New-onset diabetes after transplant (NODAT) in renal transplant recipients

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- ***DEFINITION***
- ***EPIDEMIOLOGY***
- ***RISK FACTORS***
- ***CLINICAL impact***
- ***Management***
- ***Treatment***

NODAT

- New-onset diabetes after transplant (NODAT) is associated with increased mortality and morbidity and, in particular, higher rates of cardiovascular disease and infection, which are the leading causes of death in renal transplant recipients.

DEFINITION

- Symptoms of diabetes plus random plasma glucose ≥200 mg/dL (11.1 mmol/L). Symptoms include polyuria, polydipsia, and unexplained weight loss.
- Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). An abnormal fasting blood glucose should be confirmed on another day.
- Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT).

Subdiabetic hyperglycemia also called "prediabetes

- impaired fasting glucose and/or impaired glucose tolerance and is diagnosed by a fasting plasma glucose between 100 and 125 mg/dL (5.6 and 6.9 mmol/L) or a two-hour plasma glucose between 140 and 199 mg/dL (7.8 and 11.0 mmol/L) during an OGTT, respectively, according to ADA guidelines.
- The two-hour OGTT is more sensitive than the fasting blood glucose for detecting subdiabetic hyperglycemia

HbA1c

- After three months posttransplant, a HbA1c ≥6.5 percent can be used to diagnose diabetes by ADA criteria, with a HbA1c of 5.7 to 6.4 percent consistent with prediabetic state .

EPIDEMIOLOGY

- The reported incidence of NODAT is variable and must be interpreted in the context of definition used, time from transplant, study population, and immunosuppressive agents used for individual studies.
- studies that use the current criteria for diagnosis suggest that up to one-third of nondiabetic kidney transplant recipients develop persistently impaired glucose metabolism by six months posttransplantation.

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Frequency and risk factors for posttransplant diabetes mellitus in Iranian renal transplant patients.

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Published 2009 in Transplantation proceedings •

Posttransplant diabetes mellitus (PTDM) is a frequent complication of renal transplantation. This study was performed to determine the prevalence of and risk factors for PTDM among Iranian renal transplant recipients. In this cross-sectional study, 300 patients were studied in 2007. It included questionnaires with clinical data and blood samples. PTDM was defined as DM without a pretransplant history. The 184 (61.3%) male and 116 (38.7%) female patients of overall mean age of 41.2 +/- 13.5 years were 67.4 +/- 48.6 months after the procedure. PTDM was observed in 24 patients (8%). The mean interval to develop PTDM was 19.9 +/- 31.5 months. The mean age of PTDM patients was significantly higher than non-PTDM patients: 49.4 +/- 13.4 vs 40.6 +/- 13.4

The 184 (61.3%) male and 116 (38.7%) female patients of overall mean age of 41.2 +/- 13.5 years were 67.4 +/- 48.6 months after the procedure. PTDM was observed in 24 patients (8%).

Our study showed an 8% prevalence of PTDM. Mean age, history of recent admissions and HCV infection, as well as mean plasma HDL and LDL levels were higher among PTDM patients.

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Saudi Journal of Kidney Diseases and Transplantation

Original Article

Post-Transplantation Diabetes Mellitus; Frequency and Related Risk Factors: a Single Center Study

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ABSTRACT. Post-transplantation Diabetes Mellitus (PTDM) is a serious complication after organ transplantation, which could lead to cardiovascular morbidity and mortality. The rate of PTDM increased in recent years, probably due to new immunosuppressive drugs such as Tacrolimus. In this study, we retrospectively evaluated the frequency of PTDM and related risk factors in 644 non diabetic patients who underwent renal transplantation. Data was analyzed by chi-square and Fisher's exact test in SPSS software ver11.5. Among 644 patients PTDM developed in 10.2% similar to literature. PTDM was significantly correlated to age (*P* value = 0.000), positive familial history (*P*= 0.003) and HBV infection (*P*= 0.046). In conclusion, PTDM is not uncommon in Iranian patients and a positive family history of diabetes, HBV infection and older age increases the likelihood to develop PTDM.

Introduction

classified into two groups: A group of risk fac-

RISK FACTORS

- Increased age (≥40 to 45 years)
- Obesity (body mass index of ≥30)
- African American race
- Hispanic ethnicity
- Family history of diabetes or gestational diabetes

Transplant-specific risk factors

- Medications — Antirejection medications that contribute to NODAT include glucocorticoids, calcineurin inhibitors, and mammalian (mechanistic) target of rapamycin (mTOR) inhibitors.
- Glucocorticoids — The chronic use of glucocorticoids leads to hyperglycemia among some patients.
- Higher doses of glucocorticoids among renal transplant patients have been associated with the development of NODAT
- However, complete glucocorticoid withdrawal has not been clearly shown to reduce the incidence of NODAT

Calcineurin inhibitors

- Both cyclosporine and tacrolimus increase the risk of NODAT
- Tacrolimus is more diabetogenic than cyclosporine

Calcineurin inhibitors

- Increased tacrolimus levels have strong associations with impaired glucose tolerance and NODAT.
- In one study, levels higher than 15 ng/mL were significantly associated with the development of glucose intolerance and NODAT at one year.
- Both calcineurin inhibitors cause **reversible** toxicity to islet cells and may directly affect transcriptional regulation of insulin expression. Some evidence suggests tacrolimus causes more severe swelling and vacuolization of islet cells.

SIROLIMUS

- Sirolimus — Sirolimus is diabetogenic.
- Conversion to sirolimus from tacrolimus or cyclosporine has been associated with a significant worsening rather than an improvement in insulin resistance.

AZATHIOPRINE/MMF

- Azathioprine and MMF do not have independent diabetogenic effects.
- In one large, retrospective study, the use of azathioprine and MMF was associated with a decreased risk of NODAT (relative risk [RR] 0.84, 95% confidence interval [CI] 0.72-0.97 and 0.78, 95% CI 0.69-0.88, respectively).
- This benefit may be explained by the use of lower doses of glucocorticoids with these drugs, although this is unproven.

STATINs/ACIE/ARB

- The administration of statins and use of angiotensin receptor blockers or angiotensin-converting enzyme inhibitors may be associated with a decreased risk of NODAT .

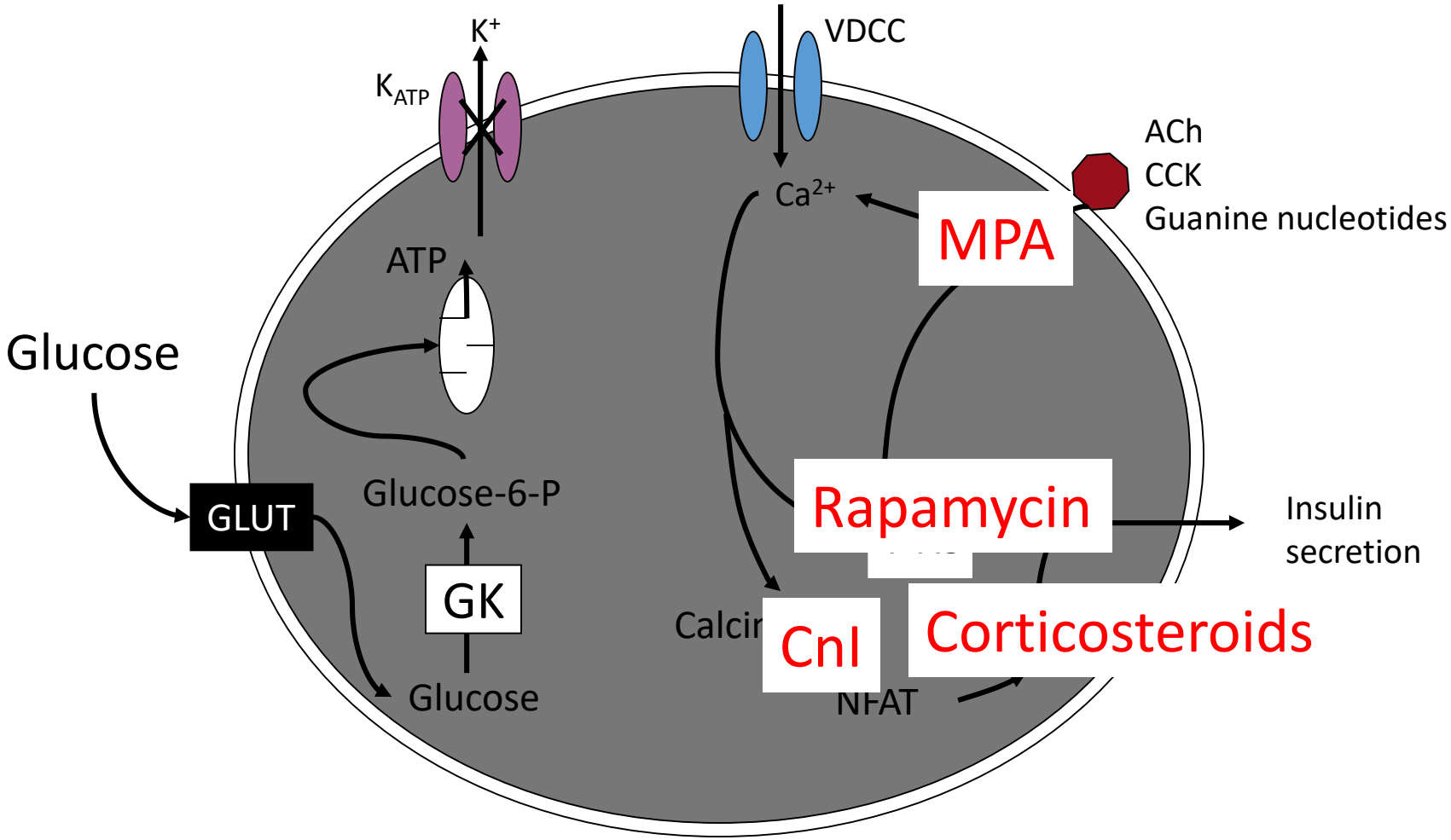
trimethoprim-sulfamethoxazole

- Long-term use of trimethoprim-sulfamethoxazole for prophylaxis for pneumocystis and bacterial infections may also reduce NODAT through a sulfonylurea-like action.

Immunosuppressive combination regimens

- ●In two studies, the combination of tacrolimus and azathioprine was associated with higher rates of NODAT, compared with tacrolimus and MMF or cyclosporine and MMF.
- ●In another study, patients treated with tacrolimus and MMF had lower rates of NODAT when compared with those taking tacrolimus and sirolimus or cyclosporine and sirolimus (14 versus 17 and 33 percent, respectively) .

Role of immunosuppressive drugs



This cannot explain pathophysiology of NODAT as the majority of patients who receive these drugs do not develop diabetes

Infection

- Hepatitis C virus (HCV) infection correlates with both pre- and posttransplant diabetes
- A meta-analysis of 10 studies involving 2502 renal transplant recipients found that anti-HCV-positive patients, compared with uninfected individuals, were nearly four times more likely to have NODAT.
- Proposed mechanisms for HCV-induced NODAT include HCV-induced islet cell dysfunction, insulin resistance due to liver dysfunction, and abnormalities in glucose metabolism
- The use of tacrolimus-based immunosuppression in HCV-infected transplant recipients may further increase the risk of NODAT.

Infection

- Cytomegalovirus (CMV) infection has also been reported to increase the risk of NODAT.
- In one study, an asymptomatic CMV infection was associated with a lower median insulin release and a fourfold increased risk of NODAT.

LETTER TO THE EDITOR

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New-onset diabetes after kidney transplantation and the role of cytomegalovirus

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Thus, we should evaluate all transplant patients with NODAT for the presence of CMV infection. It is obvious that CMV infection is an important complication after kidney transplantation and determination of this serious infection as a risk factor of NODAT could be life-saving issue.

Impaired glucose tolerance and perioperative hyperglycemia

- Preoperative impaired glucose tolerance identifies transplant candidates who are at higher risk for the development of NODAT.

Human leukocyte antigen matching and donor characteristics

- Increased human leukocyte antigen (HLA) mismatching, DR mismatch, and HLA-B27 phenotype have been associated with an increased risk of NODAT in some studies .
- Male and deceased-donor allografts have also been associated with NODAT.

Hypomagnesaemia

- Low magnesium levels have been associated with insulin resistance and diabetes in nontransplant patients .

Underlying renal disease

- Polycystic kidney disease may confer an increased risk of NODAT, although this has not been consistently observed.

	ADPKD (n=135)	Non-ADPKD (n=135)
NODAT at 12 months	17%	7.4%

RR = 2.87 (1.24-6.65)

p = 0.016

De Mattos *et al* Kidney International 7(2):714-20 *(2005)*

CLINICAL IMPACT

Patient survival

- The development of NODAT has an adverse effect upon patient survival.
- Investigators have reported that mean patient survival posttransplantation was lower with NODAT (8.1 versus 11.0 years) .
- The development of NODAT correlates with increased cardiovascular mortality, which is the most prevalent cause of poor long-term survival.

Allograft survival

- NODAT decreases long-term allograft survival.
- In one study, for example, graft survival at 12 years was 48 and 70 percent in those with and without NODAT, respectively.

Infections

- NODAT has been associated with an increased risk for infection and sepsis, with hyperglycemia possibly altering the immune response .
- Urinary tract infection, pneumonia, and cytomegalovirus (CMV) have also been reported to occur at increased rates with diabetes.

MANAGEMENT

Management includes:

- pretransplant evaluation,
- regular posttransplantation monitoring of all patients,
- consideration of immunosuppressant therapy modification based on impaired glucose tolerance, and therapy of diabetes mellitus .
- Aggressive management of other cardiovascular risk factors such as hypertension and dyslipidemia is also warranted.

Pretransplant screening

- Pretransplant assessment should include screening for risk factors for NODAT and for a history of gestational diabetes. All patients should be screened with a fasting plasma glucose, for other evidence of the metabolic syndrome, and for other cardiovascular risk factors.
- All patients should be counseled regarding their risk of NODAT and lifestyle modifications aimed at decreasing this risk.
- Individuals at high risk should be referred to a dietitian.

Posttransplant screening

- All patients, whether or not they have a pre-identified increased risk, should have a fasting blood glucose measured weekly during the first four weeks posttransplant, then at three and six months posttransplant, and then yearly.
- A glycated hemoglobin (HbA1c) can be checked after three months posttransplant
- Among patients who have HbA1c >6 percent, we recommend self-monitoring of blood glucose (SMBG) and assessment of an HbA1c quarterly.

Treatment

Treatment

- A stepwise approach is recommended for treatment of NODAT, starting with nonpharmacologic therapy, including diet, weight reduction, and exercise; followed by oral monotherapy; oral combination therapy; and finally insulin, providing metabolic decompensation has not occurred (which would require earlier insulin initiation).
- Patients with subdiabetic hyperglycemia or NODAT should also have aggressive interventions aimed at decreasing cardiovascular risk, such as lipid and blood pressure control.

Adjustment of immunosuppression

- Adjustment of immunosuppression therapy aimed at improving glucose tolerance may be considered among patients with NODAT.
- However, the potential benefit of altering immunosuppressive agents must be weighed against the risk of allograft rejection.

Glucocorticoids

- The glucocorticoid dose should be decreased as soon as possible, but complete glucocorticoid withdrawal is not recommended.

Tacrolimus

- Compared with cyclosporine, the use of tacrolimus is associated with higher rates of NODAT, particularly with tacrolimus trough levels >15 ng/mL in the first month posttransplant
- We generally do not switch affected patients from tacrolimus to cyclosporine, unless there are other tacrolimus-related side effects, since the effect of tacrolimus on glucose tolerance may be reversible even if the agent is not discontinued.
- Conversion to sirolimus is not recommended. Sirolimus may worsen insulin resistance and glycemia.

Oral therapy

- Glucocorticoid-induced diabetes, even with low-dose therapy, is characterized by fasting blood sugars only slightly above baseline, but more markedly increased postprandial blood glucose and reduced insulin sensitivity .

Oral therapy : sulfonylureas

- Sulfonylureas:

Among the sulfonylureas, glipizide and glimepiride are preferred to glyburide when the glomerular filtration rate (GFR) is less than 50 mL/min because glyburide may accumulate with renal insufficiency, resulting in hypoglycemia.

- Sulfonylureas may be expected to lower the HbA1c by 0.8 to 2 percent and may increase body weight.

Oral therapy

- Meglitinides, such as repaglinide, may be good alternatives for patients who cannot take sulfonylureas
- Repaglinide is not contraindicated in patients with renal or liver insufficiency and does not have adverse drug interactions .

Oral therapy: dipeptidyl peptidase-4 inhibitors

- Sitagliptin (Januvia) is an oral agent that inhibits dipeptidyl peptidase-4, the enzyme responsible for incretin degradation, which increases insulin synthesis and release and decreases glucagon levels.
- The dose must be adjusted for renal insufficiency.
- Although sitagliptin does not cause hypoglycemia, it may prolong the QT interval, especially if used with cyclosporine.
- Saxagliptin (Onglyza) does not prolong the QT interval
- Exenatide (Byetta), an incretin mimetic that is administered subcutaneously

Thiazolidinediones:

- Thiazolidinediones are generally not used among transplant recipients, unless there are no other alternatives.
- The thiazolidinedioness may worsen immunosuppression-associated bone loss and are commonly associated with formation of edema, which may necessitate the use of diuretics and may predispose to calcineurin toxicity.
- Use of these agents is also contraindicated in hepatic dysfunction.

Metformin

- We tend not to use metformin, because renal insufficiency increases the risk of lactic acidosis;
- It is strictly contraindicated in patients with an eGFR of <30 mL/min and not recommended if the eGFR is <45 mL/min.

Alpha-glucosidase inhibitors

- Alpha-glucosidase inhibitors such as acarbose (Precose) or miglitol (Glyset) are not considered first- or second-line agents, but may be considered if other options are not available

Insulin therapy

Insulin therapy

- Many patients will require institution of insulin, especially those with fasting blood sugars above 200 mg/dL .
- It should be better to initiate insulin therapy if oral agents have not been effective or have been accompanied by unacceptable side effects, or if HbA1c levels are consistently above 7 percent.

Insulin therapy

- ●Insulin glargine (Lantus) at night, adjusted to control the morning fasting glucose.
- ●Premeal short-acting insulin aspart (NovoLOG) or insulin lispro (Humalog), based on premeal glucose and anticipated carbohydrate ingestion.

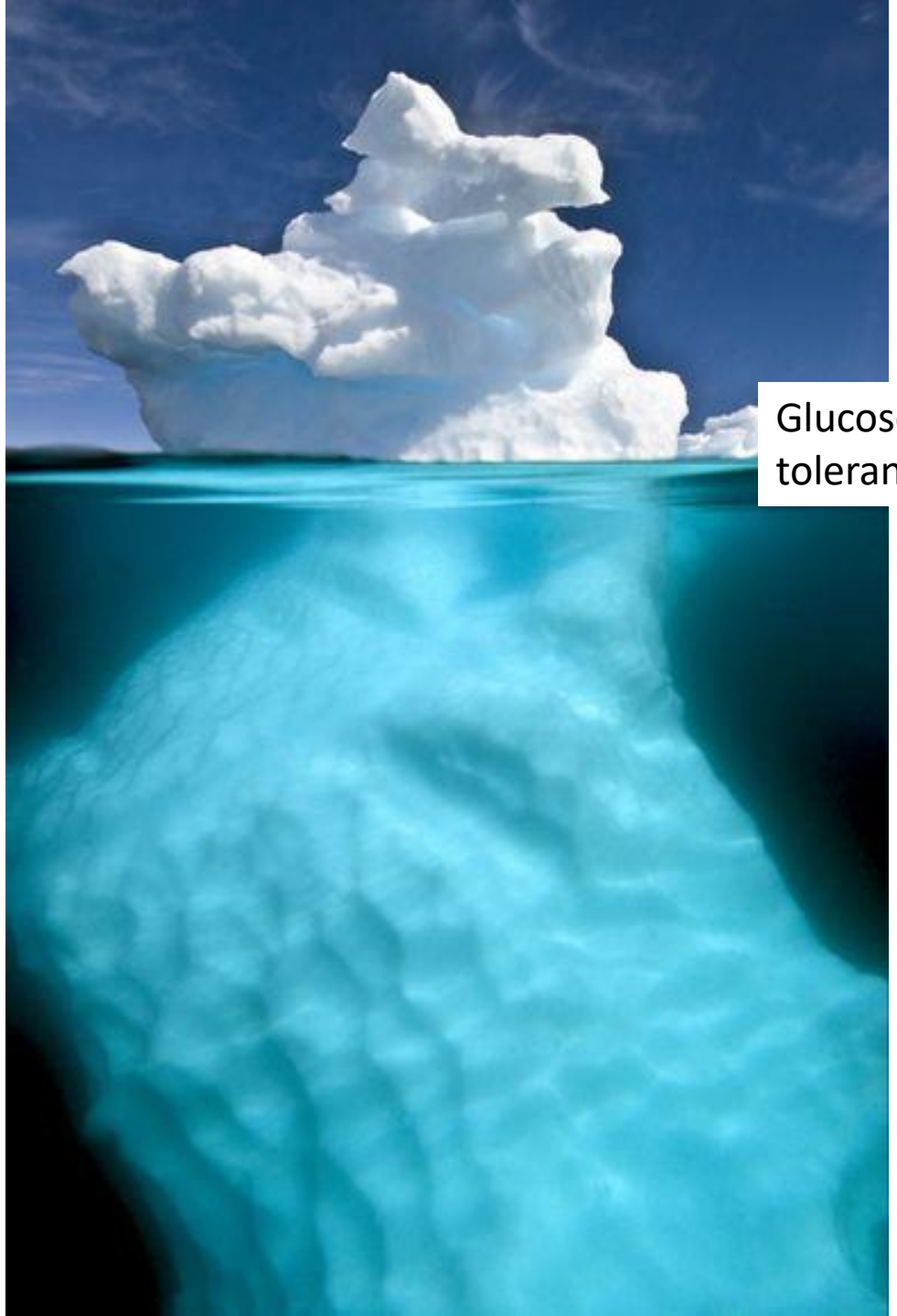
Monitoring patients with NODAT

- HbA1c should be checked every three months with a target of <7.0 percent .
- The HbA1c assay will not reliably measure average glucose levels in the setting of anemia, especially if erythropoietin replacement is being used.
- Patients should be instructed in glucose self-monitoring.
- Patients should have regular screening for retinopathy and neuropathy. Regular foot care is also indicated.

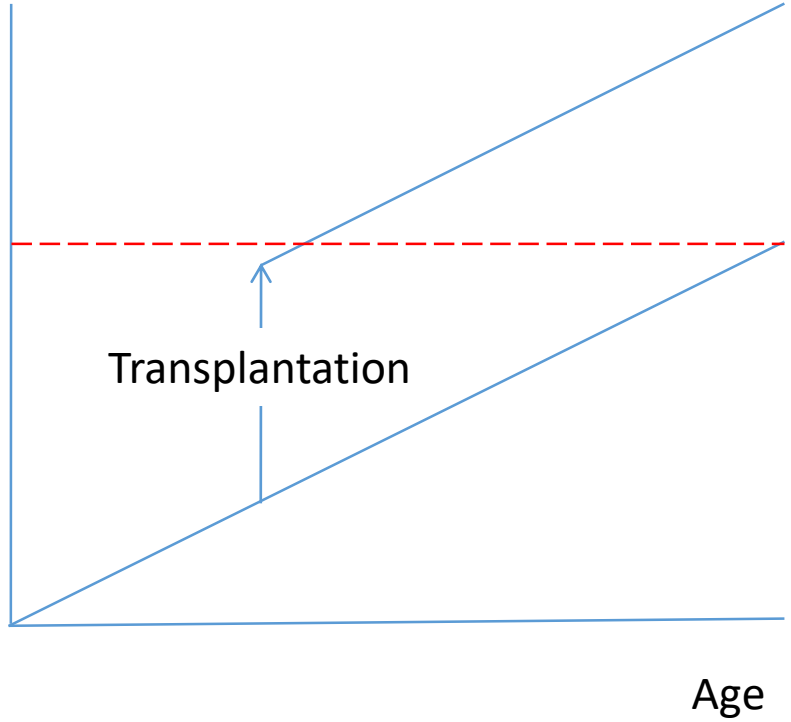
CONCLUSION:

RISK FACTORS

Age
Race
Gender
Family history of diabetes
Obesity
Cytomegalovirus infection
HLA B27, A26, A30, B8, B18
Autosomal dominant polycystic kidney disease
Prednisolone dose
Type of Calcineurin inhibitor (ciclosporin versus tacrolimus)
Calcineurin inhibitor dose



Glucose tolerance



Thanks for attention