Posttransplantation Diabetes

A systematic review of the literature

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OBJECTIVE — To systematically review the incidence of posttransplantation diabetes (PTD), risk factors for its development, prognostic implications, and optimal management.

RESEARCH DESIGN AND METHODS — We searched databases (MEDLINE, EMBASE, the Cochrane Library, and others) from inception to September 2000, reviewed bibliographies in reports retrieved, contacted transplantation experts, and reviewed specialty journals. Two reviewers independently determined report inclusion (original studies, in all languages, of PTD in adults with no history of diabetes before transplantation), assessed study methods, and extracted data using a standardized form. Meta-regression was used to explain between-study differences in incidence.

RESULTS — Nineteen studies with 3,611 patients were included. The 12-month cumulative incidence of PTD is lower (<10% in most studies) than it was 3 decades ago. The type of immunosuppression explained 74% of the variability in incidence ($P = 0.0004$). Risk factors were patient age, nonwhite ethnicity, glucocorticoid treatment for rejection, and immunosuppression with high-dose cyclosporine and tacrolimus. PTD was associated with decreased graft and patient survival in earlier studies; later studies showed improved outcomes. Randomized trials of treatment regimens have not been conducted.

CONCLUSIONS — Physicians should consider modification of immunosuppressive regimens to decrease the risk of PTD in high-risk transplant recipients. Randomized trials are needed to evaluate the use of oral glucose-lowering agents in transplant recipients, paying particular attention to interactions with immunosuppressive drugs.

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Posttransplantation diabetes (PTD) is a complication of solid-organ transplantation. Beyond the description of PTD as the development of diabetes after transplantation, there is no consensus regarding the definition of this condition. Estimates of the frequency of PTD range from 2 to 50%. Some factors, such as age of the transplant recipient, are consistently described as increasing the risk of PTD. Under dispute is the importance of other factors, such as the recipients ethnicity, body weight, immunosuppressive regimen, and family history of diabetes, as well as the vital status of the organ donor. The prognostic implications of PTD and its optimal treatment are similarly unclear.

The goals of this systematic review were to estimate the incidence of PTD, identify the risk factors for its development, determine its implications for prognosis, and discover treatment strategies that lead to improved patient outcomes.

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Abbreviations: OR, odds ratio; PTD, posttransplantation diabetes; RR, risk ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Questions asked

Our review was designed to answer four questions: *1*) For patients with no history of diabetes before transplantation, what is the risk that PTD will develop? *2*) What are the risk factors for the development of PTD? *3*) What is the prognosis for patients with PTD? *4*) Which therapies improve glycemic control and prognosis in patients with PTD?

Identification and retrieval of primary studies

We searched MEDLINE (OVID Technologies and PubMed), EMBASE (OVID Technologies), Current Contents (Institute for Scientific Information), LILACS (BIREME), ScienceDirect (Elsevier), and the Cochrane Library (Update Software) using the following subject headings (including their explosions) and text words: "diabetes mellitus," "transplantation," "immunosuppressive agents," and their synonyms and related terms. Databases were searched from their inception to September 2000 (Current Contents was searched from January 2000 to September 2000). In addition, we manually searched the January 1998 to September 2000 issues of *Transplantation*, *Transplantation Proceedings*, *Diabetes Care*, *Diabetes*, *Diabetologia*, and *Diabetic Medicine*, as well as the bibliographies of all retrieved reports. We asked five experts in transplantation care for information about ongoing studies, completed but unpublished studies, and studies missed by our search strategy. We also queried the National Library of Medicine's registry of clinical trials (www.clinicaltrials.gov).

Inclusion criteria

We sought reports (in any language) of controlled trials, cohort studies, and case-control studies that provided data on PTD after any solid-organ transplantation except pancreas and islet cell transplantation. We included only those studies that enrolled adults with no history of diabetes before transplantation and followed them

for at least 1 year after transplantation with <10% loss to follow-up. To be included, case-control studies and cohort studies must have compared all patients with PTD (cases or exposed cohort) with all, a matched set, or a random sample of others (control subjects or unexposed cohort) in whom PTD did not develop. To obtain information about strategies for treating PTD, we attempted to include clinical trials that enrolled patients with PTD and randomized them to intervention and control arms; however, we did not find any such studies and were unable to investigate this question.

Study selection, study quality, and data extraction

Two reviewers worked independently to determine whether a study met the inclusion criteria, collect information to assess the methodological validity (degree of protection against confounding and bias) of each study included, and extract data from the included studies using structured and standardized data extraction forms. Reviewers resolved discrepancies by jointly reviewing any study in question; if no consensus was reached, a third reviewer, who was unaware of the other reviewers' determinations, functioned as an arbitrator.

Data analysis and statistical methods

We quantified interobserver reliability using Cohen's κ statistic (1). We extracted the 12-month cumulative incidence of PTD and calculated its 95% CI using the exact method by Pearson. We calculated odds ratios (ORs) and risk ratios (RRs) and their 95% CIs. When these calculations could not be conducted because too little information had been published, we noted the published *P* values or other statements of statistical significance.

We did not conduct statistical pooling of the data. To explore the effect of study characteristics on the 12-month cumulative incidence (response variable), we conducted multiple linear regression (meta-regression). The response variable was calculated for each cohort of patients receiving the same immunosuppressive regimen. If this was not possible, we used the 12-month cumulative incidence of PTD for the entire study cohort and assigned the immunosuppressive regimen used by most participants developing PTD. We used square transformation of the response variable to stabilize its variance. The explanatory variables considered included the following: year when patient enrollment was started, study design (randomized trial, cohort study, or case-control study), definition of PTD (glycemic threshold, use of glucose-lowering medication, or combination of these criteria), and type of immunosuppressive regimen used (glucocorticoids, cyclosporine, high-dose tacrolimus, or low-dose tacrolimus). We used backward elimination to exclude explanatory variables that provided no significant information ($P > 0.1$). We tested the hypothesis that the resulting model was useful in predicting the 12-month cumulative incidence of PTD and calculated the coefficient of multiple determination to quantify how much of the variability in the response variable was accounted for by the explanatory variables in the model. Statistical analyses were conducted using StatsDirect 2001 (CamCode; Ashwell, Hertfordshire, U.K.).

RESULTS

Search results

After searching the electronic databases, we identified 1,339 abstracts, of which 247 were deemed relevant by title and abstract alone. Also, we found 28 reports in specialized journals and 15 reports in the bibliographies of other reports. One study protocol was found in the clinical trials registry. Evaluation of 291 full reports led to the exclusion of 264 of them. Reasons for exclusion were as follows: 113 reports were not reports of controlled trials, cohort studies, or case-control studies; 46 did not report on PTD or excluded patients with PTD; 12 included children; 63 included patients with diabetes before transplantation or did not report diabetes status before transplantation; 21 followed patients for <1 year or lost >10% of patients to follow-up; and 9 were nonrandomized or uncontrolled studies of interventions to treat PTD. The inter-rater reliability for inclusion decisions was near perfect (κ = 0.93–1).

Study characteristics and quality

A total of 27 reports (2–28) provided information on 3,611 patients in 19 studies (Table 1). The study quality and methodological characteristics of the 19 included studies are shown in Table 2. Inter-rater reliability for quality assessments was good for studies reporting on risk (κ = 0.62) and studies reporting on prognosis (κ = 0.84). None of the included studies satisfied all quality criteria.

Data synthesis

The 12-month cumulative incidence of PTD. Table 1 includes the 12-month cumulative incidence of PTD in 15 studies. Most cases of PTD were diagnosed within 3 months after transplantation. In the 12 studies of kidney transplantation, incidence estimates ranged from to 2 to 50%. In the exploratory analysis using multiple linear regression with data from 15 cohorts included in these 12 studies, the type of immunosuppressive regimen used (steroids, cyclosporine, high-dose tacrolimus, or low-dose tacrolimus) explained 74% of the variability in the 12-month cumulative incidence ($P = 0.0004$). Figure 1 shows the temporal trends in the 12-month cumulative incidence of PTD, with a bimodal distribution corresponding to the initial kidney transplantation experience 3 decades ago and to the introduction of tacrolimus in the early 1990s.

Risk factors for PTD

Risk factors for PTD included age, nonwhite ethnicity, and immunosuppression. Conflicting evidence exists regarding the importance of a family history of diabetes, impaired glucose tolerance before transplantation, increasing weight, and vital status of the organ donor. Transplant recipients with PTD were 0–12 years older than those without PTD (8–11,15,16,25,27,28). In one study (8,9), individuals whose age was >45 years and weight was >70 kg had an OR of 6.4 (95% CI 1.2–33.4) for the development of PTD. The same study (8,9) found an increased risk of PTD in recipients of cadaveric grafts (OR 3.9; 95% CI 1.1–13.7) but included cases from a series that did not meet the inclusion criteria for this review. Miles et al. (17) and Wu et al. (15) (the latter reporting only three cases of PTD) did not find a significant association between PTD and the vital status of the donor (RR 1.3, 95% CI 0.7–2.8; OR 1.3, 95% CI 0.05–30, respectively). When compared with white patients, nonwhite patients experienced a twofold increase in the risk of PTD (RR 3.3, 95% CI 1.6–7.0) (2–6).

An association between glucocorticoids (in total or maintenance doses) and

PTD has not been reported since the steroids-azathioprine era (27,28). However, an association between glucocorticoid pulse therapy, as treatment for acute rejection, and PTD has been reported before and after the introduction of cyclosporine; up to 76% of cases have been diagnosed during or in the month after antirejection treatment (2–6,25).

Tacrolimus was used in high doses ($>0.20\ mg \cdot kg^{-1} \cdot day^{-1}$) during phase II and phase III studies, including the multicenter FK506 studies of liver and kidney transplantation (2–6,20). These studies revealed a significantly higher incidence of PTD in patients treated with tacrolimus than in those treated with cyclosporine (RR 5, 95% CI 2.2–11.5). In the published multiple regression analysis, increasing tacrolimus blood concentration was a significant risk factor for PTD (2–6). The risk of PTD was lower in white patients (12%) than in nonwhite patients (29%) receiving tacrolimus (RR 0.4, 95% CI 0.2–0.8). However, compared with cyclosporine, tacrolimus was associated with a greater risk of PTD in white patients (12 vs. 1.2%; RR 10.6, 95% CI 1.8–86.7) than in nonwhite patients (29 vs. 7.8%; RR 3.7, 95% CI 1.6–9.2) (6). Compared with cyclosporine, tacrolimus was not associated with a significantly greater risk of PTD when used in lower doses ($0.15–0.2\ mg \cdot kg^{-1} \cdot day^{-1}$) (7,12).

Two studies (10,11,27,28) reported that rejection was associated with a three- to fourfold increase in the risk of PTD. However, that association was not significant in a study in which 14 of 32 cases of PTD appeared >1 year after transplantation (21). The subgroup of patients in whom PTD developed within 1 year after transplantation had a significantly greater risk of PTD during or after a rejection episode than those diagnosed with PTD >1 year after transplantation (OR 7.5, 95% CI 1.3–44).

Prognosis for patients with PTD. PTD was associated with a small increase in mortality (Table 3). The survival difference between affected and unaffected patients was consistent across studies (and immunosuppression eras). However, patient survival appeared to have improved over time in patients with PTD (Table 3). Graft survival is shown in Table 3, and Table 4 depicts cardiovascular events and infections in patients with and without PTD.

Only one study with 10 years of follow-up data provided information about diabetes-related complications. Miles et al. (17) reported that, of 40 patients with PTD, two patients were diagnosed with diabetic neuropathy and two others were diagnosed with biopsy-proven diabetic nephropathy. Also, two patients had episodes of diabetic ketoacidosis and another two of hyperosmolar coma.

The highest proportion of patients able to discontinue glucose-lowering treatment was observed in patients receiving cyclosporine-based immunosuppressive therapy (60–100%), followed by patients receiving low-dose tacrolimus and azathioprine (75–90%) and those receiving high-dose tacrolimus (40–70%). The lowest proportions were observed in patients receiving low-dose tacrolimus and mycophenolate mofetil (30–50%).

Sensitivity analysis

A total of 33 studies reported in 35 articles (29–63) were excluded because they did not contain enough information to meet our inclusion criteria and the information needed was not obtained from the authors. We assessed these studies and determined that their inclusion would not change the overall findings and conclusions of this review.

CONCLUSIONS

— As opposed to the traditional narrative review (64,65), the systematic review allows the reader to judge the appropriateness and completeness of the study selection, the quality of the included studies, and the information they provide (66). Our systematic review of studies of PTD found that the cumulative incidence of PTD has declined; age, ethnicity, and immunosuppressive regimen were the main risk factors for its development; and patients with PTD appeared to have poorer outcomes.

We attempted to minimize the limitations of this study. There is no agreed-upon way to assess whether publication bias, i.e., the preferential publication of studies with significant results (67), has affected the findings of a study like ours. To limit the possible effect of publication bias, we used several strategies for identifying studies to include. Inclusion criteria, established a priori, were chosen to increase the likelihood that high-quality studies would be included. Studies with important and valid data may not have met our inclusion criteria. However, we conducted a sensitivity analysis to assess whether our conclusions would have been affected by the results of studies not included in our review. The risk of bias and confounding in the primary studies (Table 2) suggested that pooling across studies would lead to inappropriately precise and potentially biased estimates of risk or prognosis (68). Instead, as advocated by Berlin (69), we chose to capitalize on the heterogeneity across studies to gain insights and answers to our review questions.

The studies included in our review used various definitions of PTD (Table 1). Diagnostic criteria for diabetes are based on the immediate threat to life (e.g., type 1 diabetes) or the future development of diabetes-related complications, such as retinopathy and nephropathy (70). For PTD, such data are not available. It may not be possible to extrapolate from data on type 2 diabetes to a definition of PTD because of differences in natural history (i.e., glycemic control progressively deteriorates in type 2 diabetes but may worsen or improve with changes in immunosuppression in PTD) and vascular risk at diagnosis (e.g., early clustering of dyslipidemia, decreased renal function, hypertension, and toxic immunosuppressive agents). Further research is needed to establish criteria for diagnosing PTD on the basis of its prognostic implications.

We did not find an association between PTD and body weight or BMI. One explanation is that obese patients were underrepresented in the studies included in our review. Another explanation is that intra-abdominal fat, not reported in any of the studies we reviewed, may be a more important risk factor than total body weight (71).

Nonwhite transplant recipients are at higher risk of PTD because of a greater risk of diabetes (72) and the differential diabetogenic effect of immunosuppressive agents. A multicenter trial found that African-American transplant recipients required higher doses of tacrolimus to achieve therapeutic levels, confirming the results of a pharmacokinetic study (2–6).

Immunosuppression was the factor most strongly associated with PTD. Glucocorticoids, cyclosporine, and tacrolimus have been shown to impair insulin secretion and insulin action through dose-dependent, complex, and imperfectly understood mechanisms (73–77).

Since we completed this systematic review, clinical trials of sirolimus showed

Table 1—*Studies of PTD*

Study number	Study description (immunosuppressive regimen)	Study design	Evidence of no pretransplantation diabetes	Patients without pretransplantation diabetes (*n*)	Definition of PTD (definition category*)	Patients with PTD at 1 year (*n*); 12-month cumulative incidence of PTD [% (95% CI)]†
Heart transplantation						
1. Rinaldi et al. (14)	Trial of FK506 vs. CsA	RCT	Investigator's statement	23	Development of glucose intolerance (threshold)	3; 13 (2.8–33.6)
Liver transplantation						
2. Cavaille-Coll and Elashoff (6)	FDA reanalysis of the U.S. and European phase III trials of FK506 vs. CsA	RCT	Investigator's statement	963	Use of insulin for ≥30 days with <5-day gap (medication)	110; 11.4 (9.5–13.6)
3. Wahlstrom et al. (26)	Single-center series (AZA-CsA-Pred)	CC	Investigator's statement	19 case subjects, 141 control subjects	Use of insulin (medication)	19 (160 at risk)†; 11.9 (7.3–17.9)
4. Trail et al. (22)	Single-center series (CsA-Pred, FK506-Pred)	CC	Normal fasting or random glucose concentration	26 case subjects and 26 control subjects matched for age, sex, transplantation date, liver disease, outcome, and follow-up	In first month after transplantation: two fasting glucose >8.3 mmol/l, one random value >11.1 mmol/l, or use of glucose-lowering medication (combination)	ND†
Kidney transplantation						
5. Boudreaux et al. (8,9)	Trial of ALG-AZA-Pred vs. CsA-Pred	RCT	Investigator's statement	105	Two fasting glucose ≥7.8 mmol/l and an abnormal glucose tolerance test (threshold)	7; 6.7 (2.7–13.3)
6. Isoniemi et al. (18,19)	Trial of all possible combinations of AZA, CsA, and methyl-prednisolone	RCT	Investigator's statement	98	Use of glucose-lowering medication (medication)	7; 7.1 (2.9–14.2)
7. FK506-Kidney Transplant Study Group (2–6)	Multicenter study of FK506 vs. CsA	RCT	Investigator's statement	302	Use of insulin for ≥30 days with <5 day gap (medication)	36; 11.9 (8.5–16.1)
8. Johnson et al. (7)	Multicenter study of FK506-AZA, FK506-MMF, and CsA-MMF	RCT	Investigator's statement	145	Use of insulin for ≥30 days or after 6- and 12-month transplantation (medication)	14; 9.6 (5–15.7)
9. Miller et al. (12,13)	Multicenter study of FK506-AZA, FK506-MMF 1g, and MMF 2g	RCT	Investigator's statement	126	Use of insulin for ≥30 consecutive days (medication)	15; 11.9 (6.8–18.9)
10. Arner et al. (27) and Gunnarsson et al. (28)	Single-center series (AZA-Pred)	Co	Investigator's statement	125	Two fasting glucose >8 mmol/l (threshold)	38–67; 30.4–53.6‡

11. Friedman et al. (25)	Single-center series (AZA-Pred)	CC	Investigator's statement	119 case subjects and 119 control subjects matched for transplantation date and donor vital status	Three fasting glucose >8.3 mmol/l (threshold)	116 (758 at risk)†; 15.3 (12.8–18)
12. von Kiparski et al. (21)	Single-center series (AZA-Pred, AZA-CsA-Pred)	CC	Normal fasting glucose or normal oral glucose tolerance test	32 case subjects and 32 control subjects matched for age, sex, immunosuppression, number of grafts received and function, transplantation date	Two fasting glucose >6.7 mmol/l and use of glucose-lowering medication (combination)	18 (901 at risk)†; 2 (1.2–3)
13. Ochiai et al. (20)	Multicenter phase II study of FK506 (historical CsA cohort)	Co	Normal oral glucose tolerance test	83	Hyperglycemia and use of glucose-lowering medication (combination)	18; 21.7 (13.4–32.1)
14. Wu et al. (15)	Single-center series (AZA-CsA-Pred)	CC	Normal fasting glucose concentration	3 case subjects, 21 control subjects	Two fasting glucose >7.8 mmol/l, postprandial glucose >11.1 mmol/l, or abnormal glucose tolerance test (threshold)	2 (24 at risk)†; 8.3 (1–27)
15. Sakhuja et al. (24)	Single-center series (AZA-Pred, AZA-CsA-Pred)	Co	Investigator's statement	387	Two fasting glucose >7.8 mmol/l or two 2-h postprandial values >11.1 mmol/l (threshold)	21; 5.4 (3.4–8.2)
16. Vesco et al. (10,11)	Analysis of a transplant registry (AZA-Pred, AZA-CsA-Pred)	CC	Investigator's statement	33 case subjects and 33 control subjects matched for sex, number of grafts, transplantation date	Fasting glucose >7.8 mmol/l requiring insulin therapy (combination)	ND†
17. Lanerolle et al. (16)	Single-center series (AZA-Pred, CsA-Pred)	CC	Normal oral glucose tolerance test	34 case subjects, 131 control subjects	Fasting glucose >6.8 mmol/l or 2-h glucose (75-g oral glucose tolerance test) >10 mmol/l (threshold)	ND†
18. Miles et al. (17)	Single-center prospective series (AZA-CsA-Pred, CsA-Pred)	Co	Normal fasting glucose concentration	40 case subjects and 38 unaffected patients randomly selected from a cohort of patients with graft survival>1 year	Three or more fasting glucose >8.3 mmol/l over 3 months (threshold)	ND
19. Fang et al. (23)	Single-center series (CsA-Pred)	Co	Investigator's statement	386	Three fasting glucose >7.8 mmol/l and use of glucose-lowering medication (combination)	7; 1.8 (0.7–3.7)

*PTD definition categories: threshold, glycemic threshold; medication, use of glucose-lowering medication; combination, combination of threshold and medication. †If reported in case-control studies, the total number of PTD cases in the first year after transplantation was used to calculate the cumulative incidence of PTD. ‡Data are range of cumulative incidence estimates taking the number of new cases at 3 months and the number of new cases at 20 months. ALG, antilymphocyte globulin; AZA, azathioprine; CC, case-control study; Co, cohort study; CsA, cyclosporine; FDA, Food and Drug Administration; FK506, tacrolimus; MMF, mycophenolate mofetil; ND, not determined: information needed was not available; Pred, prednisone; RCT, randomized controlled trial.

Table 2—*Quality of included studies*

Study number	PTD definition	PTD surveillance (% escaped)	Study quality indicators: Risk factor: Exposure ascertainment	Risk factor: Reporting	Outcomes: Definition	Outcomes: Ascertainment	Outcomes: Blinding	Outcomes: Reporting	Outcomes: Adjustment
1. Rinaldi et al. (14)	−	−	−	−	NA	NA	NA	NA	NA
2. Cavaille-Coll and Elashoff (6)	+	−	−	−	NA	NA	NA	NA	NA
3. Wahlstrom et al. (26)	+	−	−	−	NA	NA	NA	NA	NA
4. Trail et al. (22)	+	−	−	+	+	+	−	+	+
5. Boudreaux et al. (8, 9)	+	+ (20)	−	+	−	−	−	−	−
6. Isoniemi et al. (18,19)	+	−	−	−	NA	NA	NA	NA	NA
7. KTSG (2–6)	+	−	−	−	NA	NA	NA	NA	NA
8. Johnson et al. (7)	+	−	−	+	NA	NA	NA	NA	NA
9. Miller et al. (12,13)	+	−	−	−	NA	NA	NA	NA	NA
10. Arner et al. (27) and Gunnavvsson et al. (28)	+	+	−	+	−	−	−	−	−
11. Friedman et al. (25)	+	+	−	+	−	−	−	−	−
12. von Kiparski et al. (21)	+	−	−	+	+	−	−	−	+
13. Ochiai et al. (20)	+	+	NA	NA	NA	NA	NA	NA	NA
14. Wu et al. (15)	+	−	−	+	NA	NA	NA	NA	NA
15. Sakhuja et al. (24)	+	+ (22)	−	+	NA	NA	NA	NA	NA
16. Vesco et al. (10,11)	+	−	−	+	−	−	−	−	+
17. Lanerolle et al. (16)	+	+ (28)	−	+	−	−	−	−	−
18. Miles et al. (17)	+	NA	NA	NA	−	−	−	−	+
19. Fang et al. (23)	+	+ (42)	NA	NA	NA	NA	NA	NA	NA

PTD definition, a specified glycemic threshold, use of glucose-lowering agents, or both were used to define diabetes; PTD surveillance, a protocol to detect diabetes was described (% escaped, proportion presenting with symptomatic or complicated PTD); risk factor exposure ascertainment, methods to determine risk factors were described and similarly applied to case subjects and control subjects; risk factor reporting, all factors evaluated (not just those that were significant) were reported; outcomes definition, diagnostic criteria for all outcomes assessed were described; outcomes ascertainment, methods to determine the outcomes were described and similarly applied to patients with and without PTD; outcomes blinding, outcomes were assessed by investigators blind to diabetes status; outcomes reporting, prognostic factors entering the model and the procedures for model selection were described; outcomes adjustment, prognostic estimates were adjusted for differences between those with and without PTD; +, study met our review's methodological quality criterion; −, study did not meet our review's methodological quality criterion; NA, not applicable; KTSG, FK506 Kidney Transplant Study Group.

Table 3—*Patient and graft survival according to PTD status in kidney transplant recipients*

Investigators	Year follow-up began (mean)	Immunosuppressive regimen	Time at survival estimates (years*)	Estimated survival: Patient: PTD present (%)	Patient: PTD absent (%)	Graft: PTD present (%)	Graft: PTD absent (%)
Arner et al. (27,28)	1975	AZA and prednisone	1	NA	NA	38† 69§	81‡ 85
von Kiparski et al. (21)	1978	AZA and prednisone or triple	10	51	93‖	54	85
Friedman et al. (25)	1980	AZA and prednisone	2	67	83	55	55
Boudreaux et al. (8,9)	1984	AZA and prednisone or triple	1	71	94¶	NA	NA
Miles et al. (17)	1983	Triple	12	73	79	46	67#
Vesco et al. (10,11)	1988	AZA and prednisone or triple	6	86	93	67	93
Lanerolle et al. (16)	1993	Triple	5	85	95	NA	NA

*Number of patients at risk not reported in all studies. †For cadaveric grafts. ‡$P < 0.001$. §For living donors. ‖$P < 0.05$. ¶RR 12.1; 95% CI 2.2–58.8. #Predictors of graft loss (adjusted for age, sex, and ethnicity) were PTD (RR 3.72; $P = 0.04$) and serum creatinine at 1 year (RR 2.01; $P < 0.01$). AZA, azathioprine; triple, AZA prednisone and cyclosporine.

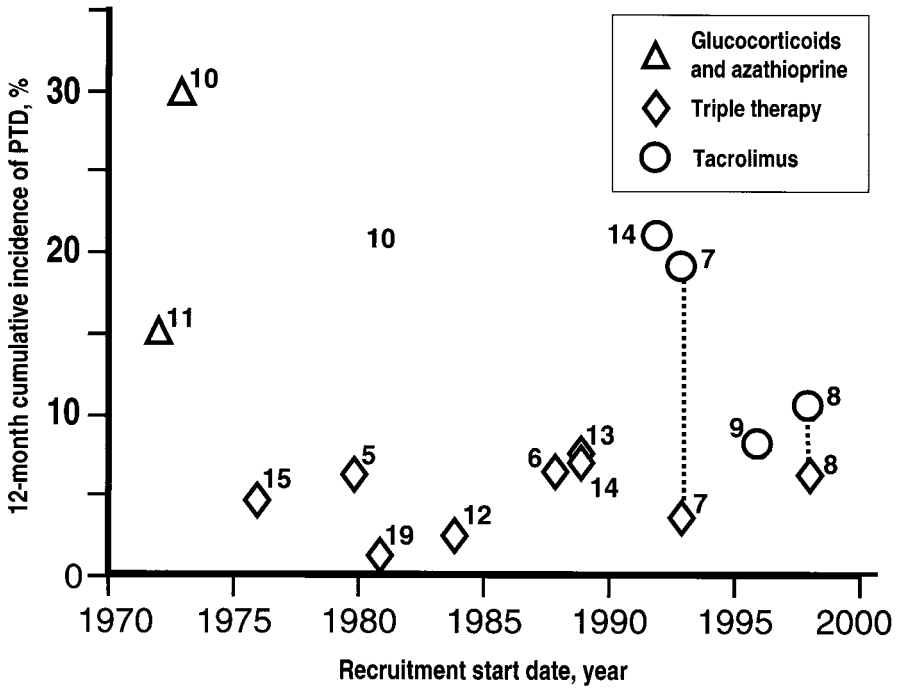

Figure 1—*Trends in the 12-month cumulative incidence of PTD. The figure includes the 15 cohorts (12 studies of kidney transplantation numbered according to Table 1) from which the 12-month cumulative incidence of PTD could be calculated. Triangles represent studies using glucocorticoids and azathioprine as the immunosuppressive regimen. The lower estimate (study 11 [25]) represents one center's experience extending up to 1982, 5 years after the 1977 completion of the study reporting the higher estimate (study 10 [27,28]). Diamonds represent the triple therapy era (cyclosporine, azathioprine, glucocorticoids). Circles represent the tacrolimus era. The circles in the early 1990s represent studies of high-dose tacrolimus. The circles in the late 1990s represent studies of low-dose tacrolimus; these circles represent average data from reports of patients receiving tacrolimus in combination with azathioprine (12-month cumulative incidence of PTD, 12–14%) and 2 g mycophenolate mofetil (4–7%). Dotted lines link the tacrolimus and cyclosporine arms of two randomized trials. In the first trial (study 7 [2–6]), testing high-dose tacrolimus, there was a significant difference in the incidence of PTD between the tacrolimus and cyclosporine arms. That difference was not significant in the lower-dose trial (study 8 [7]).*

fewer or no diabetogenic effects compared with placebo (78) and azathioprine (79).

No randomized trials have evaluated treatment regimens for PTD. Randomized trials are needed to assess whether tight glycemic control is feasible and desirable in posttransplantation patients, considering that some patients have hyperglycemia only transiently. Also, trials should evaluate the safety and efficacy of oral glucose-lowering agents in transplant recipients, paying particular attention to interactions with immunosuppressive drugs. Finally, information is needed to clarify and diminish the effect of PTD on quality of life and long-term outcomes.

In the last 40 years, transplantation care has focused successfully on achieving optimal graft function and patient survival. Today, transplantation centers are accepting candidates at higher risk for complications after transplantation. Thus, attention needs to be shifted to the prevention and control of complications because they may lead to poor quality of life and increased mortality in patients with functioning grafts.

This systematic review, the first one on PTD, provides preliminary evidence for the modification of immunosuppressive regimens to decrease the risk of PTD in high-risk transplant recipients.

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Table 4—*Cardiovascular outcomes and infections associated with PTD in kidney transplant recipients*

Outcome and investigators	Duration of follow-up (years)	Number of patients with outcome/ total number of patients (%)		RR (95% CI)
		PTD present	PTD absent	
Cardiovascular complications				
von Kiparski et al. (21)	10	9/32 (28)	3/32 (9.4)	3 (0.98–9.6)
Myocardial infarction				
Miles et al. (17)	8.5	3/40 (7.5)	3/38 (7.9)	0.95 (0.2–3.9)
Stroke				
Miles et al. (17)	8.5	2/40 (5)	1/38 (2.6)	1.9 (0.4–14.2)
Severe infections requiring hospitalization				
Boudreaux et al. (8,9)	1	6/7 (86)	40/98 (40.8)	1.9 (1–2.6)
von Kiparski et al. (21)	10	12/32 (37.5)	6/32 (18.8)	2 (0.9–4.6)
Cytomegalovirus infections				
Vesco et al. (10,11)	6	14/33 (42.4)	7/33 (21.2)	2 (0.96–4.3)
Fatal sepsis				
Lanerolle et al. (16)	3–9	3/34 (8.8)	1/131 (0.8)	11.6 (1.7–79)
Miles et al. (17)	8.5	5/40 (12.5)	1/38 (2.6)	4.8 (0.8–30)

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