Some Characteristics of Steroid Diabetes: A Study in Renal-Transplant Recipients Receiving High-Dose Corticosteroid Therapy

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Risk factors and course of steroid diabetes were investigated in 145 renal-transplant recipients who were given a high-dose steroid regimen. Persistent steroid diabetes developed in 25% of the patients and transient diabetes in another 22%. When antidiabetic therapy was required, insulin had to be given in 50%. The incidence of steroid diabetes correlated with steroid dose, age, body weight, and diabetes heredity but not with abnormal glucose tolerance or with another complication of steroid therapy, posterior-pole lenticular cataract. There was no association with HLA-A and B antigens. Thus, steroid diabetes is a frequent complication of high-dose corticosteroid therapy and is similar to type II diabetes. However, it often requires insulin therapy. DIABETES CARE 6: 23–25, JANUARY–FEBRUARY 1983.

The term "steroid diabetes" was introduced in 1941 by Ingle[1] to describe hyperglycemia in rats receiving corticosteroids. The development of this form of diabetes in human beings during steroid therapy is well known.[2–4] The mechanisms behind steroid diabetes are unclear,[5] and the pathogenesis of this condition has so far only been studied in small patient populations (fewer than 20 patients[2–4,6–10]). To better understand risk factors and the course of this condition, a systematic study of a large group of patients with steroid diabetes is required. The present study describes steroid diabetes occurring in 67 renal-transplant recipients who received high-dose glucocorticosteroids as a part of the immunosuppressive regimen, such as was used some years ago.

MATERIALS AND METHODS

The series comprised 145 consecutive nondiabetic patients who were given their first renal transplant during the years 1973–1977. Patients who lost their grafts within 2 wk were excluded. An intrafamilial graft was given to 33 patients (23%); the others received cadaver kidneys. The immunosuppressive therapy consisted of prednisone, methylprednisolone, azathioprine, and anti-human lymphocyte globulin. On the first day 200 mg prednisone was given orally. From day 3 the dose was gradually reduced, at 1 mo to 30–40 mg/day and after a year to a maintenance dose of 10–15 mg/day. If rejection occurred the dose was increased to 200 mg/day and then reduced again as above. An intravenous injection of 1 g of methylprednisolone was given on three successive days after transplantation and also in the case of rejection.

The fasting blood glucose level was checked several times a week during the first month after transplantation and thereafter between 1 and 4 times per month. Diabetes mellitus was diagnosed when the fasting blood glucose level exceeded 8 mmol/L on two occasions. The observation time was 18.3 ± 1.3 mo (mean ± SE).

An oral glucose tolerance test (OGTT) was performed in some cases. After an overnight fast 35 g/m^2 of glucose was given and the blood glucose value after 2 h was determined. Normal values adjusted for age and sex were obtained from Sartor et al.[11]

Sixty-three patients were interviewed about the occurrence of diabetes among first-degree relatives (parents, sibs, or offspring).

HLA-A and B antigens were determined in all patients through the hospital's immunologic laboratory.

The occurrence of corticosteroid-induced posterior-pole lenticular cataract was analyzed in 75 consecutive renal-transplant recipients according to previously defined criteria.[12]

Student's unpaired *t* test and analysis of variance were used for statistical comparisons.

RESULTS

Diabetes mellitus occurred in 67 of the 145 renal-transplant recipients, with an average onset of 3 mo after transplantation. Age at transplantation was 49 ± 2 yr in the steroid diabetes group as compared with 42 ± 2 yr in the nonafflicted

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TABLE 1
Incidence of steroid diabetes in relation to steroid dose*

	Group I (N = 30)	Group II (N = 30)	Group III (N = 29)
Range of steroid dose (g/m^2 of body surface)	3.5–5.1	5.2–7.9	8.0–15.0
Frequency of steroid diabetes (%)	33	43	52

*Eighty-nine renal-transplant recipients with grafts functioning for more than 3 mo were investigated during the first 3 mo after transplantation. The patient population was divided into tertiles on the basis of the total supplement of steroids.

patients ($P < 0.01$). The relative body weight was higher in the steroid diabetes group than among those not affected (91 ± 2% versus 86 ± 1%; $P < 0.01$). The development of steroid diabetes was not associated with sex or type of kidney graft or influenced by diuretic or antihypertensive therapy (i.e., the use of furosemide, beta blockers, and saluretic drugs).

There was a positive correlation between the total dose of steroids received during the first 3 mo and the frequency of steroid diabetes (Table 1).

The frequencies of the HLA antigens B28, B7, B8, and B15 were in the same range among steroid diabetic and nondiabetic patients. However, a hereditary trait for diabetes mellitus among first-degree relatives occurred 7 times more frequently ($P < 0.01$) in the patients with steroid diabetes (35%) than among the other patients (5%).

In 19 of the 67 diabetic patients the blood glucose level was normalized within 2 wk without specific treatment; the remaining 48 patients had hyperglycemia for more than 2 wk. Although ketosis was not observed, as many as 26 of the latter patients required insulin therapy. After an average of 4 mo there was a complete remission of steroid diabetes in 12 of the 48 patients. Table 2 shows some differences in the characteristics between those with and without remission of steroid diabetes. Remission correlated with lower age and less frequent insulin treatment. Thus, the incidence of permanent diabetes in the whole population was 36/145 (25%). The prevalence of diabetes mellitus was on average 16 times higher among renal-transplant recipients than among the general population in Sweden (Table 3).

OGTT was performed in four patients who had recovered from steroid diabetes and in six carefully matched nondiabetic transplant recipients (Table 4). Normal as well as pathologic OGTTs were present in both groups of patients.

There was no association between steroid diabetes and another common complication of steroid therapy, posterior-pole lenticular cataract. The frequency of cataract was 57% among steroid diabetic and 42% among nondiabetic patients.

DISCUSSION

The frequency of steroid diabetes in our series is considerably higher than has been reported by others.[4,6,10,13] We observed postoperative hyperglycemia in about half of our renal-transplant recipients and permanent diabetes requiring therapy in 25%. This difference may be due to the high proportion of elderly patients in our series. Our frequency was similar to what we previously observed[14] in a smaller series of renal-transplant recipients.

The pathophysiologic mechanisms behind steroid diabetes are unclear, but several mechanisms have been suggested to explain how glucocorticosteroids can induce glucose intolerance (see ref. 5 for a review). It is therefore surprising that we observed some normal OGTTs among those patients who had had transient steroid diabetes and pathologic OGTTs among some patients who did not develop diabetes. Thus, additional factors besides glucose intolerance may have to be present in order to develop the complication. It is interesting to note the strong similarity between steroid diabetes and type II diabetes. We found a hereditary trait for diabetes among first-degree relatives of patients who developed steroid diabetes and observed that the occurrence of steroid diabetes correlated with age and body weight, which are familiar risk factors for type II diabetes. David et al. observed an increased

TABLE 2
Characteristics of 48 patients who developed steroid diabetes after renal transplantation*

	Remission of diabetes (N = 12)	No remission (N = 36)	P
Age at transplantation (yr)	44 ± 5	54 ± 2	<0.05
Relative body weight at transplantation (%)	100 ± 4	91 ± 2	NS
Observation time (mo)	18 ± 5	15 ± 2	NS
Treatment (%)			
Diet	17	17	NS
Sulfonylurea	50	22	NS
Insulin	33	61	<0.05

*Patients were divided into two groups. In one group there was no remission of diabetes. In the other group there was a complete remission after an average 4 mo.

TABLE 3
Prevalence of persistent steroid diabetes*

Attained age (yr)	Renal-transplant recipients: All (N)	Steroid diabetes: N	Steroid diabetes: Percent	Control data (%)
0–24	20	0	0	0.17
24–44	39	5	12.8	1.07
45–54	43	10	23.3	1.29
55–64	39	20	51.3	3.02
65–74	4	1	25.0	5.30
All	145	36	24.8	1.51

*The prevalence of diabetes that occurred in renal-transplant recipients and that showed no sign of remission (see Table 2) was compared with the prevalence of diabetes in the general population of Sweden. The latter control data were obtained from tables computed by Grönberg et al.[15]

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TABLE 4
Results of an oral glucose tolerance test (OGTT) performed on renal-transplant recipients with remission of steroid diabetes and in renal-transplant recipients without evidence of posttransplantation diabetes (control group)*

	Time after transplantation (mo)	Total steroid dose at OGTT (g)	2-h OGTT value (mmol/L)	Outcome of OGTT (abnormal/normal)
Remission of steroid diabetes (N = 4)	26 (16–47)	11 (7–15)	7.4 (4.7–10.6)	2/2
Controls (N = 6)	22 (11–47)	13 (10–15)	6.9 (3.9–10.6)	2/4

*The two groups were in good health and matched for sex, age, body weight at transplantation, as well as for diet habits and drug intake. The duration of diabetes before remission ranged from 2 to 6 mo (mean 4 mo). Values are mean and range.

frequency of HLA-A28 among renal-transplant patients developing steroid-induced diabetes.[13] We observed no association between HLA antigens and steroid diabetes.

It is not probable that steroid diabetes is due to patient hypersensitivity to glucocorticosteroids, since we observed no correlation between diabetes and posterior-pole lenticular cataract, which is another complication of steroid therapy. However, that steroid diabetes is a dose-dependent complication is evident from several facts. First, signs of steroid diabetes in renal-transplant recipients are often first detected after increasing the dose of immunosuppressive drugs at rejection episodes.[14] Second, steroid diabetes after kidney transplantation is more common among recipients of cadaver organs receiving high prednisone doses than among those receiving intrafamiliar grafts and low doses of prednisone.[4] Finally, in this study we observed a close correlation between the dose of corticosteroids and the incidence of steroid diabetes.

It has been inferred that the metabolic abnormalities of steroid diabetes are mild and that the complication can usually be managed without long-term insulin treatment.[4,9,10] In the present study, however, about every second patient developing the complication needed chronic insulin therapy in order to achieve adequate blood glucose levels.

It is well known that the signs of steroid diabetes may disappear when the dose of corticosteroids is reduced. In the present series postoperative hyperglycemia remained in about half of the patients in spite of the reduction of steroid dosage to maintenance levels (10–15 mg/day of prednisone). Unfavorable prognostic signs appear to be old age and insulin requirement for glucose control.

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