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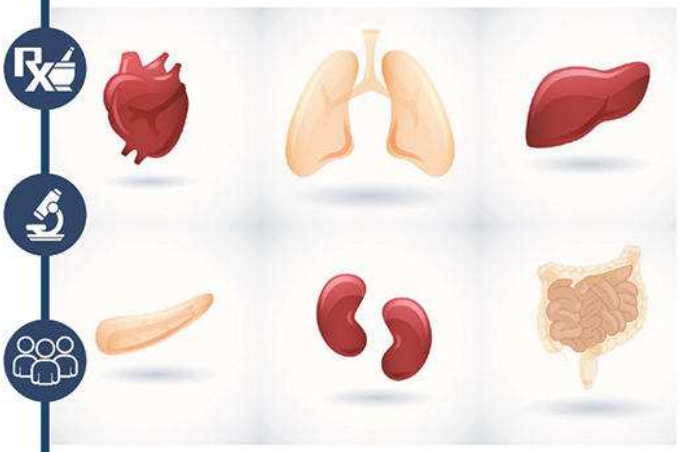

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Comorbidities after lung transplantation in CF

Long term extra pulmonary comorbidities after lung transplantation in cystic fibrosis: update of specificities

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Abstract

Lung transplantation (LT) is the standard therapeutic option for cystic fibrosis (CF) patients with end-stage lung disease. Both conditions lead to extra-respiratory complications, such as diabetes, renal insufficiency, bone disease, and cancer. The purpose of the present paper is to provide an update of the non-respiratory comorbidities following LT in adult patients with CF and their specificities regarding their multi-systemic underlying condition despite their younger age compared to other patients undergoing LT.

Diabetes, renal insufficiency, metabolic bone disease, hypertension, liver disease and cancer are the comorbidities considered in this review. The increase of CF adults living with a lung transplant justifies an update of knowledge for this specific situation (prevalence of these complications, underlying risk factors), in order to provide better medical care and establish early diagnosis strategies.

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease, caused by a mutation in a gene that encodes the CF transmembrane conductance regulator (CFTR) protein, that leads to dysfunction in multiple organ systems and progressive respiratory failure leading to death or lung transplantation (LT) [1]. Although CF was previously fatal in childhood, in countries with well-developed CF care half of CF patients are now aged more than 18 years [2,3], and from registries the median age of death ranges from approximately 25 to 30 years [4,5].

The therapeutic option for patients with end-stage lung disease is LT [6]. Between 1995 and 2014, CF accounted for approximately 25% of bilateral LT recipients and 16% of all LT recipients in the Registry of the International Society for Heart and Lung Transplantation [7], and nearly half (44%) of LT performed under 50 years of age [6]. In adults, CF patients have better survival than patients receiving LT for other indications; their overall ten-year survival was 45% over the 1990-2013 period [7] and even higher in other registries [5]. The volume of LT activity for CF has been associated with improved long-term survival in LT recipients with CF in the United States [8], perhaps partly explained by better experience for these more complex patients. In addition, despite their younger age compared to other conditions, CF patients also require specific attention due to their underlying disease and its multi-systemic complications such as pancreatic insufficiency, diabetes, osteoporosis, and malignancy [3]. For these reasons, the trajectory of CF patients may be different from other LT

patients. Infectious complications, acute rejection, and primary graft dysfunction [6,9] are well described but the extra-pulmonary comorbidities of LT are rarely reported for CF patients specifically. The aims of this review were, therefore, to update current knowledge about the non-respiratory comorbidities in CF transplanted patients and to provide data regarding management of these comorbidities in terms of detection, monitoring, and prevention.

1. CF-related diabetes

CF-related diabetes (CFRD) is well-defined and there are recommendations for early diagnosis [10-12]. The pathogenesis is multifactorial, and both dysfunctional insulin secretion and insulin resistance are implicated, leading to a disease that is distinct from classical diabetes mellitus (DM) types 1 and 2[13,14]. Fibrosis and destruction of the pancreas lead to decreased insulin secretion, whereas chronic pulmonary infection, inflammatory factors, and use of corticosteroids lead to insulin resistance [13]. A direct role of CFTR in the impairment of insulin secretion and beta cell regulation is emerging [15-17]. Age and pancreatic insufficiency are important risk factors for developing CFRD [13,18], which increases from 28.6% to 49.4% after LT [18].

In all underlying lung diseases leading to LT, prevalence of diabetes increases after transplantation [19]. Patients undergoing LT receive medications that can lead to impaired glucose tolerance, especially corticosteroids and tacrolimus [9,20,21]. Despite their younger age, CF patients have higher rates of pre- and post-transplant diabetes than non-CF patients who undergo LT [19]. Moreover, CF is identified as an independent predictor of post-transplant diabetes in LT recipients [22].

Interestingly, some CF patients experienced a better control of their CFRD after LT, with decrease of insulin requirement. Valour *et al.* published a retrospective study investigating the course of pre-existing CFRD after LT, and found better control of CFRD in two-thirds of patients. They proposed that the improvement of insulin sensitivity was related to the reduction of systemic inflammation related to chronic pulmonary infection [23]. In some studies pre-existing CFRD or development after LT did not appear to be associated with worse outcomes [18,24]; Hofer *et al.* even found a trend towards better survival after LT in patients with CFRD [25]. However, in several studies, the mortality in CF patients appears higher among those with CFRD diagnosed before LT compared to those without [19,26]. It is thought that a high rate of pre-LT pulmonary infections in diabetic patients may be related to this finding as it can lead to higher rate of post-operative complications [26]. The perioperative glycaemia may be carefully controlled regarding therapeutic strategies such as corticosteroids and immunosuppressive drugs. A strict glycemic control has to be maintained during long-term follow-up after LT, as well as a screening strategy for CFRD in non-diabetic CF LT.

2. Renal disease

Renal function does not seem primarily affected in CF despite abundant CFTR expression in all nephron segments [27], but secondary dysfunction (acute or chronic) is becoming common [28]. This may be related to chronic infection, drug toxicity (especially aminoglycosides), CFRD, nephrolithiasis, and nephrocalcinosis [28,29]. LT is also associated with renal dysfunction, and leads to an important decrease of renal function [30,31]. However, CF patients have a worse renal function evolution compared to other LT patients despite having a significantly higher pre-transplantation glomerular filtration rate (GFR) [30,32]; both the early renal function decline and the long-term rate of renal function loss is significantly greater in CF patients [32].

A retrospective cohort published in 2012 followed for 5 years after LT a total of 993 CF adults with no renal dysfunction prior to transplant. The estimated renal dysfunction (defined by estimated GFR measured < 60 mL/min/1.73m^2) was 22.5% at 1 year and 57.6% at 5 years. Renal dysfunction occurred within the first year post-transplantation in 55% of cases, and progressed to chronic stage 4 or more kidney disease (estimated GFR < 30 mL/min/1.73m^2 and/or required dialysis) in 31.5% of patients [33].

Various factors have been described to be associated with worse renal prognosis after LT in CF patients. *Age* – The risk of post-transplant renal dysfunction is reported to increase significantly with increasing recipient age [33]. One hypothesis is the correlation between older age at transplantation and greater lifetime exposure to nephrotoxic antibiotics in CF patients [33]. *Sex* – The risk of post-transplant renal dysfunction is reported to be greater for women as compared to men, which could be related to a reduced nephron mass in women that leads to inappropriate dosing of nephrotoxic immunosuppressive agents and antibiotics, and further renal damage [33]. *Immunosuppressive regimen* – Calcineurin inhibitors are described to be responsible for progressive degradation of renal function following transplantation in general [34,35]. Specific calcineurin-inhibitor nephrotoxicity was found to be present in 93% of renal biopsies taken from CF patients undergoing LT who had an episode of accelerated renal function loss [36]. Interestingly, a pharmacokinetic study concerning cyclosporine in CF subjects found that the bioavailability was lower than in healthy controls [37]. The use of higher cyclosporine doses to obtain similar serum levels in CF patients compared to other LT recipients may therefore contribute to their worse renal prognosis [32,38]. Nevertheless, the risk of post-transplant renal dysfunction has decreased since the switch from cyclosporine to tacrolimus as the first-line calcineurin inhibitor [31,33,39]. *Post-operative period and acute kidney injury* – Hypotension, hypoperfusion, administration of nephrotoxic agents such as radiocontrast, sepsis, and aggressive diuresis in the peri-operative period may precipitate acute kidney injury [35], which was associated

with a 5-fold increased risk for chronic renal failure in LT [31]. In order to minimize the risk of post-transplant renal dysfunction, a GFR measurement using a gold standard method seems to be recommended before transplantation as well as measures to prevent peri-operative hypoperfusion and a strict monitoring of calcineurin blood levels.

3. Metabolic bone disease

Low bone mineral density (BMD) is a common complication of CF, and microarchitecture assessment by high resolution peripheral scanner showed impaired volumetric density [40]. The severity of the lung disease is the main determinant of bone loss [41,42], leading to increased fracture risk [43], selectively in the spine and ribs [44,45]. Nevertheless, despite the improvement of care over recent years, a significant number of CF patients had low BMD Z-scores and reported fractures[46]. The pathophysiology is thought to be multifactorial, and recent data suggest a direct role for CFTR protein dysfunction [47]. Many risk factors have been identified to explain bone loss: chronic lung infection with elevated levels of pro-inflammatory cytokines, malabsorption leading to vitamin D and K deficiency, hypogonadism and delayed puberty, glucocorticoid therapy, physical inactivity, and low body mass index [42,47]. A recent study has confirmed that the severity of pulmonary disease is related to low BMD even in young patients [48]. Furthermore, among all patients awaiting LT the lowest BMD values are reported for CF patients [49,50], yet osteoporosis is common to all patients with end-stage lung diseases [50-52].

With prolonged immobilisation after surgery and high doses of corticosteroids, LT is known to induced severe bone loss in all patients [53] and further reduces the already relatively low BMD values in CF patients [49]. Frequently, bone loss occurs in the first year after the organ transplant despite calcium and vitamin D supplementation [52-54]. For example, Spira *et al.* found that the prevalence of osteoporosis increased from 32% to 50% at the lumbar spine, and from 54% to 78% in the femur neck 12 months following LT [53]. Furthermore, 4.8% of all patients who undergo LT surviving more than 20 years have been found to have symptomatic osteoporosis [55]. There is no specific study investigating long-term change of BMD and it consequence in patients with CF after LT.

To minimize bone loss, normal body mass index and weight bearing exercise are recommended. Moreover, lung infection and systemic inflammation must be controlled, and use of corticosteroids should be minimised. Vitamin D and calcium supplementation are also recommended [56]. Treatments such as bisphosphonates have been shown to be effective in preventing bone loss and post-transplant fracture [52,56,57]. Hence, in the European CF bone mineralisation guidelines, bisphosphonate treatment should be considered in adults with CF when the patient is awaiting or

has undergone solid organ transplantation and has a BMD Z/T-score of -1.5 or less [56]. The criteria to maintain long term low dose corticosteroids after LT remains to be well determined. Specific guidelines for diagnosis and treatment of CF bone disease in LT patients are needed.

4. Hypertension

High blood pressure is not known as a comorbidity in CF. Nevertheless, it is well known that LT leads to hypertension as it is a recognised adverse effect of cyclosporine [58,59]. In an LT cohort who initially received cyclosporine, the cumulative prevalence of new-onset hypertension at 1 year was 45%, and at 7 years reached 72% [22]. There are very few data available for CF patients, however, it is of note that in this study 7 of the 11 CF patients developed hypertension after LT, and CF was not found to be a factor associated with this [22]. Tacrolimus, which is now the first-line calcineurin inhibitor, leads to a lower incidence of hypertension than cyclosporine [60,61] but, as noted above, such drugs are associated with renal insufficiency that itself leads to hypertension. The increased oral salt intake usually recommended in the treatment of children with CF must perhaps be tempered for transplanted patients.

5. Liver disease

CF-associated liver disease (CFLD) is a well-known complication that includes a broad spectrum of hepatobiliary manifestations: specific alterations attributable to the underlying CFTR defect, lesions of iatrogenic origin, and effects of a disease process occurring outside the liver [62]. Approximately 5 to 10% of all CF patients will develop multilobar cirrhosis during the first decade of life. Most of these will develop signs of portal hypertension (PHT). The second decade of life is marked by related complications, mainly variceal bleeding [63]. Cumulative incidence of liver disease ranges from 27 to 35%, with few incident cases after the age of 18 years [62]. Nevertheless, adult-onset CFLD, in patients without biochemical or radiological evidence of liver disease during childhood, is emerging [64].

Liver cirrhosis remains the single most important non-pulmonary cause of death, accounting for 2.5% of overall CF mortality [65], and CFLD is an independent risk factor for mortality in CF [66]. Nevertheless, those with CFLD who survive into adulthood have a relatively stable disease with few deaths due to liver complications [66].

Patients with both severe respiratory failure and advanced liver cirrhosis are most often either offered combined lung-liver transplantation or excluded from transplantation; very few are considered for LT alone [67]. This is based on the assumption that these patients would be unable to survive the perioperative period or would develop hepatocellular failure. However, it has been

demonstrated that post-transplant lung function and survival is not different between patients with or without CFLD who undergo LT alone [65].

Immunosuppressive regimens are associated with cholestatic complications, especially purine antagonists (azathioprine or mycophenolate mofetil) [68]. Among the case reports of calcineurin inhibitor -induced hepatotoxicity published in lung recipients [69,70], one described a CF patient [70]. However, impairment of liver function after LT is not reported, neither in patients with pre-transplant CFLD or in those without CFLD.

6. Cancer

Over the last 30 years, the CF patient population has increasingly lived into adulthood, and cancer is emerging as a long-term complication [3]. The overall risk of cancer has been found to be similar in CF patients as compared to the general population [71,72], however, several studies have reported a greater than expected number of digestive tract cancers, particularly in the small intestine, colon, and biliary tract [71-73]. The pathogenesis of cancer in CF remains unclear, but inflammation may be a causative link [74]. The repeated and prolonged use of antibiotics to treat pulmonary infections, which alter the gut microbiota, possibly contributes to colorectal carcinogenesis [75]. A role of CFTR-related factors in digestive tract cancer risk was also investigated, and it is suggested that CFTR could act as a tumour suppressor gene [74].

Solid organ transplantation is associated with an increased incidence of cancer, and lung transplantation is particularly concerned [76]. The ISHLT registry reports that 43% of ten-year survivors after LT developed a malignant disease [7]. The risk of malignancy seems to be particularly increased in CF patients who received a LT [77], with 3-fold to 10-fold increased risk for cancer overall and 17-fold to 27-fold increased risk for digestive tract cancers [71,75,78]. A recent study confirmed that screening CF patients for colon cancer is cost effective. The authors recommended a colonoscopy every 5 years, starting at an age of 40 years, for patients with CF who never received an organ transplant; and among patients who had received an organ transplant, optimal colonoscopy screening should start earlier at an age of 30 or 35 years, depending on the patient's age at time of transplantation [79]. A recent study revealed a high proportion of cervical dysplasia and Human Papilloma Virus (HPV)-related cervical disease in transplanted and non-transplanted women with CF and highlighted the importance of a regular gynecological follow-up and cervical screening in women with CF both before and after transplantation. It also suggests that HPV vaccination in female adolescents and children with CF is an efficient method to prevent cervical disease [80].

Non-Hodgkin lymphoma (NHL) , particularly large B cell lymphoma, is one of the commonly observed cancers in CF LT, with a significant increased risk compared with non-CF LT [78]. The increased risk compared to other LT recipients seems primarily due to the younger age of the CF patients; young patients have a greater likelihood of a seronegative Epstein Barr Virus (EBV) status before LT, since lymphoproliferative disorders after LT are often related to primary infection with EBV, which is supported by the reduction in the risk after adjustment on age [78].

Organ transplant recipients experience an increased risk of developing skin cancer, particularly cutaneous squamous cell carcinoma (SCC) compared to the general population [81]. Administration of voriconazole, a broad spectrum triazole antifungal mostly used in antifungal prophylaxis regimens, especially after LT, increases the risk of developing SCC in LT recipients [82]. The duration of exposure and cumulative high-dose exposure to this drug are both factors associated independently with SCC [83]. Furthermore, a high rate of photosensitive reactions in CF patients treated with voriconazole was reported in a French population [84]. Therefore, caution should be taken when using voriconazole for *Aspergillus* in non-transplanted CF patients to limit the cumulated dose received.

An increased frequency of acute lymphoblastic leukaemia and thyroid cancer, that are known to be radio-induced, has been reported [71]. The role of radiation exposure especially with repeated computed tomography in CF patients has been studied and it was concluded that the risk associated was relatively small [85,86]. However, it has been noted that this may change owing to an increased exposure in an ever increasingly aged CF population [3,87]

7. Conclusion

CF lung transplanted patients are an increasing new sub-population of CF patients with good and durable survival. This favorable situation suffers from the potential occurrence of extra-pulmonary comorbidities after LT. The charge of either transplantation, CF or the plurality of both situations in the risk of comorbidities occurrence is complex.

To improve medical care and optimise survival we suggest in accordance to literature findings a careful specific surveillance of LT CF patients. For CFRD, we suggest a special attention to perioperative glycemic control regarding therapeutic strategies such as corticosteroids and immunosuppressive drugs; a strict glycemic control during long term follow-up after LT, as well as the maintain of screening strategy for CFRD in non-diabetic CF LT patients. In order to minimize the risk of post-transplant renal dysfunction, a GFR measurement using a gold standard method is suggested before transplantation as well as measures to prevent peri-operative hypoperfusion and a

strict monitoring of calcineurin blood levels. Exercise, vitamin D, calcium supplementation and bisphosphonates have been shown to be effective in preventing bone loss.

Colo-rectal cancer and cervical dysplasia may warrant a specific screening strategy even before LT in CF adult patients, which should start earlier and be maintained over the duration of follow-up in case of LT. A specific attention to NHL is warranted considering their frequency and the young age of CF patients at transplantation.

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Conflicts of interests

None of the authors have any relevant conflicts of interest to disclose.

Authorship

All authors have contributed to all aspects of the conception, design, writing, revisions and have approved submitted versions. The manuscript has not been submitted elsewhere.

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