ORIGINAL ARTICLE

Lung Transplantation and the Development of Diabetes Mellitus in Adult Patients With Cystic Fibrosis

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OBJECTIVE: The prevalence of diabetes mellitus is higher in patients with cystic fibrosis than in the general population.

Solid organ transplantation is a significant risk factor for diabetes mellitus, which has been linked to type of immunosuppression. The aim of this study was to analyze whether lung transplantation represents a significant risk factor for the onset of abnormal carbohydrate metabolism in cystic fibrosis, whether it affects severity of alterations, and whether there is a relation to type of immunosuppression.

PATIENTS AND METHODS: The following data were extracted retrospectively for 54 patients with cystic fibrosis: type of carbohydrate metabolism alteration and treatment received, whether or not transplantation took place, and type of immunosuppression used.

RESULTS: Twenty of the 54 patients (37%) underwent lung transplantation; 18 of them (89%) developed diabetes mellitus. Eight of the patients (24%) who did not receive a lung developed diabetes and 10 (29%) displayed carbohydrate intolerance ($P<.01$, χ^2 test). Insulin was administered to 36.3% of nontransplanted patients and 78.6% of transplanted patients. The influence of immunosuppressant used was analyzed in 15 patients. Nine out of 10 patients (90%) treated with cyclosporine and 4 out of 5 (80%) of those treated with tacrolimus developed diabetes mellitus. All received the same regimen of corticosteroid therapy.

CONCLUSIONS: For cystic fibrosis patients, lung transplantation is a significant risk factor for developing abnormal carbohydrate metabolism and it influences severity and treatment. No significant differences in the frequency of development of diabetes mellitus were found in relation to type of immunosuppression.

Key words: *Cystic-fibrosis-related diabetes. Diabetes and cystic fibrosis. Post-transplantation diabetes mellitus.*

Importancia del trasplante pulmonar en la aparición de diabetes mellitus en pacientes adultos con fibrosis quística

OBJETIVO: La prevalencia de diabetes mellitus (DM) en pacientes con fibrosis quística (FQ) es mayor que en la población general.

El trasplante de órganos sólidos es un factor de riesgo importante para el desarrollo de DM y se ha relacionado con el tipo de inmunodepresión. El objetivo del estudio ha sido analizar si el trasplante pulmonar (TP) es un factor de riesgo importante para desarrollar alteración hidrocarbonada en la FQ, si influye en su gravedad y tratamiento, y si existe relación con el tipo de inmunodepresión.

PACIENTES Y MÉTODOS: Se estudió retrospectivamente a 54 pacientes adultos con FQ, sobre los que se recogieron los siguientes datos: tipo de alteración hidrocarbonada y su tratamiento, existencia o no de TP y tipo de inmunodepresión.

RESULTADOS: De los 54 pacientes, 20 recibieron TP (37%). De éstos, el 89% (n = 18) presentó DM. Entre aquellos que no recibieron TP, el 24% (n = 8) presentó DM y el 29% (n = 10) intolerancia hidrocarbonada ($p < 0,01$; prueba de χ^2). Se pautó insulina al 36,3% de los pacientes sin TP y al 78,6% de los trasplantados. La influencia de la inmunodepresión se analizó en 15 pacientes. Desarrollaron DM el 90% (9/10) de los tratados con ciclosporina y el 80% (4/5) de los tratados con tacrolimus. Todos llevaban la misma pauta de corticoterapia.

CONCLUSIONES: El TP es un factor de riesgo importante para el desarrollo de alteración hidrocarbonada en pacientes con FQ e influye en su gravedad y tratamiento. No hemos encontrado diferencia significativa entre el tipo de inmunodepresión y la aparición de DM.

Palabras clave: *Fibrosis quística. Diabetes relacionada con fibrosis quística. Diabetes mellitus postrasplante.*

Introduction

Cystic fibrosis is a multisystemic disease, affecting the lung, the endocrine and exocrine pancreas, and other organs. With an incidence of approximately 1 in every 2500 live births,[1] cystic fibrosis is the most common severe autosomal recessive genetic disease in the white population. The exocrine pancreas is involved in 85% to 90% of patients and lesions begin to develop in the uterus. Endocrine pancreatic dysfunction, however, comes later and increases with age.[2]

The early diagnosis and treatment of cystic-fibrosis–related diabetes mellitus (CFRD) are important because inadequate control over glucose levels will worsen respiratory function in these patients and lead to higher morbidity[3] and mortality[2] rates.

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Manuscript received December 20, 2005. Accepted for publication May 16, 2006.

Abnormal carbohydrate metabolism develops in patients with exocrine pancreatic insufficiency, particularly carriers of the ΔF508 mutation, and the prevalence of diabetes is 100-fold higher in cystic fibrosis patients than in the general population. A factor that can influence the incidence of abnormal carbohydrate metabolism in these patients, lung transplantation, is an end-stage treatment and the only alternative in many cases. A serious, common complication of solid organ transplantation is diabetes mellitus. Numerous studies have analyzed the factors that affect the onset of diabetes,[4,5] and type of immune suppression employed has been identified as relevant. Studies have most often been done in the setting of kidney transplantation but similar factors must be involved in patients who undergo other procedures such as lung transplantation.

Considering that patients with cystic fibrosis are a population at risk, with greater predisposition to abnormal carbohydrate metabolism, it would seem that the incidence of diabetes in these patients would rise considerably because of added risk from transplantation and associated therapy. One recent study suggested this hypothesis.[6]

The aim of the present study was to analyze whether lung transplantation constitutes an important risk factor for developing abnormal carbohydrate metabolism in cystic fibrosis patients, whether it influences the severity and treatment of such abnormalities, and whether there exists a relation with type of immunosuppression initially employed.

Patients and Methods

This retrospective, cross-sectional study included 54 patients with cystic fibrosis treated at the endocrinology clinic of Hospital Universitario La Fe in Valencia, Spain. The following data were gathered: sex, age at the time of the study, weight, height, body mass index (kg/m^2), insulin, and glucose levels at baseline and 120 minutes after oral intake of 75 g of glucose. Glycemia was determined by the enzymatic method (glucose oxidase) with the AU5400 analyzer (Olympus Europe, Hamburg, Germany). Insulin levels were determined with a chemical luminescence immunoassay (IMMULITE 2000, Diagnostic Products Corporation, Los Angeles, California, USA). The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated according to the following formula[7]: (insulin level in μU/mL × glucose level in mmol/L)/22.5.

Type of mutation was analyzed in 31 patients; no information was available for the remaining patients. In certain cases in Hospital Universitario La Fe, exon sequences and adjacent intron sequences were amplified by way of polymerase chain reaction, followed by a search for the mutations that are most common in the Spanish population. We used single-strand conformation polymorphisms and heteroduplex analysis or restriction-enzyme digestion.

Information on exocrine pancreatic insufficiency was obtained for 45 patients by the van de Kamer method. Fat in stool collected over 3 consecutive days under a diet rich in fat starting 3 days earlier was analyzed with infrared spectrophotometry (FENIR 8820, Alerbio, Madrid, Spain). A finding of more than 6 g/d of fat in stool was considered abnormal.

Whether or not transplantation was carried out was recorded. If the procedure was performed, the following data was also noted: age at the time of transplantation, time since transplantation, whether or not there was a prior history of abnormal carbohydrate metabolism and what type, the development or not of nontransient post-transplantation diabetes mellitus, when it developed and the treatment required, and the type of immunosuppression initially used.

There are no clinical manifestations that indicate a diagnosis of abnormal glucose tolerance and the condition remains undiagnosed if it is not studied systematically.[8] Therefore, it is currently accepted that carbohydrate metabolism should be assessed when these patients have associated exocrine pancreatic insufficiency and are over 10 years old. The established protocol calls for an annual glucose tolerance test,[2,9] according to which patients are classified in 5 categories (criteria of the American Diabetes Association for 2004):

1. Normal glucose tolerance: fasting glucose level less than 100 mg/dL (<140 mg/dL at 2 hours).
2. Impaired fasting glucose tolerance: fasting glucose level of 100 to 125 mg/dL (<140 mg/dL at 2 hours)
3. Impaired carbohydrate tolerance: fasting glucose level less than 126 mg/dL (140-199 mg/dL at 2 hours).
4. CFRD, without fasting hyperglycemia: fasting glucose level less than 126 mg/dL (≥200 mg/dL at 2 hours).
5. CFRD, with fasting hyperglycemia: fasting glucose level 126 mg/dL or more (≥200 mg/dL at 2 hours).

Patients not diagnosed with diabetes who developed exocrine pancreatic insufficiency and who were followed at our clinic underwent oral glucose tolerance testing annually. Follow-up after transplantation also included fasting glucose levels. This information was not available for patients referred from other hospitals for transplantation who were not previously examined at our hospital. Carbohydrate metabolism classification of such patients was based on medical history and fasting blood tests.

Post-transplant diabetes mellitus was defined as the presence of hyperglycemia, according to the criteria of the American Diabetes Association of 2004, beyond 30 days after transplantation, whether medical treatment was necessary or not.[10,11]

Data were analyzed with the SPSS software package, version 12.0. Quantitative variables were expressed as mean (SD) and range. Qualitative variables were expressed as percentages and compared with a χ^2 test.

Transplanted patients who were already diabetic (n=4) were included in the nontransplanted treatment group; this was because transplantation could not be considered a factor that influenced treatment type in these patients, who were already receiving insulin. Therefore, treatment type was only considered for the 14 patients with post-transplantation diabetes. The 10 patients with impaired carbohydrate tolerance, the 8 nontransplanted patients with CFRD, and the 4 transplanted patients with CFRD were included in the nontransplanted group. Patients without impaired carbohydrate metabolism, who required no treatment, were excluded from both groups.

The influence of initial immunodepression was only analyzable in the 16 patients who did not have diabetes before transplantation. As information was unavailable for 1 of them the number finally analyzed was 15. All patients were on triple immunosuppression, receiving a calcineurin inhibitor (cyclosporin in 10 and tacrolimus in 5), a calcineurin-inhibitor–free immunosuppressant (azathioprine in 13 and mycophenolatmofetil in 2), and prednisone. Doses were similar for all patients.

Results

Thirty-four of the 54 patients (63%) were male and 20 (37%) were female. Mean age at the time of the study was

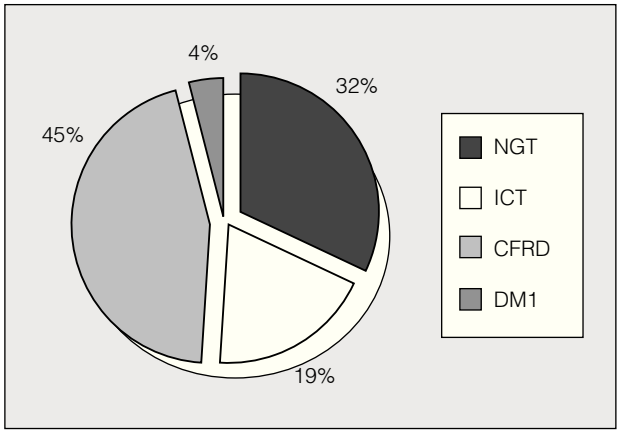


Figure 1. Distribution of carbohydrate metabolism abnormalities in the study population (n=54). DMT indicates type 1 diabetes mellitus; CFRD, cystic-fibrosis–related diabetes (including both pre- and post-transplantation cases); ICT, impaired carbohydrate tolerance; NGT, normal glucose tolerance.

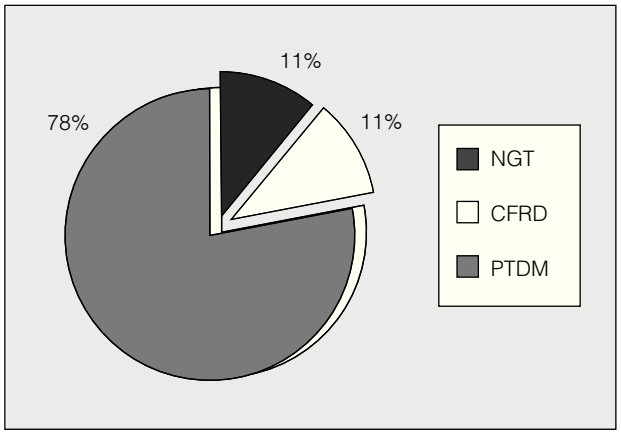


Figure 2. Distribution of carbohydrate metabolism abnormalities in transplanted patients (n=18). PTDM indicates post-transplantation diabetes mellitus (all with fasting hyperglycemia); CFRD, cystic-fibrosis–related diabetes (all with fasting hyperglycemia); NGT, normal glucose tolerance.

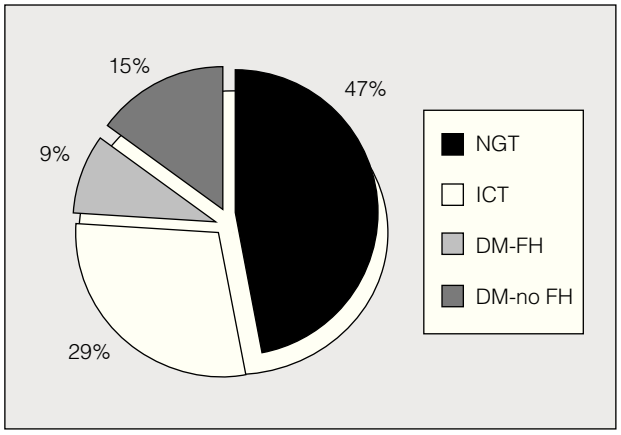


Figure 3. Distribution of carbohydrate metabolism abnormalities in patients who did not undergo transplantation (n=34). DM-FH indicates diabetes mellitus with fasting hyperglycemia; DM-no FH, diabetes mellitus without fasting hyperglycemia; ICT, impaired carbohydrate tolerance; NGT, normal glucose tolerance.

25.4 (4.7) years (range, 15-39 years). Body mass index was 20.4 (3.3) kg/m^2 (range, 14.3-28.2 kg/m^2).

The distribution of types of abnormal carbohydrate metabolism in all patients at the time of the study are shown in Figure 1. The prevalence of diabetes mellitus was 45%. The HOMA-IR index was 1.14 (0.65).

Twenty of the 54 patients included (37%) underwent transplantation. Their mean age at the time of the operation was 19.6 (4.9) years (range, 10-31 years) and mean time elapsed (between transplantation and the time of the study) was 5.3 (3.2) years (range, 2 months to 11 years).

Eighteen (58.1%) carriers of the ΔF508 mutation were heterozygous and 5 (16.1%) were homozygous; 8 (25.8%) patients carried other mutations. All ΔF508 homozygotes experienced some form of abnormal carbohydrate metabolism: 60% (n=3) developed impaired carbohydrate tolerance and 40% (n=2) developed diabetes. Half of the ΔF508 heterozygotes or carriers of another type of mutation had normal glucose tolerance and half developed impaired carbohydrate tolerance or diabetes.

Thirty-nine patients (86.7%) developed exocrine pancreatic insufficiency. Among those patients who did not (13.3%, n=6), none had abnormal carbohydrate metabolism, none underwent transplantation, none carried the ΔF508 homozygous mutation, and all were at least 23 years of age at the time of the study.

Two of the transplanted patients (Figure 2) had CFRD and another 2 had type 1 diabetes mellitus before transplantation. Fourteen of the 16 remaining patients (87.5%) developed nontransient post-transplantation diabetes mellitus and 2 maintained normal glucose levels. The 2 patients with type 1 diabetes mellitus were excluded from this analysis, as their carbohydrate metabolism abnormalities were unrelated to cystic fibrosis or transplantation.

Four of the 20 transplanted patients were already diabetics and 16 were not. Fourteen of 16 nondiabetic patients developed post-transplantation diabetes mellitus. Before transplantation, 2 had impaired carbohydrate tolerance, and 9 had no carbohydrate metabolism disorder as demonstrated by a glucose tolerance test; the 3 remaining patients reported no prior metabolic impairment but tolerance test information was unavailable as they had been treated in another hospital.

Impaired carbohydrate tolerance was more common than diabetes among the patients who did not undergo transplantation (Figure 3). The prevalence of abnormal carbohydrate metabolism was significantly related to lung transplantation ($P<.01$, χ^2 test). The prevalence of diabetes was 89% in transplanted patients (78% of those with post-transplantation diabetes mellitus and 11% of those with who already had CFRD). In patients not undergoing transplantation, 24% developed CFRD and 29% developed impaired carbohydrate tolerance; the remaining patients had normal glucose tolerance (Figure 4).

The time elapsing before the appearance of post-transplantation diabetes mellitus was 1.8 (2.5) years (range, immediately to 7 years later). Time of follow-up of post-transplantation diabetes mellitus was 4.5 (3.4) years (range, 6 months to 11 years).

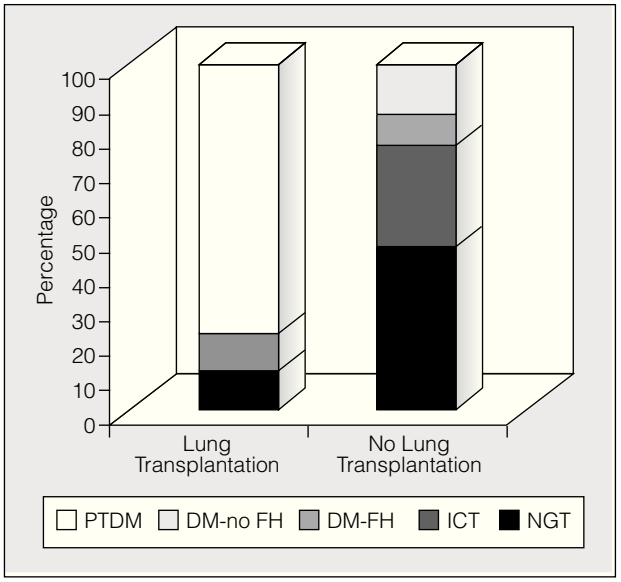
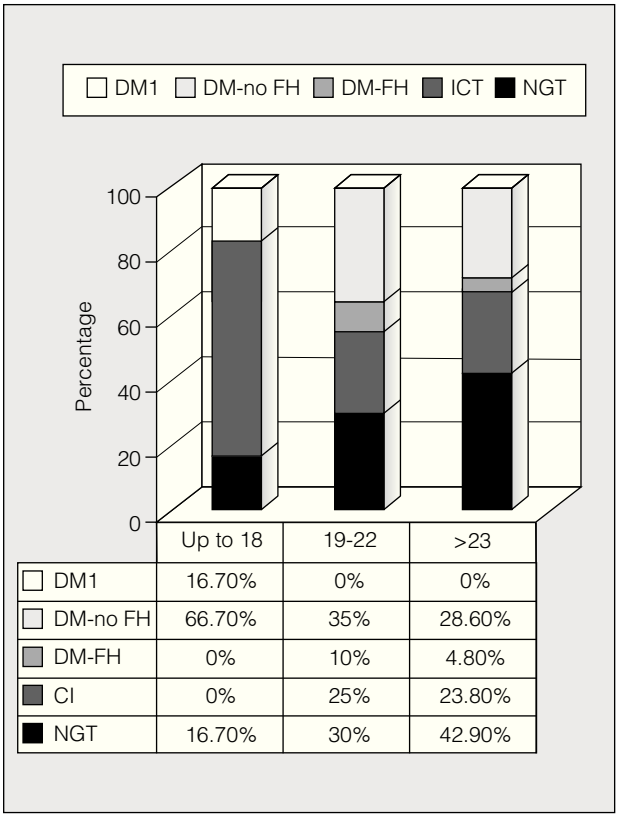


Figure 4. Abnormal carbohydrate metabolism after lung transplantation. DM-FH indicates diabetes mellitus with fasting hyperglycemia; PTDM indicates post-transplantation diabetes mellitus (all with fasting hyperglycemia); DM-no FH, diabetes mellitus without fasting hyperglycemia; ICT, impaired carbohydrate tolerance; NGT, normal glucose tolerance.



	Up to 18	19-22	>23
DM1	16.70%	0%	0%
DM-no FH	66.70%	35%	28.60%
DM-FH	0%	10%	4.80%
CI	0%	25%	23.80%
NGT	16.70%	30%	42.90%

Figure 5. Distribution of types of abnormal carbohydrate metabolism by age in years. The first bracket included all ages up to 18 years. DM1 indicates type 1 diabetes mellitus; DM-FH, diabetes mellitus with fasting hyperglycemia; DM-no FH, diabetes mellitus without fasting hyperglycemia; ICT, impaired carbohydrate tolerance; NGT, normal glucose tolerance.

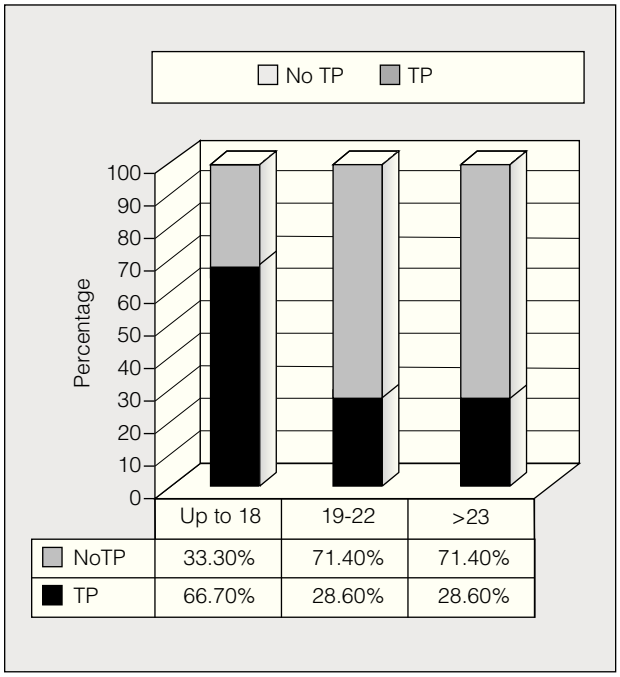
Figure 5 shows the distribution of carbohydrate metabolism abnormalities by age brackets. In patients up to 18 years old, 66.7% had diabetes, whereas the prevalence was 45% in patients aged 19 to 22 years and 33.4% in those aged 23 years or older. Thus, the prevalence of normal glucose tolerance increased with age ($P<.05$, χ^2 test). We analyzed whether age was related to lung transplantation (Figure 6). The age bracket up to 18 years had most of the diabetic patients and most of the transplanted patients (66.7%), whereas most of the patients not undergoing transplantation (71.4%) were in the other 2 age brackets, which also had most of the nondiabetic patients ($P=.05$, χ^2 test).

Analysis by treatment showed that 11of the non-transplanted patients (50%) required only dietary treatment, 3 (13.6%) required oral antidiabetic drugs, and 8 (36.3%) required insulin. Among transplanted patients, 2 (14.3%) only followed a special diet, 1 (7.1%) received oral antidiabetic treatment, and 11 (78.6%) required insulin.

Analysis by type of immunosuppression showed that post-transplantation diabetes mellitus developed in 9 of the 10 patients treated with cyclosporin (90%) and 4 of the 5 treated with tacrolimus (80%). The differences were not significant.

Discussion

In this patient series with a mean age of 25 years at the time of study, the prevalence of diabetes mellitus was 45%, slightly higher than the rates of 15% to 35% described in the literature for cystic fibrosis patients in that decade of life.[2,12-14] None of the cited studies related the prevalence of abnormal carbohydrate metabolism to lung transplantation, which could be one of the factors that



	Up to 18	19-22	>23
NoTP	33.30%	71.40%	71.40%
TP	66.70%	28.60%	28.60%

Figure 6. Distribution of patients undergoing or not undergoing lung transplantation by age in years. TP indicates transplantation

would explain a higher or lower frequency of impaired carbohydrate tolerance.

In our study the higher prevalence of abnormal carbohydrate metabolism, and especially of diabetes mellitus with fasting hyperglycemia, was observed in patients aged 18 years or younger (15-18 years). This observation is inconsistent with what might be expected, that abnormal carbohydrate metabolism would become more prevalent with age.[2] The pattern observed in our study is probably attributable to the fact that most lung transplant procedures were performed in patients in the youngest age bracket (66.7% vs 28.6% in each of the other 2 brackets); therefore, the youngest patients had a higher prevalence of abnormal carbohydrate metabolism (P=.05, χ^2 test). Lung transplantation seems to have considerable impact on the development of CFRD. One recent study compared the prevalence of diabetes before and after transplantation in the same population of cystic fibrosis patients.[6] The prevalence before transplantation of 28.6% rose to 49.4% afterwards (P=.008), thus attesting to a noteworthy influence of lung transplantation on the onset of diabetes in these patients. Another recent study described a prevalence of post-transplantation diabetes mellitus in cystic fibrosis patients of 56.3%.[15] The prevalence in our study was even higher at 89%. The differences might be attributable to differences in criteria used to define post-transplantation diabetes mellitus. We defined the condition as the persistence of high glucose levels for more than 30 days after transplantation, regardless of the need for medical treatment of the condition or not.[10,11] Other authors have used the persistence of high glucose levels beyond 60 days after transplantation to define the condition.[6] Such differences mean that studies of the prevalence of post-transplantation diabetes mellitus are difficult to compare and they explain the large discrepancies reported.

The pathogenesis of CFRD is multifactorial. The main cause is insulin deficiency because of loss of pancreatic β cells due to fibrosis and fatty infiltration of islets.[16] Insulin resistance may intervene in some situations such as when a patient is taking glucocorticoid treatment or during puberty, but outside of such contexts its role is less clear and studies have yielded inconsistent results.[17,18] The HOMA-IR values in our patients were normal, indicating absence of insulin resistance. These considerations would be important for management, given that it would be inappropriate to administer drugs to overcome insulin resistance. Instead, treatment should be based on drugs capable of stimulating insulin secretion.

We observed that the prevalence of diabetes in transplanted patients was 89% (78% with post-transplantation diabetes mellitus and 11% with CFRD before transplantation), whereas nontransplanted patients developed impaired carbohydrate tolerance (29%) more often than diabetes (24%) and 47% maintained normal glucose metabolism. The differences were statistically significant (P<.01, χ^2 test). These observations provide additional support for the hypothesis that transplantation plays an important role in the onset of diabetes in these patients. Fourteen of the 16 patients who underwent transplantation and were not already diabetic, developed post-transplantation diabetes mellitus and only 2 maintained normal glucose levels.

Numerous studies have looked at the relationship between solid organ transplantation and the development of impaired carbohydrate metabolism.[4,5,19-21] Post-transplantation diabetes mellitus is currently recognized as one of the most severe complications of this procedure, as it is associated with lower graft and patient survival rates and it increases the risk of other complications. The real incidence of this serious complication is unknown because of a lack of unified criteria for diagnosis, as can be observed in the variety of published studies that can not be compared. Diagnostic and treatment guidelines arising from consensus should therefore be followed.[10,11] A recent review of 56 publications appearing between 1992 and 2002 estimated an incidence of post-transplantation diabetes mellitus of 13.4% in solid organ recipients.[22] That review included a large number of kidney and liver transplantation procedures but a much smaller number of heart transplants and hardly any relating diabetes to lung transplantation. The incidence of post-transplantation diabetes mellitus we observed in cystic fibrosis patients was 87.5%, a much higher rate than has been reported by other authors. The discrepancy is probably attributable to a 100-fold higher prevalence of diabetes in the natural course of cystic fibrosis than is found in the general population.

Numerous studies have assessed the influence of the protocol chosen for immunosuppression on the development of post-transplantation diabetes mellitus.[23-26] Calcineurin inhibitors have long been known to be associated with higher rates of post-transplantation diabetes mellitus and a greater ability of tacrolimus to trigger diabetes in comparison with cyclosporin in the context of kidney, liver, heart, and lung transplantation was recently demonstrated by meta-analysis.[22] The concomitant use of corticosteroids to lower the risk of rejection means that there is additional risk from their effect of enhancing insulin resistance.

We failed to detect a statistically significant difference between tacrolimus and cyclosporin with regard to the onset of post-transplantation diabetes mellitus, probably owing to the small number of patients in whom that variable could be studied (n=15). It is also possible that cystic fibrosis patients make up a special group because of their greater natural tendency to diabetes. The influence of type of immunosuppression may be less pronounced in them than in other transplant recipients.

The treatment protocols used in post-transplantation diabetes mellitus are generally the same ones prescribed for type 2 diabetes mellitus.[10,11] The first intervention is a lifestyle change. The next steps are to add oral antidiabetic drugs and then insulin, depending on the level of metabolic control achieved. Patients with cystic fibrosis who undergo transplantation are a special group because of the reduced pancreatic insulin release that is natural to their disease; consequently, management of post-transplantation diabetes mellitus may be different in these patients than in other organ recipients. Over 60% of our nontransplanted patients achieved adequate control of glucose levels without insulin, with dietary changes with or without oral antidiabetic agents; over 75% of transplanted patients, however, required insulin. This may be attributed to the higher prevalence

among nontransplanted patients of impaired carbohydrate tolerance and diabetes without fasting hyperglycemia (38% diagnosed by oral glucose tolerance testing) in comparison with the prevalence of diabetes with fasting hyperglycemia (15%); the prevalence of fasting hyperglycemia among transplanted patients, in contrast, was 89%. These differences in the severity of abnormal carbohydrate metabolism would mark the difference in treatment applied. When oral antidiabetic agents were prescribed, the drugs of choice were glinides at varying dosages.

Upon reviewing the literature, we found 2 studies evaluating the incidence of post-transplantation diabetes mellitus in patients with cystic fibrosis who undergo lung transplantation.[6,15] Patients with this hereditary disease have a high prevalence of abnormal carbohydrate metabolism per se, whether in the form of diabetes mellitus or impaired carbohydrate tolerance. Therefore, they form a group of patients for whom it is logical to assume that post-transplantation diabetes mellitus would be more common if they become solid organ recipients because of the additional toxic effect of immunosuppressants on pancreatic β cells plus the effect of corticosteroids on insulin resistance, both superimposed on an already impaired pancreatic function.

We observed that lung transplantation is the most important risk factor for the development of diabetes in cystic fibrosis patients. However, we studied a small number of patients and our observations should be confirmed in a larger population. Our results should serve to underline the importance of careful monitoring of glucose levels in cystic fibrosis patients who undergo lung transplantation, even when their glucose tolerance is normal. Such monitoring should be carried out over the long term, given that the mean time elapsing between transplantation and the onset of diabetes in our study was 1.8 years and some cases did not appear until 7 years later. Detecting and treating abnormal carbohydrate metabolism early could contribute to lower morbidity and mortality rates in these patients.

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