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Title: cystic fibrosis-related diabetes

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This report was submitted to fulfill the requirements for scientific research activity.

Abstract:

Cystic fibrosis-related diabetes (CFRD) is the principle extra-pulmonary complication of cystic fibrosis, occurring in 15-30% of adults cystic fibrosis patients. The number of cystic fibrosis patients who develop diabetes is increasing in parallel with increases in life expectancy. CFRD has many complications as it significantly impacts the pulmonary function which is the most common cause of death in this condition. (CFRD) diagnosis and management have considerably changed since diabetes was first shown to be associated with a poor prognosis in individuals with CF. current trends in CFRD prevalence incidence, and mortality were determined from a comprehensive clinical database.

Showing a significant decrease in the rate of mortality in the past years, as a result of both early diagnosis of diabetes and aggressive treatment of cystic fibrosis diabetes related diabetes (CFRD).

Introduction:

Cystic fibrosis is a lethal autosomal recessive disorder that arises from mutations in chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) gene.^{1} This mutation causes the CFTR protein to become dysfunctional, as a result patients experience thick, sticky mucus secretions in multiple mucin-producing organs leading to many complications, including cystic fibrosis related diabetes.^{3}

There are two known types of diabetes in people without cystic fibrosis: Type 1 diabetes, an autoimmune disease that occurs when the body's immune system attacks and destroys the beta cells in the pancreas that make insulin. Which causes an increase in the blood sugar levels.^{4} This type of diabetes is commonly diagnosed in childhood and requires insulin injections as a treatment.^{3}

The other known type of diabetes is Type 2 diabetes, which occurs more often in adults who are overweight or obese. Type 2 diabetes is caused by the lack of the body's normal response to insulin in addition to the pancreas not making enough insulin.^{1}

Apart from these two types of diabetes there is cystic fibrosis related diabetes (CFRD), which is a common type of diabetes that is unique to people living with cystic fibrosis-related diabetes. Approximately 40-50% of adults with cystic fibrosis have (CFRD).^{1}

People with (CFRD) may not develop any symptoms, although other patients may suffer from some symptoms which are similar to diabetes mellitus symptoms, some of these symptoms include, increased thirst and urination which caused by High blood sugar levels known as hyperglycemia.^{3} Other symptoms of (CFRD) are excessive fatigue, weight loss and unexplained decline in lung function. Micro vascular complications are also common finding in individuals with (CFRD).^{{3}{1}}

The relation between cystic fibrosis and diabetes mellitus is that the mutation of CFTR gene, results in: thick mucus secretions blocking the pancreatic duct, leading to fatty infiltration and fibrosis. The islet cells become amyloid making the insulin secretion delayed and dysfunctional leading to Hyperglycemia.^{4}

Diagnosis and management of cystic fibrosis related diabetes have considerably changed since diabetes was first shown to be associated with a poor prognosis. Nowadays the management and treatment of cystic fibrosis-related diabetes has been highly increased.{2}

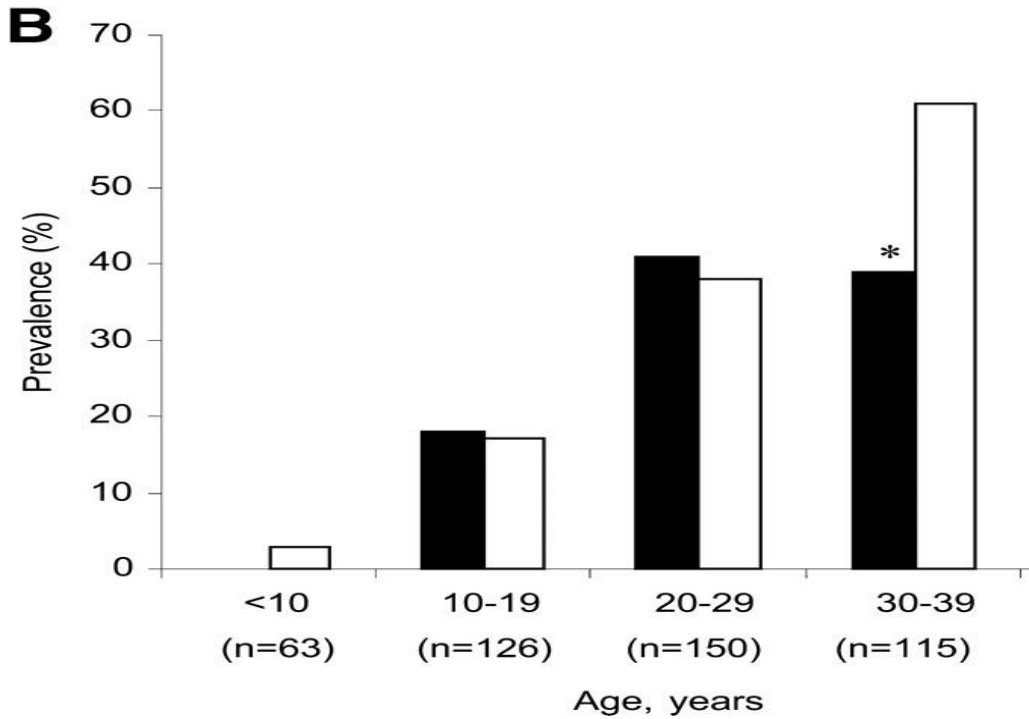
The aim of the study to describe the Current trends in CFRD prevalence, incidence, and mortality.

METHOD and MATERIALS: Clinical information was reviewed from a total of 872 patients followed at the University of Minnesota Cystic Fibrosis Center from 1 January 1992 to 15 September 2008. CF patients were routinely seen at quarterly intervals, and patient data are recorded in the Minnesota Cystic Fibrosis Database. The information was collected includes demographic and anthropometric data, pulmonary function tests, other laboratory tests, data on medication use, and clinical characteristics, and it was order to examine the temporal changes, the data were examined for three consecutive intervals: 1 January 1992 through 31 December 1997, 1 January 1998 through 31 December 2002, and 1 January 2003 through 15 September 2008. All patients seen in a clinic during an interval were included in calculations for that interval. Prevalence percent and counts were compared between groups with logistic regression. Incidence and mortality rates were calculated and were compared between groups. {2}

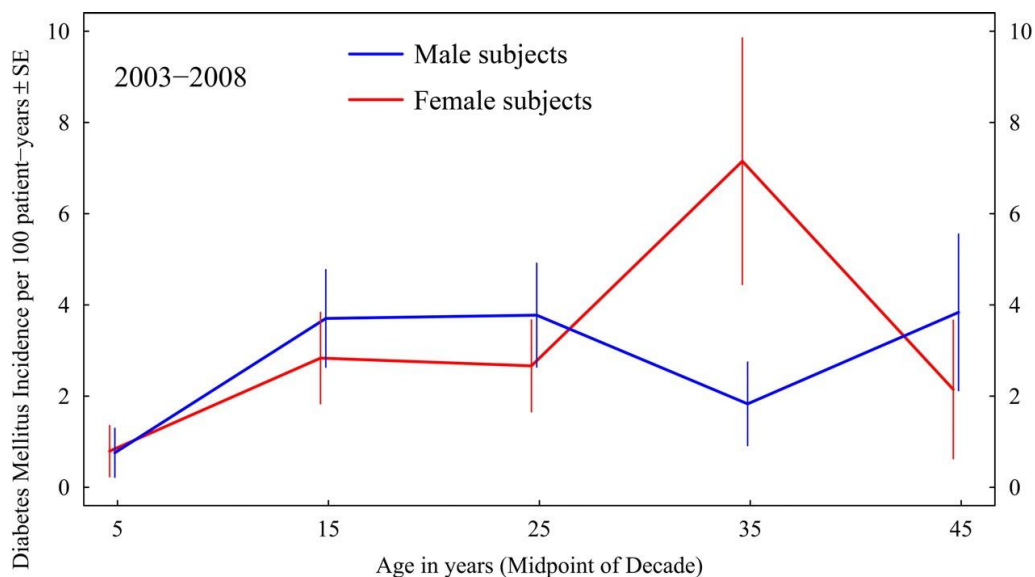
RESULTS:

CFRD prevalence: In September 2008, there were 527 pediatric and adult patients actively followed at the University of Minnesota Cystic Fibrosis Center. Of these, 33% who had diabetes—the figure similar to the 30% at the end of 2002 but showing a significant increase from the 20% of patients known to have diabetes at the end of 1997. In all three periods, the prevalence of diabetes rose steadily with age through the 30–39 age decade and after the age of 40 years remained at 45–50% (**Fig. 1A**).

Fig. 1A:



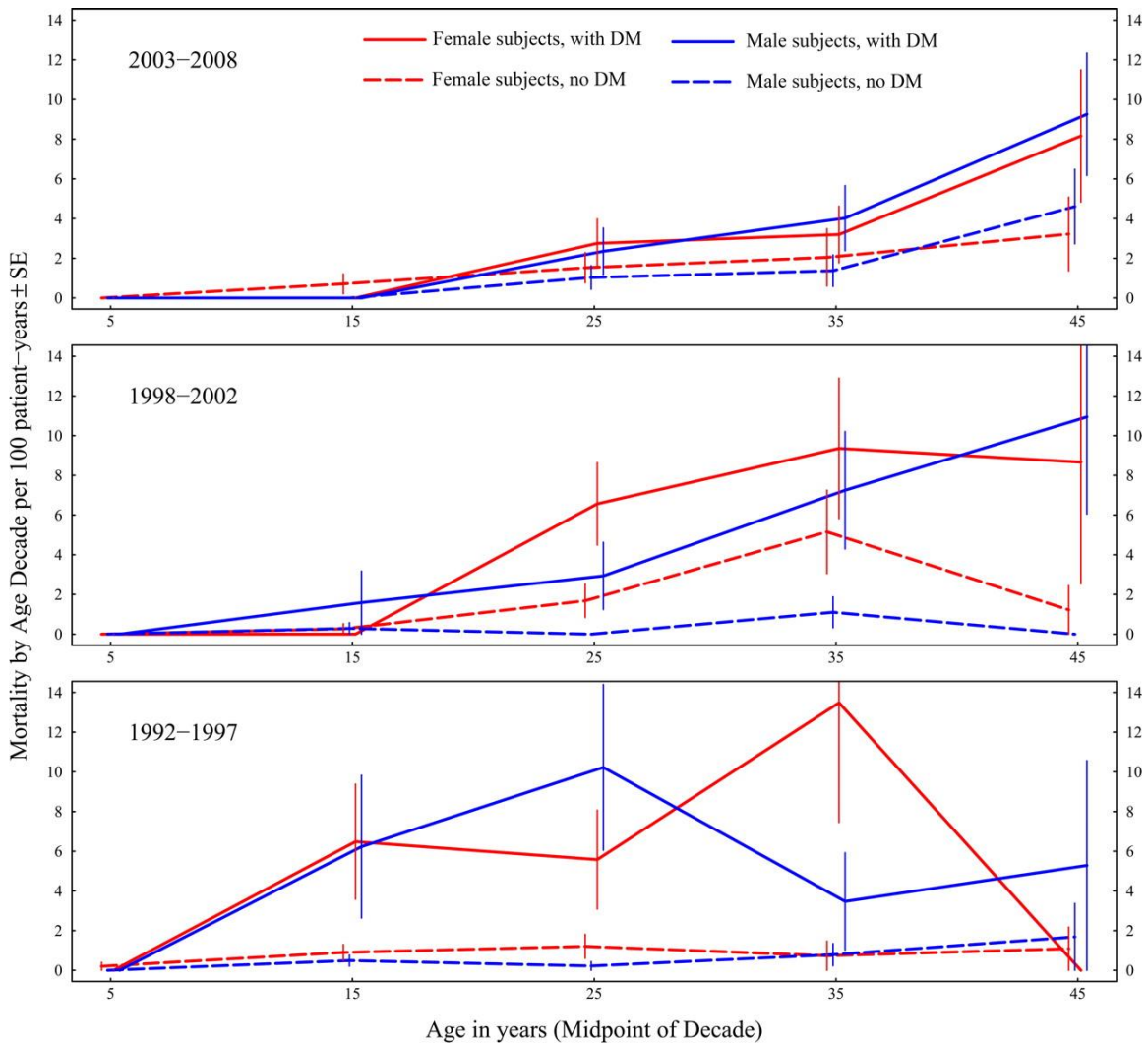
CFRD incidence: While diabetes prevalence rose, incidence fell significantly: from four cases per 100 patient-years during the 1998–2002 interval to 2.7 cases per 100 patient-years during 2003–2008, representing a 40% decrease in the number of diabetes diagnoses ([Table 1](#)). The decrease in incidence has occurred for both male and female subjects, there was a larger decrease in female subjects. Currently, a peak in incidence is noted in women aged 30–39 years ([Fig. 2](#)).



CFRD mortality: The increase in diabetes prevalence with a decrease in diabetes incidence resulted from a significant decrease in mortality in patients with diabetes. From 1992–1997 to 2003–2008, mortality in female subjects with diabetes dropped by >50%, from 6.9 to 3.2 deaths per 100 patient-years, and the decrease in male subjects was nearly as large, from 6.5 to 3.8 deaths per 100 patient-years (Table 1). During the earlier two time periods, diabetes was frequently diagnosed as a perimorbid event. Of 108 patients diagnosed with diabetes during 1992–1997, 18 died during that same interval, and results were nearly identical during 1998–2002. During 2003–2008, 61 patients were diagnosed with diabetes, of whom only 2 died during the interval.

Mortality is shown in [Fig. 3](#) by diabetes status, sex, and age decade over the three time intervals. Over time, there has been a steady decrease in mortality in CF patients with diabetes. In the most recent time period, overall mortality still remained significantly higher in those with CFRD compared with those without diabetes, but the gap has considerably narrowed compared with the earlier time periods. Importantly, during 2003–2008, sex differences in mortality by diabetes status appear to have disappeared.

Fig3:



Discussion:

As our study clarified, CFRD is currently present in 2% of children, 19% of adolescents, and 40–50% of adults, where the Incidence and prevalence are higher in female subjects aged 30–39 years; otherwise, there are no sex differences. In younger individuals. {2}Moreover, although CFRD prevalence is higher at every age in females than in males, CFRD has been associated with worse survival to a greater degree in males than females the mechanism underlying this sex difference is unknown but recent work suggest greater

lean body mass deficits in males than females with CF may represent one avenue by which CFRD differentially affects CF outcomes.^{{4}{2}}

CFRD mortality has significantly decreased over time. From 1992–1997 to 2003–2008, mortality rate in female subjects dropped by >50% from 6.9 to 3.2 deaths per 100 patient-years and in male subjects from 6.5 to 3.8 deaths per 100 patient-years. There is no longer a sex difference in mortality.^{2} Diabetes was previously diagnosed as a perimorbid event in nearly 20% of patients, but of 61 patients diagnosed with diabetes during 2003–2008, only 2 died. Those with CFRD, like all patients with CF, almost always die from pulmonary failure rather than from the macrovascular and microvascular disease associated with death in persons with type 1 and 2 diabetes.^{2} The mortality associated with this condition has steadily and substantially decreased over time. We speculate that this is related to both earlier detection of diabetes and more aggressive treatment. CFRD is generally clinically silent and only detected by screening. In the past, diabetes was often diagnosed in patients with existing but previously undetected (and untreated) disease, often in the perimorbid period routine screening now ensures that diabetes is detected early in its course. CFRD treatment is also much more aggressive today than in the past. The goals of treatment are to achieve near normalization of blood glucose levels and to deliver as much insulin as possible without producing hypoglycemia in order to maximize the anabolic effects of insulin.^{{4}{2}}

Conclusion:

Diabetes is an expected complication as individuals with CF grow older. It is encouraging to note that previous sex differences in mortality have disappeared and that the gap in mortality between CF patients with diabetes and CF patients without diabetes has considerably narrowed. Although many factors have changed in the management of individuals with CF over the last decade, we believe that early diagnosis and aggressive treatment of CFRD have played a major role in improving survival in these patients. ^{2}

References:

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