Outcome of Cystic Fibrosis-Related Diabetes Two Years after Lung Transplantation

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Key Words

Cystic fibrosis • Diabetes mellitus • Lung transplantation

Abstract

Background: Although transplantation is known to impair glucose tolerance, evolution of pre-existing diabetes after lung transplantation (LT) in cystic fibrosis (CF) has never been described. **Objectives:** We aimed to assess the outcome of CF-related diabetes (CFRD) after LT, with the hypothesis that suppressing chronic inflammatory foci may improve glucose tolerance in some patients. **Methods:** In a retrospective study of 29 CF diabetic patients treated with insulin and undergoing LT, CFRD control was assessed 3 months before LT and 1 (n = 27) and 2 (n = 18) years after LT by measuring insulin dosage, fasting blood glucose and glycosylated hemoglobin (HbA1c) levels. Patients with HbA1c ≤ 7% and an insulin dose ≤ 1 UI/kg/day were defined as having controlled CFRD (group A). Other patients were assigned to group B. **Results:** Before LT, 19 (65.5%) patients were in group A. At 2 years, 6 of 10 (60%) patients who were in group B prior to LT had moved into group A, which then comprised

77.8% of all patients. Insulin could have been stopped in 5 patients. Uncontrolled CFRD before LT (OR = 16) and a long delay between the diagnosis of CFRD and LT (OR = 1.3) were significant predictors of uncontrolled CFRD at 1 year. **Conclusions:** LT does not seem to worsen CFRD in some patients, suggesting that in some cases, glucose tolerance may be improved by the suppression of chronic pulmonary infection.

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Introduction

Cystic fibrosis (CF) is the most common severe autosomal recessive genetic disease in Caucasians. It is caused by a mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride ion channel whose abnormal function leads to hyper-viscosity of exocrine secretions and obstructive damage

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in many organs, including the airways, exocrine pancreas, vas deferens and hepatobiliary tract. Exocrine pancreatic insufficiency occurs in about 85 to 90% of CF patients [1]. These patients are at risk of developing cystic fibrosis-related diabetes (CFRD) because of the combination of decreased insulin secretion (caused by chronic pancreatic obstruction) and insulin resistance, which is heightened by chronic pulmonary infection and the use of corticosteroids [2, 3]. The prevalence of CFRD increases dramatically with age, from 9% in patients aged 5–9 years to more than 50% in patients over 30 years old [3, 4]. Concomitantly, despite the fact that advances in treatment have moved the median survival time to 40 years, age remains strongly associated with a progressive decline in pulmonary function. This loss of function leads more than 95% of CF patients to die of respiratory failure [5].

In the past 10 years, bilateral lung transplantation (LT) has emerged as the most effective means of improving survival rates and quality of life in CF patients with end-stage respiratory disease. In 2009, CF accounted for 26.6% of all bilateral lung transplants reported in the registry of the International Society for Heart and Lung Transplantation (ISHLT) [6]. A recent French series reported that 28% of CF patients undergoing LT were being treated with insulin for diabetes mellitus [7]. Following transplantation, immunosuppressive medications, such as corticosteroids and tacrolimus and the major stress response caused by surgery can cause impaired glucose tolerance and CFRD. In some cases, however, it seems that CFRD is improved after LT, possibly because a chronic inflammatory focus has been suppressed. Until now, the progression of pre-existing CFRD following LT has not been described.

In this study, we aimed to describe the evolution of metabolic status after LT in diabetic CF patients treated with insulin before transplantation. We hypothesized that the condition of patients suffering from highly impaired insulin secretion might worsen with immunosuppressive drugs and that these patients should benefit from combined lung and pancreatic islet transplantation. Conversely, we supposed that patients with diabetes mainly due to insulin resistance might actually see an improvement in their glucose tolerance following LT because of the suppression of chronic pulmonary infection.

Material and Methods

In a retrospective observational study, we analyzed data from diabetic CF patients who had undergone LT for CF in one of four French reference centers between 2005 and 2010. Only patients treated with insulin before transplantation were included. Diabetic

control was assessed according to (1) laboratory testing of fasting blood glucose (FBG) level (normal value in our laboratory: 3.85–6.05 mmol/l); (2) glycosylated hemoglobin (HbA1c) level, considered as a marker of diabetes progression [8], although it can be normal in CF patients regardless of the degree of hyperglycemia [4, 9] and (3) daily insulin dose, considered as an indirect marker of pancreatic function and diabetes control in this context of possible increased insulin requirements due to immunosuppressive drugs such as corticosteroids and tacrolimus. Data were collected during a single clinic visit in the 3 months preceding transplantation and during routine consultations at 1 and 2 years after transplantation. In the absence of a currently reliable definition of diabetes control in CF patients, CFRD balance was considered to be satisfactory for (1) $\text{HbA1c} \leq 7\%$, the usually recommended target in diabetic CF patients [3, 4] and (2) a daily insulin dose $\leq 1 \text{ IU/kg}$, the initial recommended dosage in diabetes caused by an insufficient insulin secretion and known as the baseline insulin requirement of most controlled type 1 diabetic patients. These patients were assigned to group A. Other patients were considered to have uncontrolled CFRD and were assigned to group B.

We used descriptive statistics to estimate the frequencies of the study variables, described via median and interquartile ranges (IQR). The Wilcoxon signed-rank test was used to compare continuous variables measured at baseline (prior to surgery) and at the 1- and 2-year follow-up time points, with a significance level of 0.05. We performed a linear mixed regression analysis to estimate mean HbA1c levels by considering ‘patient’ variation and ‘HbA1c measure’ variation. We then conducted logistic regression analysis using a linear mixed model to adjust uncontrolled CFRD at 1 and 2 years according to sex, age, body mass index (BMI), time between diagnosis of diabetes and LT and dosages of corticosteroids and tacrolimus. This study received the approval of the French South-East ethics committee (reference number CAL 2011-022). All analyses were performed using SAS software v9.1 (SAS Institute Campus Drive, Cary, N.C., USA).

Results

In total, we collected data from 31 CF patients with CFRD treated with insulin before transplantation. Two patients were excluded from the statistical analysis because they had received simultaneous lung and pancreatic islet transplants.

Data at the Time of Transplantation

At the time of transplantation, the median age of the remaining 29 patients was 29 years (IQR 24–34) and there were 16 (55.2%) males. The median weight was 48 kg (IQR 43–52), and the median BMI was 18 (IQR 17–19). All patients had been supplemented for exocrine pancreatic insufficiency since childhood. Before transplantation, 11 patients (37.9%) received corticosteroids at a median dosage of 10 mg/day (IQR 10–20) of prednisone or equivalent. Twenty-three (79.3%) received more than 3 courses of antibiotics per year. The median time between CFRD

Table 1. General and metabolic parameters before LT and at the 1- and 2-year follow-up

	Before LT	At 1 year	At 2 years
Number	29	27	18
Age at LT, years	29 (24–34)	–	–
Sex			
Males	16 (55.2)	15 (55.6)	9 (50)
Females	13 (44.8)	12 (44.4)	9 (50)
Weight, kg	48 (43–52)	54 (50–58)*	55 (53–57)*
BMI	18 (17–19)	20 (18–21)*	21 (19–22)*
Antibiotic dependence	23 (79.3)	–	–
Delay between CFRD diagnosis and LT, years	2 (1–6)	–	–
Insulin dosage, UI/kg/day	0.6 (0.4–0.8)	0.6 (0.3–0.9)	0.45 (0–0.6)
FBG II, mmol/l	4.4 (3.85–6.6)	5.06 (4.57–6.6)	5.5 (4.90–6.88)
HbA1c, %	6.6 (6.1–7.4)	5.9 (5.6–6.7)*	5.9 (5.5–6.7)*
Corticosteroids			
Number	11 (37.9)	27 (100)	18 (100)
Dosage of prednisone or equivalent, mg	10 (10–20)	10 (7.5–15)	5 (5–8)
Tacrolimus			
Number	–	26 (96.3)	17 (94.4)
Dosage, mg	–	5 (3–10)	5 (2.75–10)
Presence of at least 1 episode of acute rejection per year	–	9 (33.3)	0
CFRD control			
Group A	19 (65.5)	21 (77.8)	14 (77.8)
Group B	10 (34.5)	6 (22.2)	4 (22.2)

All results are expressed as median (IQR) or number (percentage).

Group A: controlled CFRD (HbA1c ≤7% and daily insulin dose ≤1 IU/kg/day). Group B: uncontrolled CFRD.

* Indicates a significant difference between the pretransplantation rate and the 1- or 2-year rate (Wilcoxon signed-rank test, $p < 0.05$).

diagnosis and LT was 2 years (IQR 1–6), although the time of diagnosis of diabetes was unknown in 3 patients. Nineteen of 29 (65.5%) patients were in group A prior to transplantation, and the remaining 10 (34.5%) were in group B. The median HbA1c level was at 6.6% (IQR 6.1–7.4), and the median FBG was 4.68 mmol/l (IQR 3.85–5.5). The median daily insulin requirement was estimated to be 0.6 IU/kg (IQR 0.4–0.8) (tables 1, 2).

One-Year Follow-Up

At the 1-year follow-up, the study population was reduced to 27 patients: one had died, and another had undergone transplantation too recently to be included. The median weight of the remaining patients was 54 kg (IQR 50–58) and the BMI was 20 (IQR 18–21), significantly higher than before LT ($p < 0.05$). All patients were treated with corticosteroids at a median dosage of 10 mg/day (IQR 7.5–15) of prednisone or equivalent, and 26 (96.3%) also received tacrolimus at a median dosage of 5 mg/day (IQR 3–10). Nine patients (33.3%) presented at least 1 episode of

acute rejection in the first year. The median HbA1c level was 5.9% (IQR 5.6–6.7), which was significantly lower than before LT ($p < 0.05$). Twenty-one of the 27 (77.8%) patients were in group A 1 year after transplantation. Five of the 10 (50%) patients who were in group B prior to transplantation improved their diabetes control and moved into group A 1 year after transplantation. CFRD control actually declined in 1 patient, and he was moved into group B at the 1-year follow-up (tables 1, 2; fig. 1).

Two-Year Follow-Up

Eighteen patients were included in the 2-year follow-up (3 patients had died in the second year following transplantation, and transplantation had occurred too recently in 6 other patients). All of the remaining patients received corticosteroids at a median dosage of 5 mg/day (IQR 5–8) of prednisone or equivalent. Seventeen (94.4%) were also treated with tacrolimus at a mean dosage of 5 mg/day (IQR 2.75–10). There was no acute rejection recorded in the second year following transplantation. The

Table 2. Comparison of general and metabolic parameters between group A and B patients before transplantation and at the 1- and 2-year follow-up

	Before LT		At 1 year		At 2 years	
	group A	group B	group A	group B	group A	group B
Number	17	10	21	6	14	4
Weight, kg	49 (46–52)	45 (40–52)	54 (50–55)	55 (51–60)	54 (53–56)	58 (57–47)
BMI	18 (17–19)	17 (15–19)	20 (19–21)	21 (18–22)	20 (19–22)	22 (18–24)
Insulin dose, IU/kg/day	0.40 (0.30–0.60)	0.85 (0.50–1.20)	0.60 (0.30–0.70)	1.05 (1.00–1.30)	0.40 (0–0.60)	1.10 (0.85–1.35)
HbA1c, %	6.1 (6.0–6.6)	7.8 (7.4–8.3)	5.8 (5.6–6.2)	8.6 (6.4–11.9)	5.8 (5.5–6.1)	7.5 (6.1–10.3)
FBG, mmol/l	4.4 (3.8–5.5)	6.71 (4.02–8.75)	5.0 (4.62–5.89)	7.54 (4.4–10.45)	5.34 (4.9–6.71)	6.71 (5.17–9.02)
Corticosteroids, mg	10.5 (10–20)	10 (10–17.50)	10 (7.5–12.5)	9 (7.5–20)	5.0 (5.0–8.0)	7.5 (6.0–9.0)
At least 1 acute rejection in the year, n (%)	–	–	7 (33.3)	2 (33.3)	0	0

All results are expressed as median (IQR) or number (percentage).

Group A: controlled CFRD (HbA1c $\leq 7\%$ and daily insulin dose ≤ 1 IU/kg). Group B: uncontrolled CFRD.

Fig. 1. Evolution of metabolic status of diabetic CF patients undergoing LT at the 1- and 2-year follow-up. Group A: controlled CFRD (HbA1c $\leq 7\%$ and insulin daily dose ≤ 1 IU/kg). Group B: uncontrolled CFRD.

median HbA1c level was 5.9% (IQR 5.5–6.7), significantly lower than before transplantation ($p < 0.05$). Fourteen of the 18 (77.8%) patients were in group A 2 years after transplantation; 1 more patient who was in group B prior to transplantation moved into group A at the 1-year follow-up, but 2 of those who were in group A at the 1-year follow-up were moved into group B at the 2-year follow-up (tables 1, 2; fig. 1). Only 1 patient who was in group B before transplantation and whose glucose tolerance had improved at 1 year (group A) returned to their original group at 2 years because of a slight increase in HbA1c (7.1%). Moreover, insulin could have been stopped in 5 patients (27.8%).

Most patients classified in group B required high doses of insulin (5/6 at 1 year, 3/4 at 2 years) and did not have an isolated high level of HbA1c, suggesting that they were not undertreated.

Evolution of HbA1c

Our linear mixed regression analysis estimated a mean HbA1c level of 6.8% ($p < 0.0001$) for all CF patients, with a standard deviation of 1.37 and a high degree of significance ($p = 0.0006$). Our slope estimation of -0.27 suggested that the mean HbA1c level decreased with time, but this result was not significant ($p = 0.092$). After adjusting for other covariates (sex, age at transplant, BMI, existence of acute rejection, time between diagnosis of diabetes and LT and corticosteroid and tacrolimus dosages), no factor was found to lead significantly to the decrease in HbA1c levels.

Logistic Regression Analysis

Univariate analysis showed that uncontrolled CFRD prior to LT (OR = 16 and $p = 0.022$) and a long delay between CFRD diagnosis and transplantation (OR = 1.3

Table 3. Results of univariate logistic regressions to adjust uncontrolled CFRD at 1 and 2 years after LT with other covariables

Parameter	At 1 year		At 2 years	
	OR (95% CI)	p	OR (95% CI)	p
Sex, male	0.75 (0.12–4.6)	0.76	1.0 (0.11–9.23)	1.0
Age at LT	1.02 (0.89–1.17)	0.78	1.08 (0.92–1.27)	0.32
BMI <20 before LT	6 (0.80–44.95)	0.08	1.22 (0.09–16.43)	0.88
Delay between diagnosis of CFRD and LT	1.34 (1.03–1.74)	0.03	0.86 (0.46–1.60)	0.63
Corticosteroids daily dosage	0.88 (0.72–1.08)	0.21	ND	ND
Tacrolimus daily dosage	1.04 (0.85–1.26)	0.72	0.72 (0.45–1.16)	0.17
At least 1 acute rejection in the year	1.0 (0.15–6.85)	1.0	–	–
Group B pretransplant	16 (1.50–171.20)	0.02	7.50 (0.59–95.38)	0.12
Group B at 1 year	–	–	13 (0.77–219.1)	0.075

Group B: uncontrolled CFRD (HbA1c >7% and insulin daily dose >1 IU/kg). ND = Not documented.

and $p = 0.032$) were significant predictors of uncontrolled CFRD 1 year after transplantation. The effects of sex, age at transplant, BMI, dosages of corticosteroids and tacrolimus and the existence of acute rejection were not significant (table 3). Multivariate analysis did not confirm these results.

Discussion

LT is now the only therapeutic option for CF patients with end-stage pulmonary disease, but it has a good long-term prognosis. The ISHLT registry reports that LT has survival rates of about 83% at 1 year, 57% at 5 years and 40% at 10 years [6]. This increase in life expectancy, however, is associated with the development of extra-pulmonary complications such as CFRD, which has become the leading comorbidity in lung transplant patients. CFRD occurs in 15% of patients with pancreatic insufficiency and increases in prevalence as patients age, from 10% of the patients younger than 10 years to more than 50% of those older than 30 years [2–4].

The pathophysiology of CFRD is complex and shares features of both type 1 and type 2 diabetes [2, 3]. First, chronic obstruction of the pancreatic duct leads to delayed and dysfunctional insulin secretion [10]. The second mechanism that leads to glucose intolerance with CFRD is increased insulin resistance [10, 11], which is related to chronic pulmonary infection and inflammatory factors such as tumor necrosis factor α and interleukin 6 [12], in addition to the use of corticosteroids [13].

Among patients whose endogenous insulin secretion has been greatly affected, LT may cause a significant imbalance of diabetes, which exacerbates morbidity and mortality after transplantation by increasing the risk of infection and rejection [6, 14, 15]. Indeed, CF patients who undergo LT risk developing impaired glucose tolerance and CFRD as a result of immunosuppressive drugs and the stress induced by surgery. Corticosteroids are known to impair glucose metabolism [13], and tacrolimus can also lead to impaired glucose tolerance [16]. Even in non-CF patients, diabetes occurs rather frequently after LT, with reported incidences of 26.1 and 37% at 1 and 5 years after transplantation, respectively [6]. The presence of diabetes prior to transplantation increases one's relative risk of mortality 1.21 times (95% CI 1.06–1.38 and $p = 0.0044$) [6]. To the best of our knowledge, however, this study is the first to observe the evolution of metabolic control in pre-existing CFRD following LT. A few studies have focused on the development of CFRD at this stage. In a retrospective study of 77 CF patients with pancreatic insufficiency undergoing LT, Hadjiliadis et al. [14] confirmed a significant increase in the prevalence of CFRD from 28.6% before transplantation to 49.4% after transplantation ($p = 0.008$). Similarly, Navas de Solis et al. [17] compared 20 diabetic CF patients undergoing LT to another 34 diabetic CF patients and found a significantly higher rate of glucose intolerance or CFRD in the transplant patients (89 vs. 53% in the other patients), along with higher insulin requirements among the transplant patients (78.6 vs. 36.3%). Unfortunately, these studies did not assess the evolution (and improvement) of pre-exist-

ing CFRD. Moreover, such studies face two major difficulties: first, isolated assessment of the prevalence of CFRD after transplantation does not take the natural history of the disease into consideration, and second, follow-up must be sufficiently long to evaluate the long-term outcomes for glucose tolerance while excluding the effects of surgery-induced stress and the high dosages of corticosteroids used just after transplantation.

Based on the results of this study, it appears that some lung transplant patients experience an improved diabetes balance: the proportion of patients with controlled CFRD was higher at the 1- and 2-year follow-up time points (77.8%) than before transplantation (65.5%). Moreover, insulin could have been stopped in 5 patients (28%) at the 2-year follow-up. Based on the pathophysiology of CFRD, we suggest that these patients were those whose endogenous insulin secretion was originally slightly altered and in whom diabetes was mainly due to insulin resistance. Their diabetic status was improved by LT because of the suppression of the chronic pulmonary inflammatory focus, despite undergoing diabetogenic immunosuppressive therapy. However, because of the retrospective nature of our study, we have only indirect evidence for this hypothesis. First, in most patients, diabetes appeared shortly before LT, suggesting that the insulin resistance induced by respiratory aggravation was implicated in their glucose intolerance. Then, doses of steroids did not decrease significantly during follow-up, thereby negating their involvement in the observed differences in terms of glucose tolerance. Finally, the significant increase in weight would be more in favor of an increase in insulin requirements. However, by reducing insulin requirements, the likely increase in physical activity after transplantation could be a confounding factor.

To correct both exocrine and endocrine pancreatic disease, some have proposed simultaneous bilateral lung and pancreas transplantation. To date, the reported cases of this surgery have revealed satisfactory respiratory and metabolic results, but at the cost of major surgical complications [18]. An alternative would be combined pancreatic islet and lung transplantation, which has been shown to lead to significant improvements in metabolic control for a minimum of 4 years and to insulin independence in 10% of patients with type 1 diabetes [19]. In 1994, Tschopp et al. [20] reported the first case of simultaneous pancreatic islet and bilateral lung transplantation in a patient with CF with good short-term metabolic results. Since then, additional published cases have shown that most recipients experience a significant improvement in glycemic control, even if insulin independence is not usu-

ally seen beyond 1 year after surgery [19, 21]. Importantly, restoring metabolic control in the early postoperative period may decrease the complication rate. Moreover, a reduction in long-term insulin requirements has sometimes been observed [22]. Notably, the 2 patients in our study who received combined lung and islet transplantations were in group B before transplantation, and at the 1- and 2-year follow-ups, their insulin requirements decreased after transplantation, but remained stable at 50 IU/day during follow-up.

Although the mechanisms leading to the development of CFRD are not fully understood, existing data suggest that patients whose diabetes results mainly from decreased insulin secretion would benefit from pancreatic islet transplantation. Further studies are needed to assess whether clinical or biological measurements of the risk factors for impaired insulin secretion (e.g. genetic or immunologic factors) might be able to help physicians identify which patients would benefit from islet transplant.

Our study has some important limitations. The small number of patients does not allow the assessment of prognosis factors of CFRD after LT or the comparison of patient outcomes according to their metabolic status. Moreover, the retrospective nature of our data does enable any confirmation of the pathological origin of diabetes, i.e. insulin resistance or altered insulin secretion, to be provided. Finally, the implication in diabetes control of potential infections following transplantation could not have been investigated, even if these infections generally occur in the early weeks following surgery and it is unlikely that they influence the diabetes balance at 1 year [6, 23]. Future studies that collect prospectively more precise metabolic variables with a larger number of patients would answer these questions.

In this study, LT did not seem to worsen CFRD at the 1- and 2-year follow-up time points, possibly in patients whose diabetes was mainly due to insulin resistance. Patients who would benefit from a simultaneous lung and pancreatic islet transplant should be identified based on reliable, as of yet undetermined criteria, which should include markers that differentiate between decreased insulin secretion and insulin resistance.

Financial Disclosure and Conflicts of Interest

All authors report no conflicts of interest.

References

- O'Sullivan BP, Freedman SD: Cystic fibrosis. *Lancet* 2009;373:1891–1904.
- Brennan AL, Geddes DM, Gyi KM, Baker EH: Clinical importance of cystic fibrosis-related diabetes. *J Cyst Fibros* 2004;3:209–222.
- Nathan BM, Laguna T, Moran A: Recent trends in cystic fibrosis-related diabetes. *Curr Opin Endocrinol Diabetes Obes* 2010;17:335–341.
- Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W: Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care* 2009;32:1626–1631.
- Buzzetti R, Salvatore D, Baldo E, Forneris MP, Lucidi V, Manunza D, Marinelli I, Messore B, Neri AS, Raia V, Furnari ML, Mastella G: An overview of international literature from cystic fibrosis registries. I. Mortality and survival studies in cystic fibrosis. *J Cyst Fibros* 2009;8:229–237.
- Christie JD, Edwards LB, Aurora P, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Taylor DO, Kucheryavaya AY, Hertz MI: The Registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult lung and heart-lung transplantation report – 2009. *J Heart Lung Transplant* 2009;28:1031–1049.
- Mordant P, Bonnette P, Puyo P, Sage E, Grenet D, Stern M, Fischler M, Chapelier A: Advances in lung transplantation for cystic fibrosis that may improve outcome. *Eur J Cardiothorac Surg* 2010;38:637–643.
- Brennan AL, Gyi KM, Wood DM, Hodson ME, Geddes DM, Baker EH: Relationship between glycosylated haemoglobin and mean plasma glucose concentration in cystic fibrosis. *J Cyst Fibros* 2006;5:27–31.
- Holl RW, Buck C, Babka C, Wolf A, Thon A: HbA1c is not recommended as a screening test for diabetes in cystic fibrosis. *Diabetes Care* 2000;23:126.
- Yung B, Noormohamed FH, Kemp M, Hooper J, Lant AF, Hodson ME: Cystic fibrosis-related diabetes: the role of peripheral insulin resistance and beta-cell dysfunction. *Diabet Med* 2002;19:221–226.
- Hardin DS, Leblanc A, Marshall G, Seilheimer DK: Mechanisms of insulin resistance in cystic fibrosis. *Am J Physiol* 2001;281:E1022–E1028.
- Fernandez-Real JM, Ricart W: Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocr Rev* 2003;24:278–301.
- Kimberly RP: Glucocorticoids. *Curr Opin Rheumatol* 1994;6:273–280.
- Hadjiliadis D, Madill J, Chaparro C, Tsang A, Waddell TK, Singer LG, Hutcheon MA, Keshavjee S, Elizabeth Tullis D: Incidence and prevalence of diabetes mellitus in patients with cystic fibrosis undergoing lung transplantation before and after lung transplantation. *Clin Transplant* 2005;19:773–778.
- Rosenblatt RL: Lung transplantation in cystic fibrosis. *Respir Care* 2009;54:777–786.
- Letko E, Bhol K, Pinar V, Foster CS, Ahmed AR: Tacrolimus (fk 506). *Ann Allergy Asthma Immunol* 1999;83:179–189.
- Navas de Solis MS, Merino Torres JF, Mascarell Martinez I, Pinon Selles F: Lung transplantation and the development of diabetes mellitus in adult patients with cystic fibrosis. *Arch Bronconeumol* 2007;43:86–91.
- Fridell JA, Wozniak TC, Reynolds JM, Powelson JA, Hollinger EF, Duncan MW, Sanuti A, Milgrom ML: Bilateral sequential lung and simultaneous pancreas transplant: a new approach for the recipient with cystic fibrosis. *J Cyst Fibros* 2008;7:280–284.
- Vantyghem MC, Kerr-Conte J, Arnalsteen L, Sergeant G, Defrance F, Gmyr V, Declercq N, Raverdy V, Vandewalle B, Pigny P, Noel C, Pattou F: Primary graft function, metabolic control, and graft survival after islet transplantation. *Diabetes Care* 2009;32:1473–1478.
- Tschopp JM, Brutsche MH, Frey JG, Spiliopoulos A, Nicod L, Rochat T, Morel P: End-stage cystic fibrosis: improved diabetes control 2 years after successful isolated pancreatic cell and double-lung transplantation. *Chest* 1997;112:1685–1687.
- Badet L, Benhamou PY, Wojtusciszyn A, Baertschiger R, Milliat-Guittard L, Kessler L, Penforis A, Thivolet C, Renard E, Bosco D, Morel P, Morelon E, Bayle F, Colin C, Berney T: Expectations and strategies regarding islet transplantation: metabolic data from the GRAGIL 2 trial. *Transplantation* 2007;84:89–96.
- Kessler L, Greget M, Metivier AC, Moreau F, Bosco D, Santelmo N, Helms O, Pinget M, Berney T, Massard G, Kessler R: Combined pancreatic islet-lung transplantation with islet percutaneous portal embolization in cystic fibrosis. *Transplantation* 2008;85:1670–1671.
- Kanj SS, Tapson V, Davis RD, Madden J, Browning I: Infections in patients with cystic fibrosis following lung transplantation. *Chest* 1997;112:924–930.