CONCLUSIONS

Patients with diabetes mellitus are known to have a worse prognosis than nondiabetic individuals after myocardial infarction (1). Several studies have reported that nearly 50% of patients with no previous history of glucose intolerance have high (>8 mM) admission blood glucose levels (2,3). Over 30% of these patients have random blood glucose levels >12 mM (4). Sowton (5) reported that if a glucose tolerance test is performed early after a myocardial infarction, >70% of patients will have abnormal results. Clearly, these abnormalities are not due to undiagnosed diabetes but are related to the stress of the acute event and return to normal in most subjects (6,7). Increased production of catecholamines and corticosteroids or altered liver perfusion are acute events that may be responsible for a short-term disturbance in glucose handling. Abnormalities do persist in a small number of patients but the follow-up data available is based on few patients and needs to be enlarged (7). We measured fasting blood glucose levels in a large group of patients with acute myocardial infarction and found that 3% of patients with no known history of glucose intolerance had abnormal results (>8 mM). These patients were older and had a significantly worse prognosis than the normoglycemic group when age was taken into account. The fact that the hyperglycemic group tended to have more complicated infarcts gives further support that the abnormal glucose handling is related to the stress of infarction. Cardiac enzymes did not differ significantly between the groups, but it has been shown that the release of certain stress hormones is not directly related to infarct size (4). Fasting blood glucose measurement identifies a small group of patients with a poor in-hospital prognosis that was not due to larger infarct size, as reflected in peak levels of cardiac enzymes. Because random blood glucose measurements are abnormal in nearly 50% of acute infarcts, fasting levels would appear to be a much more specific way of detecting abnormal glucose handling at infarction.

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Retrospective Analysis of Posttransplantation Diabetes Mellitus in Black Renal Allograft Recipients

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Objective: To study the incidence, outcome, and possible etiopathogenic factors involved in posttransplantation diabetes mellitus in cyclosporine-treated black renal allograft recipients. Research Design and Methods: One hundred thirty-eight nondiabetic black renal transplant recipients whose grafts survived >1 yr were studied retrospectively. Results: Twenty-eight (20.3%) patients developed posttransplantation diabetes mellitus, 46 and 75% were diagnosed by 6- and 12-mo posttransplantation, respectively, and 46% were insulin dependent. Diabetes was more frequently encountered in older recipients and recipients of cadaveric kidneys but was independent of sex, number of transplants, incidence of acute rejection, percentage of body weight gain, steroid or cyclosporine dose, and use of β-blockers and/or diuretics. Renal function was similar in the diabetic group compared with the control group. Actuarial 5-yr graft survival was 82% in the diabetic cohort compared with 78% in the control group, with chronic rejection accounting for all graft losses within the diabetic group. Conclusions: Twenty percent of black cyclosporine-treated renal allograft recipients developed diabetes mellitus in the posttransplantation period. However, its presence did not appear to influence intermediate-term graft or patient survival. *Diabetes Care* 14:760–62, 1991

New-onset diabetes mellitus, as defined by an abnormal glucose tolerance test or persistent hyperglycemia in the posttransplantation period, is a well-known complication of renal transplantation. Originally recognized by Starzl et al. (1) in 1964, the reported incidence in renal allograft recipients in the azathioprine era varied between 5 and 100% and was attributed to steroid intake (1–3). An increased incidence of new-onset diabetes has been noted among cyclosporine-treated renal allograft recipients (4), despite lower dosages of steroids, which suggests that cyclosporine may have an independent effect on carbohydrate metabolism.

This retrospective study was conducted among black renal allograft recipients to analyze the incidence and characteristics of posttransplant diabetes mellitus in the cyclosporine era and to determine the relative role of pre- and posttransplant factors in its etiopathogenesis.

RESEARCH DESIGN AND METHODS

Between 1983 and 1989, a total of 234 renal transplants were implanted in 229 black uremic subjects. All 138 nondiabetic adult (age >18 yr) recipients whose allografts survived >1 yr and whose pretransplant fasting serum glucose levels were normal (4.4–6.7 mM) on several occasions were retrospectively analyzed for the development of new-onset diabetes. In this study, new-onset diabetes was defined as the presence of three consecutive fasting serum glucose values >8.3 mM in former nondiabetic recipients (3). Immunosuppression consisted initially of cyclosporine (10–15 mg · kg^{-1} · day^{-1}) and prednisone (1 mg · kg^{-1} · day^{-1} postoperatively to 0.25 mg · kg^{-1} · day^{-1} at 3 mo) for living-related and cadaver donor transplants performed between 1983 and 1987. Subsequent to 1987, this protocol was confined to recipients whose allografts functioned immediately. Those with delayed graft function received antilymphocyte preparations until serum creatinine decreased by 50% without dialysis, at which time cyclosporine was instituted at 8 mg · kg^{-1} · day^{-1}. Cyclosporine dose was adjusted to maintain trough whole-blood level between 100 and 200 ng/ml by high-performance liquid chromatography. Azathioprine was added at a dose of 0.5–1 mg · kg^{-1} · day^{-1} to all recipients with symptoms or signs suggestive of cyclosporine toxicity. Treatment of acute rejection consisted of pulse methylprednisolone succinate followed by antilymphocyte preparations in nonresponders. The incidence, time of onset of diabetes, and requirement for insulin were noted. The influence of donor source; maintenance immunosuppression; recipient age; sex; HLA type; antihypertensive medications, specifically diuretics and β-blockers; renal function; incidence of rejection; and percentage of body weight gain in the 1st yr posttransplant were each studied by comparing black recipients who developed diabetes to all nondiabetic black recipients whose grafts survived >1 yr. Finally, actuarial 5-yr patient and graft survivals decaying from 100% at 1 yr were determined with the actuarial method. Student's unpaired t test and χ^2-analysis were used where appropriate.

RESULTS

Mean follow-up period for diabetic and nondiabetic black recipients was 3.7 ± 1.7 and 3.9 ± 1.6 yr, respectively. New-onset diabetes occurred in 28 (20.3%) recipients. There were 27 primary transplants, 16 men, and 1 recipient of a living-related kidney. Hypertension was presumed to be the most common cause of end-stage renal disease followed by glomerulonephritis (25%). Histological confirmation of renal disease was obtained in 8 patients. The mean age of diabetic recipients was significantly older compared with nondiabetic recipients (45 ± 9 vs. 40 ± 10 yr, respectively, $P < 0.01$). Posttransplantation diabetes was more frequently encountered in recipients of cadaveric allografts compared with recipients of living-related kidneys (24 vs. 4%, respectively, $P < 0.05$). Ten (36%) patients with new-onset diabetes had a family history of diabetes compared with 22 (20%) in the nondiabetic group. HLA-A30 and Bw42 were more frequently encountered in the diabetic group (32 vs. 19% and 18 vs. 7%, respectively, NS). The incidence of posttransplantation hypertension was similar in the diabetic group compared with the control cohort (71 vs. 70%, respectively). Both percentage of body weight gain (14 vs. 14%) and diuretic and β-blocker usage were also similar in diabetic and nondiabetic groups (100 vs. 97% and 61 vs. 65%, respectively). The most common presentation of posttransplantation diabetes was a persistently elevated serum glucose during a follow-up visit. Only 1 patient presented with diabetic ketoacidosis. Thirteen (46%) and 21 (75%) recipients, respectively, had developed diabetes by 6 and 12 mo, respectively. Three patients were diagnosed in the 2nd yr posttransplant and 2 patients each in the 3rd and 4th yr. Insulin and oral hypoglycemic agents were required in 13 (46%) and 9 (32%) recipients, respectively, with 6 patients achieving glucose control solely by diet. Only 1 patient who required insulin initially was subsequently controlled by diet alone. Posttransplantation diabetes was independent of both cyclosporine and prednisone dosage at 1, 3, 6, 9, and 12 mo posttransplantation. Likewise, the mean cyclosporine levels at 1 yr posttransplant were similar in diabetic recipients (133 ± 48 ng/ml) compared with the control group (149 ± 61 ng/ml). Furthermore, the incidence of acute rejection was similar in both groups (46% in diabetic patients and 49% in nondiabetic recipients). Actuarial 5-yr patient and graft survivals were 96 and 82%, respectively, in the diabetic cohort compared with 88 and 78%, respectively, in the nondiabetic group (NS). Chronic rejection, confirmed histologically,

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accounted for all five graft losses within the diabetic group. Renal function, as assessed by serum creatinine, was similar in both diabetic and nondiabetic groups, i.e., 205 and 197 μmol/dl at 1 yr and 231 and 239 μmol/dl at 3 yr, respectively.

CONCLUSIONS

Posttransplantation diabetes mellitus in the precyclosporine era was attributed to corticosteroids. Ruiz et al. (5) noted a decreased incidence of new-onset diabetes when the prednisone dosage was reduced, thus corroborating the term *steroid diabetes*. With the introduction of cyclosporine, its incidence increased in some (4) but not all studies, despite a lower incidence of rejection and lower dosages of steroids. This may be due to a direct diabetogenic effect of cyclosporine or an indirect effect due to the inclusion of older patients in the recipient pool. Diabetes increases with age in all ethnic groups, particularly black, Hispanic, and Native and Asian Americans (6). This retrospective analysis shows a 20.3% incidence of posttransplantation diabetes mellitus in a group of cyclosporine-treated black renal allograft recipients, which is significantly higher than a 3.6% incidence among whites of similar age followed at the same center (7) but slightly in excess of the 12.9% prevalence rate among American blacks in the same age-group (8). The mean age of the diabetic cohort in this study and most others (2,5) was greater than that of control subjects, in keeping with the known increased incidence of diabetes with age. A family history of diabetes was more frequently observed in those who developed diabetes posttransplant but did not appear to significantly segregate to a specific HLA-DR type, in general agreement with the literature (2). Surprisingly, in view of the known increased expression of diabetes with weight gain, there was no correlation between the incidence of posttransplantation diabetes and actual body weight at time of transplantation or weight gain posttransplantation, similar to some but not all previous studies. (3,9).

Diabetes was more frequently encountered in recipients of cadaveric kidneys compared with those who received living-related grafts and was independent of the steroid dose and number of rejection episodes. This may be attributed to selection bias, because diabetes has a strong familial predisposition, thus precluding living-related transplantation. Also, blacks, with their greater incidence of diabetes compared with whites, donate organs less frequently than whites (10). These factors may thus lead to a preponderance of candidates at high risk for the development of diabetes within the cadaveric recipient pool.

The natural history of posttransplantation diabetes is not yet well defined. Boudreaux et al. (9) noted poorer patient survival in their posttransplantation diabetic patients. Other studies, including this one, could not discern an unfavorable effect on patient and graft survivals, at least in the short term (5,11).

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