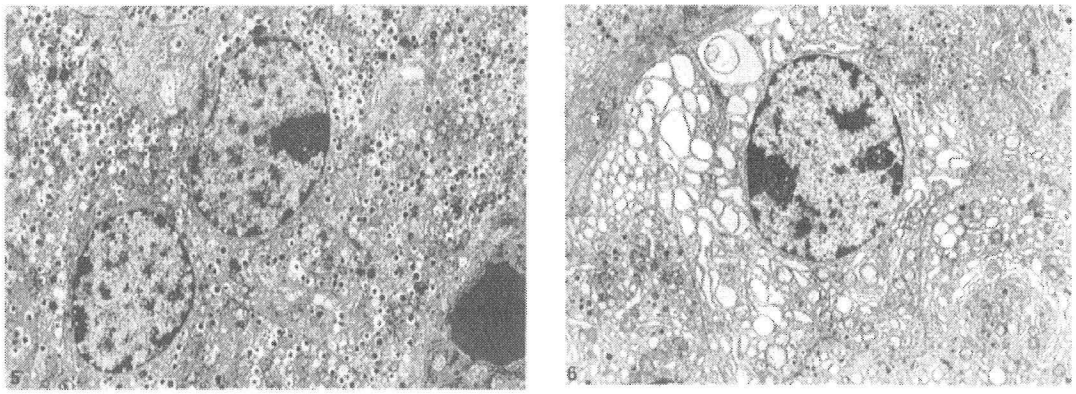
Calcineurin Inhibitors and Post Transplantation Diabetes mellitus

In general, the toxicities of tacrolimus and cyclosporine are similar, mostly incidence of lymphoproliferative disease, nephrotoxicity, neurotoxicity (more common with FK506),

gastrointestinal disturbances (FK506>CyA), hypertension/Dyslipidemia (CyA>FK506) and hirsutism/gingival hyperplasia (rare with FK506).
There has been numerous reports on the effects of the choice of cyclosporine versus tacrolimus as main immunosupression agents that indicate that the latter is associated with greater rate of Post transplantation diabetes in renal, liver and heart transplant recipients.(48, 51,52,60,62,90,100,101,108,151,157,176,193,203,217,221)
There is a large amount of data accumulated on the metabolic effects of cyclosporine and tacrolimus in glucose homeostasis, specifically to insulin secretion and insulin sensitivity in animal models (9,18,19,37,39,45,46,57, 59,65,70,81,84,91,97,108, 131,136,137, 138,168, 172,182,188,189,194,198,208,210,213,214,215,216) and humans(62,86,87,100,101,118, 119,164,166).
It is noteworthy, however, that these effects of cyclosporine on beta cell function have been mainly observed in vitro, and that in vivo studies have given controversial results

The deleterious effects of of cyclosporine and tacrolimus on beta cells are morphologically characterized by degranulation, vacuolization, swelling of rough endoplasmic reticulum, Golgi apparatus and mitochondria. (10,71,141)

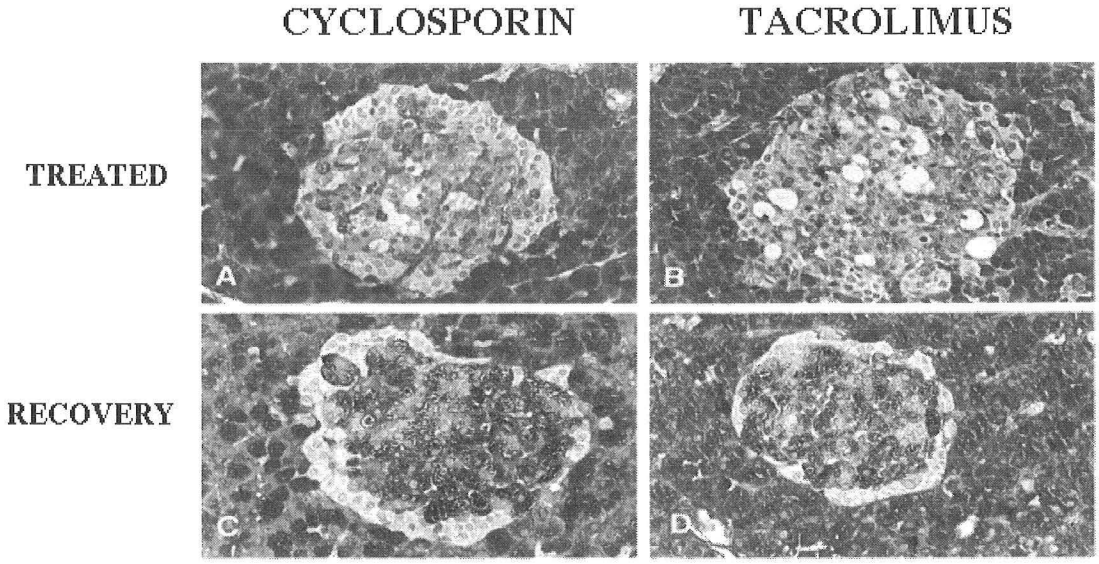
Ultrastructural effects on rat islet cells by Cyclosporin



NORMAL CYCLOSPORIN

Bani-Sacchi, T et al Transplantation 49:982-987, 1990

Morphological changes of islet cells in Tacrolimus/Cyclosporin treated rats

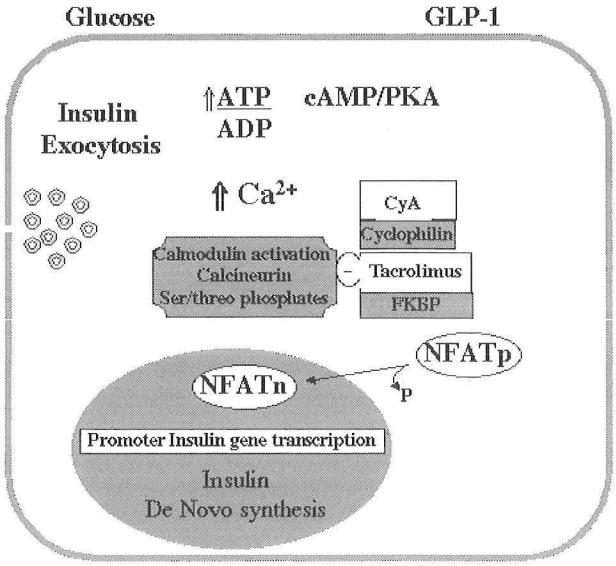


Hirano, Y et al Transplantation 53: 889-894,1992

Similarities on the beta cell and T-cell signaling pathways for gene activation

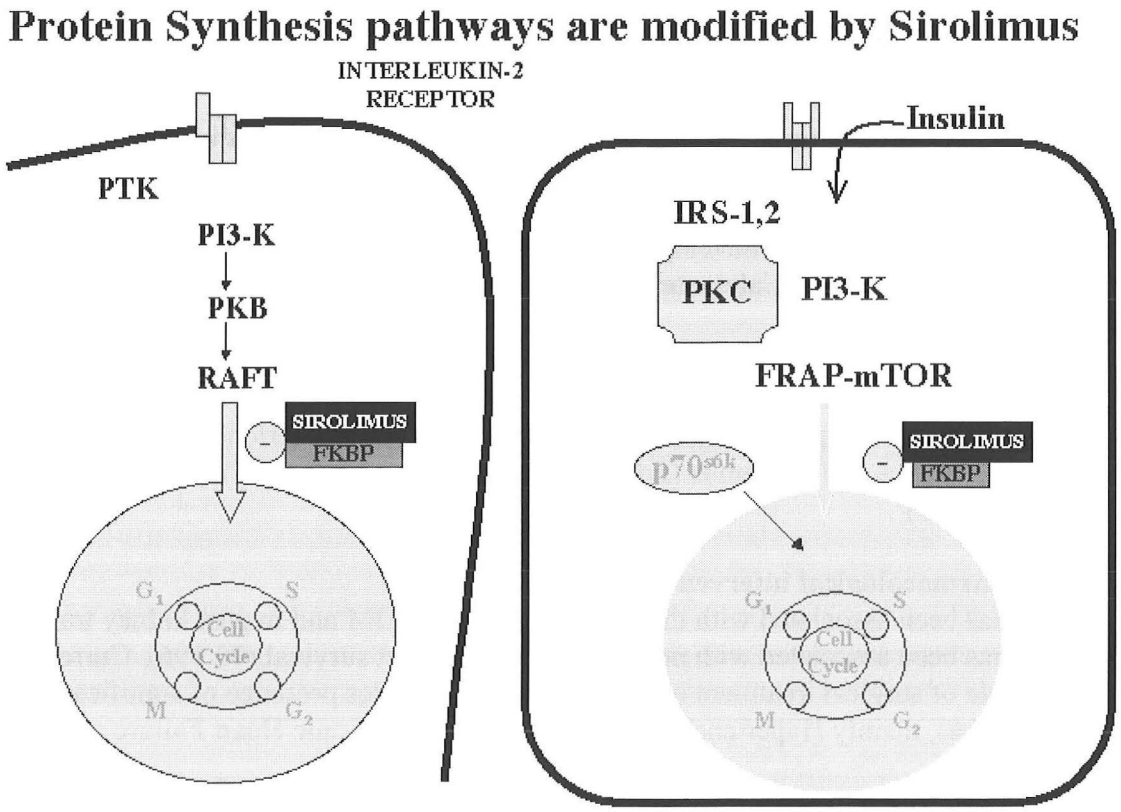
There is a striking similarity between the signaling pathways in the immune cells and the beta cell of the pancreas.(107)

Selective insulin signaling pathways modified by immunosuppresives agents



Lawrence, MC et al Diabetes 51: 691-698,2002

The observation has been made that the effects of CsA and tacrolimus on insulin secretion appear to be more important than those on insulin sensitivity.(116)
Upon cyclosporine treatment, proinsulin biosynthesis and insulin release are reduced. The latter effect seems to be located in distal steps of the stimulus-secretion coupling of glucose-induced insulin release. In this regard, the drug is able to impair the intracellular transport of the hormone from the sites of synthesis to the secretory granules. Indeed, exposure of human pancreatic islets to cyclosporine induces inhibition of insulin release and a concomitant increase of the residual insulin content. This latter finding can explain the observation of recovery and hypersecretion of insulin after withdrawal of short-term cyclosporine therapy.
At the molecular level, the drug acts through calcium and cAMP dependent pathways, which involves the calcium-modulin dependent phosphodiesterases and the regulatory proteins Gs and Gi. (42,109,122,139,179,181)
The drug seems to be able to inhibit insulin gene transcription, leading to a decline of insulin mRNA levels and insulin synthesis. An interesting hypothesis, is that tacrolimus, by its binding to FK506BP, renders this latter protein less available for association with cyclic ADP-ribose , that is a second messenger for calcium mobilization, this would reduce the amount of cytosolic calcium, that is essential for insulin release.(162,194,195)
Another pathway of interest has been the mammalian target of rapamycin (mTOR), a serine and threonine protein kinase that regulates numerous cellular functions, in particular protein translation.(83)
Phosphorilation mediated by mTOR controls both the translational repressor eukaryotic initiation factor 4E bnding protein-1 and p70S6 kinase, early events in the translation initiation process.(127,187)



J Am Med Sciences 314:415-435,1997 Diabetes Metab 28: 166-175, 2002.

Principles of therapy

Standards of care for patients with Diabetes Mellitus (American Diabetes Association)should be applied to all patients who develop PostTransplantation Diabetes.(8)
These standards include:

- Activity,Exercise and Life style interventions
- Medical Nutritional Therapy
- Glycemic control
- Blood pressure control
- Lipid control
- Prevention and management of diabetic complications

There has been also specific recommendations on nutritional therapy for renal transplant recipients. (40)
The majority of pharmacological agents currently approved for the treatment of Type 2 Diabetes can be used in the post-transplant recipient, with two notable exceptions: metformin and acarbose for the renal impaired and with caution , the thiazolidinediones in the chronic heart failure and liver insufficient recipients.
Agents such as sulfonylureas have been studied in these patients and appear to be safe and lack drug-drug interactions.(170)

Immunosuppression modification

1-Steroids

Modification of steroid component of the current protocols can been proposed, specifically related to the dose of prednisolone administered, as well taking into consideration the age of the recipient with special care for African American individuals.
(72,73,74,200)
Several attempts have been made to try to minimize the impact of these agents on glucose homeostasis, including conversion to deflazacort (95) , reduction of drug (72,73,74,80) or alternate day dosing (28)

2-Calcineurin Inhibitors

There has been several reports trying to modify glucose abnormalities by either rapid withdrawal of cyclosporine (65,210,211), conversion from tacrolimus to cyclosporine (106) or rapid reduction of tacrolimus dosing (51,52)
There has been recently the development of immunosupression strategies that avoid corticosteroid and rely on Calcineurin inhibitors with less effects on insulin secretion such as Sirolimus:

- Induction therapy with polyclonal antithymocyte globulin + Calcineurin Inhibitor + mycophenolate mofetil
- Induction therapy with monoclonal antibodies against Interleukin 2 in addition to Tacrolimus and Sirolimus (Edmonton protocol for Islet Cell Transplantation)(99, 152,169)

3-Non pharmacological interventions

Obesity has been associated with the development of T2DM and in post kidney transplant patients has been associated with negative impact on graft survival.(79,196) Current criteria for the role of surgical treatment of morbid obesity includes presence of significant complications, mainly Hypertension, Diabetes Mellitus, Chronic Heart Failure and a BMI > 35 kg/m2.
Marterre reports the use of a Roux-en-Y gastrojejunostomy to a 30 ml stapled gastric pouch, created with the jejunojejunostomy (both loops) 80-120 cm from the ligament of Treitz, in three morbidly obese (200-260% IBW) patients 6-8 years following kidney transplantation.

By 12 months post surgery , weight loss leveled off at 100-150% IBW. Both patients who developed PTDM, had complete resolution within 9 months and on average the patients required 3 less antihypertensive medications and 2 of the patients were off medications at the end of the observation period (12 months). Of note, cyclosporine dose requirements increase after surgery as a consequence of defunctionalized intestine.(121)

3-Guidelines from a recent consensus Conference

A recent review focused on the management of this disorder, and emphasize on the importance on both prevention and treatment issues.(11)

On February 19, 2003 an International Expert Panel Meeting was held in Barcelona, Spain and the Proceedings are currently in press for publication. These guidelines outline the rationale and recommended steps for managing patients who develop diabetes after transplantation in order to minimize the impact of the disease.

The key aims for managing patients were define as:

- Resolve the symptoms of diabetes through adjustment of immunosuppressive therapy
- Prevent complications of diabetes through appropriate management of diabetes: monitoring, treatment and patient education.

Diabetes after Transplantation
2003 International Consensus Guidelines

PreTransplant Evaluation	**Screening for Diabetes Risk Factors** **Counseling on weight control, diet, exercise and compliance**
Individualization of Therapy	**Considerations for high risk patients:** **Decrease steroids doses ASAP** **Adjunct treatment with induction Ab** **Consider CsA as CI for maintenance Immunosuppression (switch Tac to CsA)**
Monitoring post-transplant	**FPG** **Weekly for 1st 4 weeks PTx** **3 and 6 mo after Tx** **Annually** **OGTT**

Davidson, J Wilkinson,A Transplantation In press, 2003

Patients with impaired glucose tolerance or impaired fasting tolerance should be identified and treated early as this condition is thought to be a risk for the development of diabetes mellitus (Davidson, J personal communication)

4-Prevention

There has been at least 4 randomized control trials using life style interventions or pharmacological agents to prevent the progression to T2DM of individuals with impaired glucose tolerance (STOP_NIDDM, DIABETES PREVENTION PROGRAM, FINNISH LIFE STYLE INTERVENTION) or history of recent gestational diabetes.(TRIPOD)

There is no evidence of the validity of applying these results to PTDM but future studies can be designed using the same or similar strategies.

5-Patient and graft survival

Several studies have looked into the effects of PTDM on graft survival.(26)
Miles et al reported a 12 year graft survival of 48% for the diabetic individuals compared to 70% in non diabetic individuals (p=0.004) The patient survival was not different for the period of follow up.(133)

5-Cardiovascular risk factor intervention

There are no controlled studies showing as a primary end-point the differences between immunosuppressive agents with regard to the risk of CVD. There is no reason to consider risk factors such as hyperlipidemia, hypertension and diabetes mellitus in transplant recipients differently from the general population. In addition, there are specific transplantation risk factors such as acute rejection episodes and the use of immunosuppressive drugs. (26,47,77,78,180)
Data from the US Renal Data System in 1999 documents that cardiac diseases accounts for 15-36% mortality in all age groups of transplant recipients. (47)
Chronic renal transplant dysfunction, also known as transplant atherosclerosis, is a leading cause of late allograft loss. To date, no specific treatment for chronic renal transplant is available. Although its precise pathophysiology remains unknown, it is believed that it involves a multifactorial process of alloantigen-dependent and alloantigen-independent risk factors. Obesity, PTDM, dyslipidemia, hypertension and proteinuria have all been identified as alloantigen independent risk factors. Notably, these recipient-related risk factors are well-known risk factors for cardiovascular disease, which cluster within the insulin resistance syndrome in the general population. Insulin resistance is considered the central pathophysiologic feature of this syndrome. It is therefore tempting to speculate that is insulin resistance that underlies the recipient-related risk factors for chronic renal transplant dysfunction.(32,33)

Summary

The development of potent pharmacological immunosuppressants allowed successful transplantation of allograft kidneys, essentially revolutionizing end-stage organ disease care. However, each of these drugs is associated with toxicity and side effects. One of the earliest recognized side effects was an increase in the incident rate of diabetes/glucose intolerance. In the era when high-dose corticosteroids and azathioprine were standard immunosuppression, post-transplant diabetes was called steroid-induced diabetes because of the relationship between steroid dose and development of diabetes. It was hoped that the introduction of the CsA and more recently tacrolimus, which allow transplantation using lower doses of corticosteroids, would result in a decrease of cases of new-onset diabetes. However, the prevalence rates did not decrease, leading to the conclusion that these agents themselves have adverse effects on glucose tolerance. The observation that steroid withdrawal protocols were associated with a lower incidence of diabetes but that the incidence was not zero also suggested that Cyclosporin and tacrolimus have independent effects on pancreatic function or insulin sensitivity. In addition, unfortunately, the increased risk for acute rejection engendered by steroid withdrawal protocols, necessitating high-dose steroid exposure, obviated the benefits of a mild improvement in glucose tolerance. The term for new onset diabetes after transplantation was changed from steroid-induced diabetes mellitus to post-transplant diabetes mellitus(PTDM) and the problem remains significant to this day.(118,119)

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