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Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Case Report

Bariatric surgery in a patient with cystic fibrosis and diabetes: A case report

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ARTICLE INFO

Article history:

Received 8 July 2022

Revised 29 December 2022

Accepted 16 January 2023

Available online xxx

Keywords:

Diabetes

Cystic fibrosis

Bariatric surgery

Obesity

ABSTRACT

Cystic fibrosis (CF) is incurable and chronic, causing severe multisystemic damage and long-term complications. The most prominent extrapulmonary long-term complication is CF-related diabetes, which is the most reported form of diabetes in individuals with cystic fibrosis. Here we present the first case of an individual with cystic fibrosis who developed type 2 diabetes due to obesity rather than CF-related diabetes. The type 2 diabetes went into remission due to extreme weight loss after gastric bypass surgery. To our knowledge, this case is also the first report describing the effect of bariatric surgery in a patient with CF. This case demonstrates that patients with CF may present with type 2 diabetes instead of CF-related diabetes. Differential diagnosis of these two types of diabetes is essential for optimal treatment and quality of life.

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1. Case report

We describe a patient with a mild form of CF who had type 2 diabetes (T2D). As a child, she never had pulmonary complaints. At 17, she had tracheobronchitis caused by *S. aureus*, after which she needed regular antibiotics to treat bacterial pneumonias. CF was suspected and she was referred to a pulmonologist at our outpatient clinic, Erasmus MC, where several diagnostic tests revealed a mild form of CF at 23. Genetic analysis identified a heterozygous $\Delta F508$ mutation and a heterozygous pathogenic mutation in the CF gene 3272–26A->G. Chloride sweat test results were as follows: left and right arm respectively 108 and 105 mmol/L Na^+ , 86 and 84 mmol/L Cl^- , sweat weight of 183 and 152 mg. The accepted reference ranges for sweat chloride concentrations are: >60 mmol/L is considered diagnostic for CF; 30–60 mmol/L borderline; and <30 mmol/L normal. Rectal biopsies identified a pattern of electrophysiological chloride characteristic for CF, but a residual chloride secretion was present.

Since diagnosis, the patient had CF exacerbations once a year, which were treated with antibiotics. She never used corticosteroids. At 42, she developed obesity due to unhealthy lifestyle.

Her energy intake exceeded the expenditure due to no exercise and unhealthy diet. Thereby, she suffered from stress due to personal problems. She was referred to a multidisciplinary obesity center, where she was connected to an exercise coach, a dietician and a psychologist. Over the next 4 years, her body mass index (BMI) increased to 35.2 kg/m², accompanied by diabetes. This was diagnosed by the following oral glucose tolerance test (OGTT) results: her fasting plasma blood glucose level was 6 mmol/L (108 mg/dL) and increased to 14 mmol/L (252 mg/dL) after an oral glucose load. Her HbA1c level was 44 mmol/mol (6.2%). Despite the lifestyle advices to treat her diabetes and to promote weight loss, she did not lose weight. Her family history was negative for obesity, hypertension and diabetes mellitus.

At 48, her BMI was 34.0 kg/m², HbA1c was 49 mmol/mol (6.6%), with OGTT results of 6.2 to 10.8 mmol/L (111.6 to 194.4 mg/dL), indicating development of overt diabetes. Her pulmonary function was stable: forced vital capacity (FVC) was 84% and forced expiratory volume in one second (FEV_1) was 69%. There were no indications of exocrine pancreatic insufficiency, except for a reduced 25-OH-vitamin D concentration (45 $\mu\text{mol/L}$). Vitamins A and E were respectively 1.77 and 22.4 $\mu\text{mol/L}$. DEXA scan results showed normal bone density. Furthermore, her liver function was normal (ASAT=18 U/L and ALAT=30 U/L), as was her kidney function (creatinine=80 $\mu\text{mol/L}$) and thyroid function (TSH=2.26 mIU/L). Her medical history included a severe form of preclamp-

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<https://doi.org/10.1016/j.jcf.2023.01.008>

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Table 1

Overview of longitudinal data regarding clinical, vital and laboratory parameters.

Year, month	2016, May	2018, Nov**	2019, June	2019, Nov	2020, Jan***	2020, June	2020, July	2021, March	2021, Aug	2022, June
BMI (kg/m ²)	35.2	34.0	36.0	35.1	35.34	27.2	27.0	23.15	24.0	24.1
HbA1c (mmol/mol)	44	49	61	52		48		44		42
HbA1c (%)	6.2	6.6	7.7	6.9		6.5		6.2		6.0
Glucose (mmol/L)	*		9.3	4.4		6.2		4.9	4.8	5.2
Glucose (mg/dL)			167.4	79.2		111.6		88.2	86.4	93.6
OGTT (mmol/L)	6.0 → 14.0	6.2 → 10.8					6.9 → 8.0			
OGTT (mg/dL)	108 → 252	111.6 → 194.4					124.2 → 144			
FEV ₁ (%)	75	69	69	66		61		59	72	75
FVC (%)		84	84			82		82		91
Vitamin A (µmol/L)	2.15	1.77		1.96			1.45	1.34		1.71
Vitamin D (µmol/L)	53	45	65	55	91		83	71		84
Vitamin E (µmol/L)	26.0	22.4		26.7			25.4	29.1		31.5
Triglyceride (mmol/L)			2.03	1.76		0.82		0.60		
Total cholesterol (mmol/L)			4.7	3.9		3.7		4.2		
HDL-cholesterol (mmol/L)			1.13	1.13		1.07		1.69		
LDL-cholesterol (mmol/L)			2.66	2.97		2.26		2.54		

*Empty boxes indicate that measurement values are unknown; **Diagnosis diabetes mellitus; ***Laparoscopic sleeve gastrectomy.

sia. She had no further medical comorbidities like hypertension or dyslipidemia. All results are summarized in Table 1.

Based on these results, her treating physicians strongly suspected that her diabetes was not CF-related diabetes (CFRD) and more likely to be T2D. Therefore, metformin (1dd, 500 mg) was prescribed as a first-line treatment. She never used insulin. However, one year later, her HbA1c levels had increased to 61 mmol/mol (7.7%) and her BMI to 36.0 kg/m². Given her continuing weight increase and poor glycemic control, her doctors decided to follow the clinical practice guidelines and proposed bariatric surgery [1], despite her CF. Prior to surgery, her vitamin levels and lipid profile were both within normal ranges. She only used daily supplementation of calciumcarb/colecalciferol (1.25 g/400IE) and azitromycine (3 times a week, 500 mg).

At 49, in January 2020, she underwent a laparoscopic sleeve gastrectomy with no complications. Post-surgery, she directly started multivitamin supplementation as advised by guidelines [1]. After six months, her total weight loss was 22.7%, BMI was down to 27.2 kg/m², HbA1c to 48 mmol/mol (6.5%), with a blood plasma glucose level of 6.2 mmol/L (111.6 mg/dL). Metformin was stopped. OGTT results were 6.9 to 8.0 mmol/L (124.4 to 144 mg/dL) after an oral glucose load. Moreover, she felt well and her condition improved. A fasting blood test showed plasma insulin at 38 pmol/L and C-peptide at 0.56 nmol/L. In March 2021, her HbA1c levels were reduced to 44 mmol/mol (6.2%) and BMI was 23.15 kg/m². Spirometry showed a FVC of 3.55 L (82%) and a FEV₁ of 2.02 L (59%). In June 2021, she started with her first CFTR modulator Symkevi and switched to Trikafta, in May 2022. 2.5 years after bariatric surgery, in June 2022, her BMI and HbA1c levels remained stable at respectively 24.1 kg/m² and 42 mmol/mol (6.0%). Her FEV₁ increased to 2.44 L (72%). Moreover, soluble vitamins levels remained stable under supplementation and lipid levels reduced. Noteworthy, under supplementation of Trikafta, her weight remained stable at a BMI of 24.2 kg/m², which was measured in December 2022. These collective findings indicated that her T2D and obesity went into remission after bariatric surgery and that her pulmonary function remained stable.

2. Discussion

To the best of our knowledge, this is the first report of an individual with CF to be diagnosed with T2D due to obesity instead of CFRD. This is also the first published description of the effect of bariatric surgery in CF.

In patients with a classical severe CF phenotype, the nature of diabetes is CFRD, which occurs in 40% of adults and is associ-

ated with poorer survival [2]. However, the CFTR class V mutation in this patient ($\Delta F508;3272-26A \rightarrow G$) indicates a mild clinical CF phenotype due to residual CFTR function [2-4]. In the current era of genomics, an increasing number of patients are being diagnosed with milder CF phenotypes [3]. Such individuals are more likely to be pancreatic sufficient (PS), have better pulmonary function and good survival [2,3]. In contrast to pancreatic insufficient CF, PS CF rarely causes CFRD due to maintained β -cell function [4]. Due to increased survival, these patients are at risk of developing chronic diseases such as obesity, which in turn can lead to T2D [1]. The prevalence of obesity in CF adults is thought to be as high as 30% [5]. In view of this, and based on this case and other patients at our outpatient clinic, we are convinced that more CF patients with a mild phenotype and diabetes are likely to have T2D rather than CFRD.

Among overweight and obese CF cohorts, higher rates of exocrine PS and mild genotypes have been reported [6,7]. In contrast with these findings, pancreatic insufficiency has been associated with malnutrition, and may result in a lower risk of developing obesity. However, pancreatic insufficient CF patients can still have higher BMI's [8]. It must be noted that BMI does not capture all the nuances that contribute to optimal health status. With regards to pulmonary function, prognosis is negatively associated with weight loss and malnutrition in CF: the lower the BMI, the lower the pulmonary function [9]. Two studies showed a limit to this relationship [8,9]. Contrary to overweight/obese CF, the greatest pulmonary benefit is seen after an increase in BMI in undernourished CF patients [8,9]. These studies report a threshold of BMI 25-29 kg/m², above which pulmonary function improvement becomes significantly minimal [8,9]. Regarding cardiovascular disease (CVD), results of a cohort study indicate that overweight/obese CF patients may be at risk of developing CVD [7]. However, data on CVD in CF remain limited.

Unlike in CFRD, healthy lifestyle interventions are cornerstone treatments for T2D, and may even reverse disease [10]. Multiple approaches are available to promote weight loss, such as regular exercise, low-calorie diet and medication options advised and guided by professionals in multidisciplinary teams for obesity. However, for those individuals not capable of losing weight with non-surgical procedures, bariatric surgery could be considered [1]. For non-CF patients, surgery is clinically more effective than medical treatment for weight reduction and maintenance [1]. Data on treatment options for weight loss and bariatric surgery on safety and efficacy in CF is lacking. Reducing energy intake and increasing physical activity is a first step approach, extrapolating from Endocrine Society Guidelines [1]. In this obese CF patient, how-

ever, bariatric surgery had a good clinical result in terms of T2D management and weight loss. With regular follow-up and guidance, she lost 40 kg, and this weight loss has remained stable until present. Moreover, we observed no significant adverse events. Pulmonary function and soluble vitamins remained stable.

CFRD shares features of type 1 diabetes (T1D) and T2D. Similar to T1D, the primary pathologic feature is insulin insufficiency due to β -cell function loss [2,4]. More in line with T2D, insulin resistance is mildly present [4]. For differential diagnosis of CFRD and T2D in CF with a mild phenotype, we consider that clinical presentation carries the most importance. If inconclusive for PS CF, we recommend fasting plasma insulin and C-peptide measurements to distinguish between both diseases, which is also the case with T1D and T2D [11]. As in T1D, CFRD is caused by loss of β -cell function, and C-peptide levels are significantly lower in CFRD (<0.2 nmol/L) than in CF patients without CFRD [12]. In individuals with T2D, C-peptide levels are normal/high [11]. Unfortunately in this case report, C-peptide and fasting insulin were only measured once after surgery in June 2020.

In conclusion, this case demonstrates that CF patients can develop T2D instead of CFRD. Given the increasing number of diagnoses of mild CF coupled with the increase in overweight/obese patients, it is likely that T2D in CF patients will increase. Doctors should therefore be aware that patients with overweight and CF may also have T2D. With good diagnostics and treatment, T2D can go into remission, thereby improving quality of life. In overweight CF patients, bariatric surgery may be considered as an option to achieve and maintain weight loss, and, if necessary, to treat diabetes. However, bariatric surgery must be considered carefully given the potential cause of adverse effects, such as malabsorption, vitamin and mineral deficiencies. In our view, both T2D and bariatric surgery are new phenomena in CF that will both require further research to determine their effects on the quality of life of patients with CF.

Patient consent

The patient consented to the use of her data for this case report

Credit author statement

N.R.A. Bruijn: Conceptualized this manuscript, investigated literature, managed project administration, wrote the original draft

M.A.E.M. Wagenmakers: Conceptualized this manuscript, provided critical reviewing and editing, approved final version

M. van Hoek: Conceptualized this manuscript, provided critical reviewing and editing, approved final version

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Declaration of Competing Interest

None.

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