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Original Article

Prevalence and characteristics of chronic kidney disease among Danish adults with cystic fibrosis

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Abstract

Background: With improved prognosis of CF, comorbidities including chronic kidney disease (CKD) are becoming increasingly important. Identification of those at highest CKD risk is hence a priority.
Methods: In this cross-sectional study, adults with CF attending the Copenhagen CF Centre at Rigshospitalet with ≥2 measurements of serum creatinine from 2013 to 2015 were included. Data was obtained from an electronic CF database, which contains anonymised clinical and laboratory data on all individuals attending the clinic. CKD was defined as a confirmed (≥3 months apart) estimated glomerular filtration rate ≤ 60 mL/min/1.73m^2.
Results: Of 181 individuals, the CKD prevalence was 2.7% and increased to 11% after inclusion of lung transplanted patients. Individuals with CKD were generally older (median 39 (IQR, 36–45) vs. 31 (IQR, 24–39) years; $p < 0.001$), diabetic (86% vs. 41%, $p < 0.001$), with longer median duration of chronic pulmonary infection (28.3 (20.0–35.8) vs. 20.0 (9.9–34.7) years; $p = 0.008$) and with longer intravenous aminoglycosides use (606 (IQR, 455–917) vs. 273 (IQR, 91–826) days, $p = 0.005$).
Conclusions: The CKD prevalence is high and related to age, diabetes, chronic infection, transplantation and aminoglycosides use. These observations call for longitudinal studies investigating CKD predictors in adults with CF.

1. Background

The number of adults living with cystic fibrosis (CF) has increased [1] due to the continuous improvement in care, with an expected median survival of 41,6 years [1]. Comorbidities such as chronic kidney disease (CKD) are therefore becoming increasingly important causes of morbidity also in the CF population.

Preserved kidney function is important for many reasons including prevention of accelerated cardiovascular disease, osteoporosis, anemia, the ability to tolerate continued antibacterial treatment as well as eligibility for lung transplants. Individuals with CF possess serveral potential risk factors for kidney disease including CF-related complications such as CF-related diabetes mellitus (CFRD), lung transplantation [2,3] and intravenous use of aminoglycosides.

Due to repeated exacerbations in their chronic pulmonary infection, CF individuals are repeatedly exposed to aminoglycosides and other potentially nephrotoxic antibiotics such as colistin [4,5]. Intravenous use of aminoglycoside antibiotics, such as tobramycin, are widely used in combination with other antibiotics, as they are highly effective against gram-negative pathogens common to CF such as *Pseudomonas aeruginosa* [6]. As renal hyperfiltration is common in CF individuals, higher doses of antibiotics are required to achieve therapeutic concentrations [7]. Thus, CF individuals have a well known increased risk of acute kidney injury (AKI) [8,9], but potentially also chronic kidney disease (CKD).

Whereas AKI has been well investigated in the CF litterature [10], the prevalence of CKD in CF individuals is widely unknown. There is a need to identify and characterize the extent of CKD in adults with CF to aid identification of those at highest risk, who can benefit from interventions to prevent development of CKD.

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We hypothesize that CKD is highly prevalent in the adult CF population as compared to the general adult Scandinavian population, and that CFRD and longer cumulative intravenous use of potentially nephrotoxic antibiotics are the most important characteristics of those with CKD.

2. Methods

2.1. Individuals

This cross-sectional study included all adults (age > 18 years) under active follow-up at The Copenhagen (CPH) CF Centre at Rigshospitalet from January 1st 2013 to January 1st 2015 with ≥2 serum creatinine measurements. We defined a two-year observation period to ensure sufficient data collection to define CKD. The CF diagnosis was based on sweat chloride testing and confirmed by genetic testing [11].

Data was obtained from the clinical CF database, holding prospectively entered patient data. Thus, the analyses were based on preexisting clinical and laboratory data collected as part of the patients' regular medical care. Demographics (age and gender), serum creatinine levels, CF genotype, chronic infection status, body mass index (BMI), lung function, CFRD status, transplantation status and data on lifetime exposure to the intravenous nephrotoxic antibiotics were obtained from the clinical CF database. Exclusion criteria were lack of creatinine data or kidney transplantation prior to January 1st 2013.

2.1.1. Definitions

Characteristics of the participants were recorded at first visit after study initiation, January 1st 2013.

To assess kidney function, estimated glomerular filtration rate (eGFR) was calculated using the abbreviated modification of diet in renal disease (aMDRD) equation [12]. Mild, moderate and advanced CKD were defined as confirmed (≥3 months apart) eGFR >60–≤90, >30–≤60 and ≤30 mL/min/1.73 m^2, respectively. Normal kidney function and hyperfiltration were defined as a confirmed eGFR between >90–≤120 mL/min/1.73 m^2 and >120 mL/min/1.73 m^2, respectively. Due to the relatively low number of individuals with advanced and end-stage kidney disease, our main analyses focused on comparing those with or without moderate CKD (confirmed eGFR >60 vs. ≤60 mL/min) (Table 1).

Chronic pulmonary infection was defined as infection with the same pathogen for at least six consecutive months, or less with increasing specific IgG bacterial antibodies [13]. Individuals with unknown start date of infection were given a surrogate date using one of three different options: 1) Missing data on date, known month and year: the 15th in the known month/year; 2) Missing data on date and month: 1st of July in the known year; 3) Missing data on date, month and year: Jan 1st 2013 (date of study initiation).

We included all chronic infections with pathogens causing enhanced inflammatory response in CF individuals [14–16] (Supplement Table 1), focusing on the clinically most important pathogen per individual (Table 1 and Supplement Table 2).

Because of the lack of evidence of a pathogenic effect of *Stenotrophomonas Maltophilia* [17], *S. Maltophilia* was not included, therefore individuals chronically mono-infected with *S. Maltophilia* were considered non-chronically infected (Supplement Table 2).

The antibiotics considered nephrotroxic in the analyses were the intravenous administered aminoglycosides; tobramycin and amikacin, and the polymyxin colistin. Tobramycin has always been given under dose and kidney function monitoring and in the latest years it has been given once daily. Inhalation antibiotics were considered to have negligible systemic effect and therefore not included [18].

Forced expiratory volume in 1 s (FEV_1) was expressed as a percentage of the normal predicted values for height and sex using the Hankinson reference norms [19]. Diagnosis of CFRD was defined using the WHO diagnostic criteria [20]; an oral glucose tolerance test with 2-h non-fasting plasma glucose ≥11.1 mmol/L (200 mg/dL) consecutive augmented home glucose monitoring and insulin treatment. BMI was calculated as weight (kg)/height^2 (m), underweight defined as BMI < 18.50 kg/m^2.

2.1.2. Statistical analysis

Baseline characteristics were analyzed descriptively; normally distributed data was reported as mean with standard deviation (SD) and skewed data as median with interquartile range (IQR). Mean differences in continuous data were compared using two-sample *t*-test, if normally distributed and two-sample Wilcoxon-Mann-Whitney, if skewed. Mean differences between more than two groups of normally distributed continuous data were analyzed using One-way ANOVA and Kruskal Wallis test if data was skewed. Mean differences in categorical data were analyzed using chi^2-test. For all analyses, *p*-values <0.05 were considered statistically significant.

In a sub-group analysis, we analyzed the prevalence of CKD among patients without prior lung transplantation, censoring data on kidney function collected post lung transplantation for patients transplanted between January 1st 2013 and January 1st 2015 and excluding patients transplanted prior to January 1st 2013.

All statistical analyses were performed using STATA version 12.1 software.

3. Results

As of January 1st 2013, 211 adults with CF were alive and registered at the Copenhagen CF Centre (Fig. 1).

Of these, 86% (n = 181) had sufficient creatinine data and were included in the study. Included individuals were 51% (n = 92) female, predominantly homozygous for Delta F 508 (73%, n = 132) and with a median age of 32 years (Supplement Table 2). Excluded individuals were predominantly male (67%, n = 20) non-chronically infected (57%, n = 17) and non-diabetic (83%, n = 25).

During the two-year period a total of 4.509 creatinine measurements were recorded, with a median of 14 measurements/individual (IQR, 7–28).

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