Emerging Obesity in Adult Patients with Cystic Fibrosis

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Abstract

Cystic fibrosis (CF) is often associated with malabsorption due to pancreatic insufficiency. The maintenance of a normal body mass index (BMI) is associated with better pulmonary function (FEV_1) and survival. However, as major advancements in respiratory therapies and nutritional optimization continue to optimize the health of patients with CF, there is an emerging sub-population with excessive and/or rapid weight gain in some patients. The long term complications of obesity in this population have not been well characterized to date.

For this work, baseline data from 290 adult patients with CF from the Montréal CF Cohort were collected. Observational follow-up data of 158 of those patients, over an average of 3.5 years, were also collected. At baseline, we characterized patients according to their BMI: underweight (UW < 18.5 kg/m^2), normal (NW 18.5-26.9 kg/m^2), and overweight/obese (OW≥ 27 kg/m^2). Prospective observational analyses were then performed using follow-up data. The follow-up data was categorized based on weight change over the 3.5-year period: weight loss (WL > 10% weight change), stable (WS), and weight gain (WG > 10% weight change). BMI categories and follow-up data were compared to FEV_1 and cardiometabolic parameters, such as glucose tolerance, estimated insulin resistance (IR), blood pressure (BP), and lipid profile.

At baseline, we found that the majority of patients were NW (81.0%), while 12.1% were UW and 6.9% were OW. Our results showed that OW patients tended to be older, were less likely to have pancreatic insufficiency, a higher systolic BP, higher LDL, and higher IR. In addition, compared to UW patients, OW patients had a better FEV_1.

For the follow-up weight change analysis, 4.4% patients lost weight (WL group) while 84.8% kept a stable weight (WS group) and 10.8% gained weight (WG group). While WL and WS patients had a decrease in FEV_1, WG patients had a 5% increase in FEV_1. The WG group also had higher IR and triglycerides compared to the WL and WS groups. No differences were observed for glucose tolerance for neither BMI nor weight change.

Together, our results showed that a greater absolute weight and greater weight gain over time are associated with a better lung function but unfavorable cardiometabolic trends.

Résumé

La fibrose kystique (FK) est souvent associée à une malabsorption lipidique due à une insuffisance pancréatique. Le maintien d'un indice de masse corporelle (IMC) normal est associé à une meilleure fonction pulmonaire (VEMS) et à une meilleure survie. Cependant, alors que les avancées majeures dans les thérapies respiratoires et l'optimisation nutritionnelle continuent d'optimiser la santé des patients atteints de la FK, il y a une sous-population émergente avec une prise de poids excessive et/ou rapide chez certains patients. Les complications à long terme de l'obésité dans cette population n'ont pas encore été bien caractérisés.

Pour cette étude, les données de base de 290 patients adultes atteints de FK de la cohorte FK de Montréal ont été recueillies. Des données de suivis observationnels de 158 de ces patients, sur une durée moyenne de 3,5 ans, ont également été collectées. À la visite initiale, nous avons caractérisé les patients en fonction de leur IMC: poids insuffisant (IN < 18,5 kg/m^2), normal (NO 18,5 – 26,9 kg/m^2), et en surpoids/ obèse (SO ≥ 27 kg/m^2). Des analyses observationnelles prospectives ont ensuite été effectuées à l'aide des données de suivi. Les données de suivi ont été classées en fonction du changement de poids sur la période de 3,5 ans: perte de poids (PP > 10% de changement de poids), stable (PS), et gain de poids (PG > 10% de changement de poids). Les catégories d'IMC et les données de suivi ont été comparées au VEMS et au statut cardiométabolique, tels que la tolérance au glucose, la résistance estimée à l'insuline (RI), la tension artérielle (TA) et le profil lipidique.

À la visite de base, nous avons observé que la majorité des patients étaient NO (81,0%), tandis que 12,1% étaient IN et 6,9% étaient SO. Nos résultats ont montré que les patients SO avaient tendance à être plus âgé, étaient moins susceptibles d'avoir une insuffisance pancréatique, une TA systolique

plus élevée, un LDL plus élevé et une RI plus élevée. Comparé aux patients IN, les patients SO avaient aussi un meilleur VEMS.

Pour l'analyse de suivi du changement de poids, 4,4% des patients ont perdu du poids (groupe PP) tandis que 84.8% ont maintenu un poids stable (groupe PS) et 10,8% ont pris du poids (groupe PG). Alors que les patients PP et PS avaient une diminution de VEMS, les patients PG avaient une augmentation de 5% de VEMS. Le groupe PG avait également des niveaux plus élevés de RI et de triglycérides comparé aux groupes PP et PS. Aucune différence n'a été observée pour la tolérance au glucose ni pour les groupes d'IMC ni pour les groupes de changement de poids.

Ensemble, nos résultats ont démontré qu'un poids absolu plus élevé et un gain de poids plus importants au fil du temps sont associés à une meilleure fonction pulmonaire mais également à des tendances cardiométaboliques défavorables.

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Statement of Originality

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received, sources cited, and collaborators worked with while preparing this thesis have been acknowledged. This thesis has not been submitted for the attainment of any other degrees.

The manuscript included in this thesis has been published in the journal *Clinical Nutrition* [1] as original literature and is a product of my own work in collaboration with the authors listed. The manuscript will not be used in my first co- author's thesis and she has provided a written agreement stating that the manuscript can be used in this thesis.

Contributions of Authors

Anne Bonhoure – first co-author of the manuscript and author of this thesis. Contributed to data collection, research design, conducting research, analyzing data, and writing of the paper. Also had shared responsibility for the final published manuscript.

Valérie Boudreau – first co-author of the manuscript and has given permission for the use of it in this thesis. Provided support and teaching for the writing of the thesis and the manuscript. Also contributed to data collection, research design, conducting research, analyzing data, and writing of the paper. Provided extensive revisions and comments and had shared responsibility for the final published manuscript.

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Abbreviations

AGT	abnormal glucose tolerance
ANOVA	analyses of variance
ASL	apical surface liquid
AUC	area under the curve
BIA	bioelectrical impedance analysis
BMI	body mass index
CF	cystic fibrosis
CFRD	cystic fibrosis-related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
CVD	cardiovascular disease
DXA	dual-energy X-ray absorptiometry
FEV_1	forced expiratory volume in 1 s
FFM	fat free mass
GI	gastrointestinal
HDL	high-density lipoprotein
IGT	impaired glucose tolerance
INDET	indeterminate glucose tolerance
IRT	immunoreactive trypsinogen

LDL	low-density lipoprotein
MCFC	Montreal Cystic Fibrosis Cohort
NGT	normal glucose tolerance
NW	normal weight
OGTT	oral glucose tolerance test
OW	overweight
PI	pancreatic insufficiency
PS	pancreatic sufficiency
REE	resting energy expenditure
T1D	type 1 diabetes
T2D	type 2 diabetes
UW	underweight
WL	weight loss
WS	weight stable
WG	weight gain

Thesis Overview

This thesis is structured to present and elaborate on a publication investigating the impact of overweight, obesity and significant weight change on cardiometabolic risk, pulmonary function and nutritional status in adult patients with Cystic Fibrosis (CF). Chapter 1 is a general introduction to the pathophysiology, clinical context and current treatment of CF, as well as background context for obesity and diabetes. Chapter 2 will be a short preface leading to Chapter 3, which will consist of the manuscript, detailing the impact of a high Body Mass Index (BMI) and weight change on adult patients with CF who are part of the Montréal CF Cohort. Finally, Chapter 4 and 5 will be the general discussion and the conclusion of the thesis.

Thesis Rationale

CF is the most common fatal genetic disease in Caucasian people, caused by mutation in the CF transmembrane conductance regulator (CFTR) gene [2]. This results in impaired movement of chloride ions and leads to thickened mucus secretions in multiple organ systems. In the respiratory system, impacted viscous secretions cause airway obstruction and reduced airflow, and increased risk of lung infections, pulmonary exacerbations and respiratory failure [3]. In the gastrointestinal system, thick mucus impairs secretion of digestive enzymes from the exocrine pancreas, thus impairing digestion and absorption of nutrients. In turn, this places patients at high risk of suboptimal nutrition and difficulty maintaining body mass [3]. Endocrine pancreatic function is also impaired by bystander effect in a chronically inflamed pancreas, which predisposes patients to beta cell dysfunction and eventual diabetes mellitus.

In patients with CF, the maintenance of a normal BMI is associated with better pulmonary function (FEV_1) and survival [4, 5], and thus is a key therapeutic objective. A high calorie, high fat diet and

pancreatic enzyme replacement therapy were introduced to optimize weight gain [6]. In the midst of these changes, a small but significant proportion of patients are now showing obesity or excessive weight gain [4, 5]. However, the impact of being overweight or rapid weight gain on clinical outcomes, such as FEV_1 & cardiometabolic complications, remains unknown.

Thesis Objectives

The objectives of this thesis are to **1)** compare the cardiometabolic profile and lung function status between various BMI categories (underweight, normal and overweight/obese) in adult patients with CF of the MCFC; and **2)** investigate the impact of significant weight change (>10% weight gain or loss) in the same patients with CF over a 3-year period on the same clinical parameters.

Thesis Hypothesis

Our hypothesis was that overweight/obese patients with CF, as well as those who gained weight, will have more favorable, or even improved, lung function. However, these patients will also have less favorable cardiometabolic profiles compared to their respective counterparts.

1 Introduction

1.1 Introduction to CF

1.1.1 Pathophysiology of CF

Cystic Fibrosis (CF) is a multi-system recessive genetic disease primarily involving the respiratory and gastrointestinal (GI) tracts [2]. It is largely characterized by salty sweat, thickened mucus secretions, frequent chest infections and reduced pulmonary function. In 1938, CF was first identified as a distinct disease associated with excess mucus secretion and an estimated life expectancy of six months [7]. At first, the disease was thought to be a result of abnormal exocrine duct function and frequent lung infection. However, the disease was discovered to have a further reaching impact when a sweat chloride defect in people with CF was identified in the 1950s [7].

In 1989, it was established that CF is caused by mutation in the gene encoding the CF transmembrane conductance regulator (CFTR) protein, a membrane glycoprotein expressed on the apical membrane of secretory and absorptive epithelial cells [8, 9]. There are 6 mutation classes (Figure 1.1) that can be divided into two main categories: mutations that reduce CFTR protein function and mutations that reduce the quantity of CFTR protein [10, 11]. Disrupted chloride ion transportation in epithelial cells results in the dehydration and thickening of mucus secretions in exocrine-containing tissues, such as the exocrine pancreas and skin. In the pancreas, digestive enzyme movement through pancreatic ducts is impaired, often leading to local autolysis from enzymes stuck in pancreas [12]. Organ systems that rely on ciliary function, such as the respiratory and reproductive tracts, are also affected by thick mucosal secretions [3, 13]. For instance, the impaired digestive enzyme movement from the exocrine pancreas leads to maldigestion due to the lack of enzymes in the GI tract. Viscous secretions can then lead to airway obstruction and

increased risk of infection in the respiratory system, as well as exocrine and endocrine insufficiency in the pancreas [2, 3].

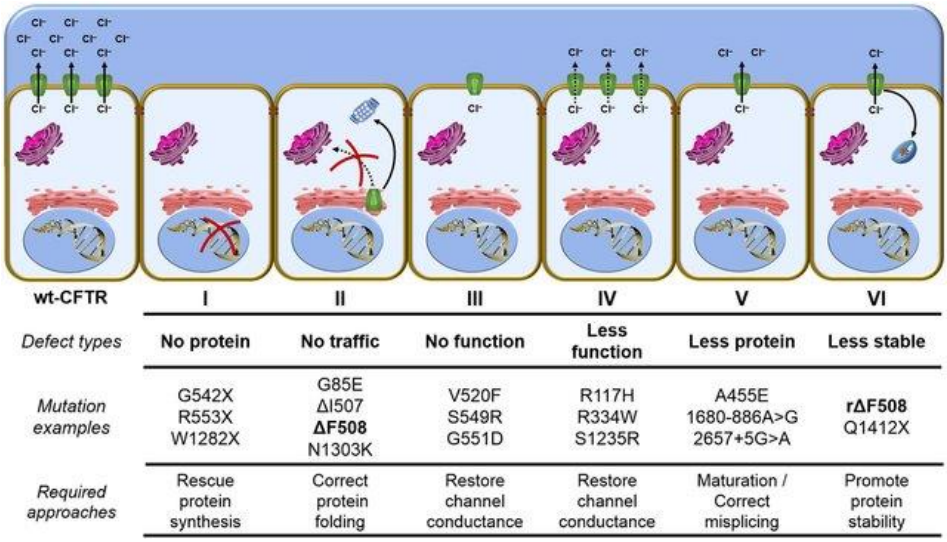

Fig. 1.1 Classes of CFTR mutations
Distribution of CFTR mutations into six functional classes according to the primary molecular defect [11]

1.1.2 Diagnosis of CF

As CF is such a life-threatening disease, early diagnosis is critical to begin specialized medical care and improve survival. CF screening initially depended on clinical recognition of characteristic signs and symptoms, such as persistent cough, sinusitis, malnutrition, steatorrhea, and pancreatitis [14]. However, a widespread increase in CF newborn blood spot screening (NBS) in the past decade has made it possible to diagnose CF in asymptomatic or minimally symptomatic infants after a positive NBS result [15, 16]. NBS works by screening a small blood sample that is taken shortly after birth for several different health conditions. CF is screened by testing for immunoreactive trypsinogen (IRT), a chemical made by the pancreas. High levels of IRT caused

by blockage of pancreatic ducts, pancreatic auto-digestion, and leakage of digestive enzymes, results in a positive screening [13, 16, 17].

While a screening test is used for individuals who are considered at high risk of developing a disease and to determine whether a diagnostic test is necessary, a diagnostic test is performed to establish a definitive diagnosis and often have a precisely defined cutoff for a positive result [18]. The NBS is a screening test for CF. A confirmatory diagnostic test must be performed in order to confirm a positive screening and to make a diagnosis of CF. The gold standard for CF diagnostic testing is the sweat chloride test. A sweat chloride concentration $\geq$ 60 mmol/L confirms the diagnosis of CF [15].

The majority (60%) of individuals with CF are diagnosed before the age of one. However, a small proportion (7.7%) of patients are diagnosed later in life. Many in this latter group were born before the adoption of the NBS [19]. In these cases, the sweat chloride test is often used to diagnose these patients when they begin showing signs and symptoms of CF [14]. In addition to sweat chloride testing, genotype analysis is typically performed when the sweat chloride concentration is indeterminate, or between 30 and 59 mmol/L [15]. The presence of two CF causing mutations of the CFTR gene confirms diagnosis. There are over 2,000 mutations, but the most common mutation of the CFTR gene in patients with CF is the ΔF508 mutation, accounting for approximately 70% of CF chromosomes worldwide [15]. Patients who are homozygous for ΔF508 tend to have higher disease severity than patients who are heterozygous for ΔF508 or have two non- ΔF508 alleles [20]. Once a CF diagnosis is made, an assessment of the respiratory, hepatic, gastrointestinal, pancreatic and reproductive systems are made to determine disease severity, best practice and follow-up frequency [15, 21].

1.1.3 Epidemiology of CF

CF is increasingly prevalent with over 70, 000 cases worldwide and over 4,370 cases in Canada [19]. According to Cystic Fibrosis Canada, CF is the most common genetically fatal disease in Caucasian people, with 92.6% of Canadian patients with CF being Caucasian [19]. The majority of patients with CF are young adults. In Canada, the median age of all individuals with CF was 23.5 years in 2018, with 61.5% of patients being adults (over 18 years of age), 15.9% being over 40 years of age, and 0.5% being over 70 years of age [19]. The increase of older patients with CF matches the increase in the median age of survival. The estimated median age of survival for individuals with CF in Canada has significantly improved in the past decades (from 33 years in 2001 to 52.1 years in 2018), thanks to the development of specialized comprehensive care networks and new medications and therapies for the treatment of CF-related disease [6, 13, 19].

1.2 Lung Function in CF

The respiratory system is the most significantly impacted organ system in patients with CF, with respiratory failure causing more than 80% of deaths in CF [22]. Deterioration of lung function often begins during infancy in individuals with CF. Chronic cough, sputum overproduction, tenacious mucus, and recurrent and persistent lung infections are all clinical manifestations of CF that begin during childhood. Progression of lung disease continues in adulthood with the onset of impaired pulmonary function, chronic infection with bacterial colonization, pneumothorax, and possible respiratory failure [11]. In patients with CF, Staphylococcus aureus and Pseudomonas aeruginosa are common pathogens that remain inside the respiratory tract and colonize [7, 13]. The growth and expansion of these pathogens, among others, leads to frequent chest infections and pulmonary exacerbations [23, 24].

The pathogenesis of impaired respiratory function stems from reduced CFTR activity in the sinuses and respiratory tract. Impaired CFTR function leads to volume depletion and/or decreases in the pH of the lung apical surface liquid (ASL). This increases the amount and viscosity of mucus, resulting in increased adhesiveness and cohesiveness of airway phlegm [3, 11, 13]. The accumulation of mucus leads to a cycle of airway obstruction, inflammation, and bronchiectasis. In addition, the clearance issues caused by the excess mucus allow pathogens to frequently colonize the airways and increase the recruitment of inflammatory cells [11]. Furthermore, neutrophilic inflammation from the long-term bronchiolitis and air trapping add to the vicious cycle of airway obstruction, inflammation and infection that leads to epithelial damage, lung tissue remodeling, reduction of gas exchange area, and end-stage lung disease or respiratory failure [11, 13].

The frequency of pulmonary exacerbations and hospitalizations is associated with survival and health related quality of life in patients with CF [25]. Together, the chronic obstruction, infection and inflammation contribute to a lifelong degradation of lung anatomy and function. Clinically, these contribute to increased work of breathing, wheezing, daily coughing, and even the need for oxygen in severe cases [26].

Patients routinely undergo pulmonary function testing to optimize their lung health in an outpatient environment and minimize the frequency of pulmonary exacerbations. Assessment involves the use of spirometry, chest imaging and quality-of-life questionnaires [27]. Forced Expiratory Volume in one second (FEV_1) is derived from spirometry testing in liters (L) and represents the maximal amount of air that is forcefully exhaled in one second. FEV_1 percentage ($\%FEV_1$ predicted) is then predicted for patients with CF by comparing their FEV_1 to the average FEV_1 of a similar healthy population [19]. $\%FEV_1$ predicted is the best and most common measure of lung

function in CF as it has been shown to be strongly associated with mortality, BMI, and pancreatic status [28]. FEV_1 is currently a key measure used to define disease stage, to make decisions on treatment, for comparison between centers and countries, and as a primary outcome in clinical studies [27].

Patients with CF experience a greater annual decline in lung function as compared to healthy counterparts. One longitudinal study performed in the U.S.A. found that 174 patients with CF had a mean rate of decline in $\%FEV_1$ of 3.89% per year [29]. Furthermore, persons with CF that experience more frequent pulmonary exacerbations have accelerated disease progression and decline in FEV_1 [30], suggesting an association between pulmonary exacerbations frequency and airflow limitation. Respiratory health has improved in many patients in contemporary cohorts. Although individuals with CF have a significant decline in lung function as they age, the median FEV_1 of patients with CF at 23 years of age (the median age of patients with CF) has risen from 58.6% in 1998 to 69.5% in 2018 as respiratory therapies and CF-specialized treatments are improving [19].

1.3 Gastrointestinal Tract and Pancreatic Function in CF

The gastrointestinal (GI) tract is also significantly impacted by reduced CFTR function. CFTR is found in all of the epithelia throughout the GI tract, including pancreatic and digestive systems [31]. In the exocrine pancreas, impaired digestive enzyme movement from the pancreas, caused by decrease CFTR function, leads to maldigestion due to the lack of enzymes in the digestion organs. The clinical manifestations of the GI complications often begin during infancy, with some patients with CF presenting with meconium ileus (MI), a neonatal bowel obstruction, and are present throughout the patient's life [32]. The CF population is also at increased risk of

gastroesophageal reflux disease (GERD), pancreatic ulcer disease, small intestinal bacterial overgrowth (SIBO), and distal intestinal obstruction syndrome (DIOS) [32]. Furthermore, the majority of the CF population have reduced exocrine pancreatic function, marked as having pancreatic insufficiency (PI), with 84.4% of Canadians with CF having PI [19].

In a healthy population, normal CFTR function is important for secretion of digestive enzymes and neutralization of gastric secretions [33]. Chloride and bicarbonate ion secretion drives a dilute alkaline fluid into ducts, allowing the movement of macromolecules, such as proteins and mucins, along the ducts. Bicarbonate is also essential for normal mucus formation; it plays a significant role in the viscosity of mucins and mucus by controlling swelling and dispersion [33-35]. Bicarbonate ions also protect epithelium from acids and optimize duodenal pH for digestive enzyme function [33].

In patients with CF, the impaired transport of both chloride and bicarbonate causes a cascading effect leading to microbial dysbiosis, altered immune responses, and inflammation [36]. Altered gastrointestinal pH homeostasis impairs pancreatic development in utero. The pancreatic damage in patients with CF often results in PI due to inflammation and premature activation of pancreatic enzymes destroying the acinar cells (exocrine) of the pancreas [37]. The destruction of acinar cells results in reduced digestive enzyme production and secretion of those enzymes into the small intestine [12]. The combination of thick mucus, acidic pH, and reduced digestive enzymes results in an increase of protein concentration within the pancreatic tissue, leading to compromised blood flow and ischemic damage. This injury then causes atrophy, fibrosis, and fatty infiltration of the exocrine pancreas [38, 39]. Altogether, this destructive cascade leads to impaired digestion, nutrient malabsorption and malnutrition, which are associated with worse lung function and increased mortality [24, 36].

As PI leads to maldigestion and malabsorption of nutrients, it is difficult for patients to maintain an optimal nutritional status [32]. Therefore, early diagnosis of PI in the CF population is critical so that pancreatic enzyme supplements can be prescribed. Until recently, tests to determine the presence of PI were invasive and required patients to stop taking their pancreatic enzyme supplements for the duration of the test [32]. Recently, a more pleasant method, with a higher sensitivity and specificity, was adopted. PI is now determined using a human monoclonal enzyme-linked immunosorbent assay (ELISA) for fecal elastase-1 [40]. Another commonly used method, especially by clinics, is quantification of fecal fat by the classical Van de Kamer test, which is the gold standard for diagnosing fat maldigestion [41]. Patients with CF that are determined to have PI are then prescribed lifelong pancreatic enzyme supplements to help with digesting and absorbing food [42], Thus, any person with CF who is taking pancreatic enzyme supplements is considered as having PI and is classified in their respective national registries as such [40].

Pancreatic disease in the CF population can range from complete loss of exocrine function to nearly normal pancreatic function (pancreatic sufficiency (PS)). In some persons with CF, pancreatic disease can evolve into acute pancreatitis and eventually chronic pancreatitis. Pancreatitis is inflammation in the pancreas caused by digestive enzymes that are activated in the pancreas instead of the small intestines [43]. Although patients with CF and PI can develop chronic pancreatitis (~0.5%), patients with CF and PS are at higher risk of developing it (10.3%) [44]. The most probably reason for this is that there is enough pancreatic tissue present that can be irritated and damaged among those with PS. Clinically, pancreatitis is typically accompanied by upper abdominal pain and weight loss. Pancreatitis has also been associated with complications such as pancreatic infections and worsened lung function [43]. Thus, a significant fraction of patients living with CF will have a combination of exocrine and endocrine pancreatic dysfunction.

The major endocrine pancreatic function includes the secretion of insulin by beta cells and the secretion of glucagon by alpha cells in order to regulate blood glucose regulation [45]. In patients with CF, the disruption of the Islets of Langerhans is accompanied by progressive loss of beta-cell mass and progressive loss of beta-cell function [39, 46]. In a research setting, the endocrine pancreatic function in those with CF is often assessed using first-phase response of insulin to oral glucose (first-phase insulin secretion) [39]. Several studies have shown that persons with CF have impaired first-phase insulin secretion, even with a normal glucose tolerance [39, 47]. The major consequence of this largely reduced insulin secretion is a very high prevalence of glucose abnormalities (see section 1.4).

Together, maldigestion and malabsorption in the gastrointestinal tract and loss of calories from inefficient insulin secretion (e.g. inability to store nutrients, impact of hyperglycemia, etc.), significantly impact the ability of an individual with CF to maintain sufficient caloric intake for their metabolic needs. Adequate nutrition is a critical factor in the maintenance of pulmonary function in patients with CF.

1.4 Cystic Fibrosis-Related Diabetes

As patients with CF are living longer, there is an increase in the incidence of comorbid conditions with a variety of dysglycemic conditions, the most important being CF-related diabetes (CFRD). CFRD is the most common comorbidity in individuals with CF, affecting up to 50% of adults with CF [48].

Although the exact pathogenesis of CFRD is not fully understood, a key factor is a reduction in insulin secretion. In CF, insulin secretion is reduced far more than in type 2 diabetes, but not completely as in type 1 diabetes [39]. CFRD likely consists of a combination of insulin deficiency,

insulin resistance and a genetic predisposition for the development of diabetes [39]. The primary cause of CFRD is the loss of beta-cell mass and function due to chronic pancreatitis. CFTR dysfunction is indirectly related to CFRD, however, as CFTR is not expressed in human beta cells. In the context of significantly reduced insulin secretion, insulin resistance may also play a role in abnormal glucose levels and CFRD development [49].

Insulin is an essential anabolic hormone and a deficiency can be linked to protein catabolism [50]. Furthermore, the reduced insulin secretion capacity associated with CFRD could impact the ability to retain and utilize calories, putting patients in a catabolic state. Meanwhile, the related hyperglycemia could favor exacerbations further increasing metabolic requirements [51, 52]. Furthermore, CFRD is associated with worsened pulmonary pathology and nutritional status, higher prevalence of bacterial colonization by *Pseudomonas aeruginosa* and *Burkolderia cepacia*, higher prevalence of liver disease, and increased early mortality [39].

In order to minimize its morbidity, routine screening (described in section 1.6) starting at the age of 10 years is strongly recommended for all CF patients. These screening visits aim to diagnose CFRD as early as possible so that early intervention, including insulin therapy, can occur [53]. When a patient with CF is diagnosed with CFRD, close monitoring of their health follows. In contrast to T1D and T2D, there is no documented risk of macrovascular disease, such as atherosclerosis and cardiovascular disease, in the CFRD population [39]. However, microvascular complications, such as retinopathy and nephropathy, commonly develop after CFRD has been present for 5 years. Thus, after 5 years of being CFRD, patients should have annual visits monitoring for retinopathy, nephropathy, and peripheral neuropathy [39]. However, long-term vascular complications do not reflect the primary consequences of CFRD, which are impaired nutritional status and pulmonary function.

1.5 Nutritional Status in CF

As described previously, the impaired function of the GI tract and the pancreas in persons with CF leads to impaired digestion, nutrient malabsorption and malnutrition. As a result, nutritional optimization and maintenance of an ideal BMI is difficult for patients with CF. Furthermore, individuals with CF have a high basal metabolic rate mainly due to increased resting energy expenditure (REE). The REE in the CF population is about 10-20% greater than the general population [54, 55]. The gene defect, the effects of chronic pulmonary infection (ie. inflammation, airway obstruction, etc.), and altered lung mechanics are all possible mechanisms that contribute to the high metabolic rate in CF [54]. The abnormal lung mechanics are often a result of continuous injury to the lungs leading to progressive parenchymal fibrosis and airway obstruction. In order to overcome the increased resistive and elastic loading of the respiratory system, due to the enlarged physiologic dead space and hypoxemia, the respiratory muscles must consume more oxygen resulting in increased oxygen cost and work of breathing [54, 56]. Furthermore, chronic pulmonary infection can lead to an imbalance between anabolic and catabolic hormones favoring a catabolic state in patients with CF [57], thus continuing the cycle of lung function and nutritional status degradation.

Several studies have found that increased REE is strongly associated with decreased lung function and nutritional status in patients with CF [54-56]. The increased REE, accompanied by the impaired digestion and absorption found in CF, suggest that patients with CF have to meet higher than normal caloric needs in order to optimize their weight, energy balance, and lung function [56]. A cross-sectional and longitudinal study by Steinkamp et al. also found that nutritional status and lung function are strongly associated. In comparison with healthy individuals of similar height and age, they observed that a lower nutritional status was associated with both lower FEV_1 and

forced vital capacity (FVC), both of which are measures of lung function [58]. Thus, nutritional status in CF is closely monitored as it is an important predictor of normal growth, lung disease severity, and survival [1, 5].

Traditionally, BMI is used to assess and monitor nutritional status. However, BMI is based on body size (weight (kg)/ (height (m))^2) and doesn't measure metabolically active parameters such as fat-free mass (FFM) and fat mass [59]. FFM refers to lean body mass (e.g. muscle, organs, and water) plus skeletal mass, while fat mass refers to body components composed strictly of fat [60]. These parameters, as well as muscle mass and bone density, can be measured using dual-energy X-ray absorptiometry (DEXA). However, this technology is limited to tertiary care centers. Bioelectrical impedance analysis (BIA) is an alternative method that is easier to use and portable [61]. However, BIA does not measure bone density and is not as accurate as DEXA at estimation of fat and lean masses [61].

Recent studies have found that looking at body composition may be better as a measure of health than BMI in patients with CF [59, 61]. A significant proportion of adults with CF have low FFM, but a fat mass and percent body fat similar to non-CF individuals. This discordance may be explained by a chronic catabolic state favoring depletion of FFM [59]. FFM depletion is associated with greater disease severity, including worse lung function, more frequent pulmonary exacerbations, and increased inflammation [57, 59, 61]. A lower FFM is associated with weakened inspiratory muscle work capacity, as well as reduced diaphragm muscle mass [62]. Studies show decreased muscle mass and bone mineral density in patients with CF; both of these correlate strongly with FFM and lung function [57, 58]. DEXA is routinely performed to assess bone density in this population. Clinical availability of DEXA-based nutritional indices would lead to a more informed assessment of true nutritional status.

Patients with CF are typically followed by a dietician specializing in CF nutrition. Dieticians optimize caloric intake, enzyme supplementation and vitamins. While the pancreatic enzyme supplementation targets PI, vitamin supplementation targets the vitamin deficiencies often found in patients with CF. A cross-sectional Canadian study found that 95% and 82% of pediatric patients with CF had a vitamin D and K deficiencies, respectively [63]. According to European CF guidelines, vitamin D should be prescribed to any patients with CF who have a deficiency or insufficiency, while vitamin K should be prescribed to any patients with CF and PI [64].

In the early 1970s, the Cystic Fibrosis Clinic of Toronto began to advocate for an unrestricted high calorie (120-150% of recommended daily intake) and high fat (35-40% of energy) diet, accompanied by increased pancreatic enzyme supplements to enhance digestion [65]. Prior to adoption of this diet, patients with CF were encouraged to follow low fat, but carbohydrate-rich diets. It was thought that a lower fat intake would improve bowel symptoms and reduce stool bulk [65]. The high fat, high calorie diet led to a more favorable nutritional status and median age of survival in Toronto patients with CF (30 years) compared to Boston patients with CF (21 years). Widespread adoption of this diet took place in the 1980s and has led to progressive improvement in the mean BMI of patients with CF [6, 65]. The mean BMI of Canadian adults with CF has risen from 21.6 kg/m^2 in 2002 to 22.5 kg/m^2 in 2018. Furthermore, 64% of adults and 75% of children with CF have an adequate weight [19, 66]. In parallel, the median age of survival has risen from 20 and 30 years in the 1980s to 52.1 years in 2018 [6, 19].

1.6 Clinical Care and Treatment in CF

As previously mentioned, patients with CF are closely monitored. In Montréal, patients with CF receiving specialized care at the CF Clinic of the Centre Hospitalier de l'Université de Montréal

are followed every three months. Clinic visits consist of physical examination, pulmonary function testing, anthropometry, and occasionally cardiopulmonary exercise testing. Patients with CF are typically evaluated by a multidisciplinary CF-specialized team including: physicians (including a pulmonologist and if needed an endocrinologist), specialized nurses, nutritionist, social worker, and physiotherapist. Physiotherapists play an important role in airway clearance, which is performed regularly in order to prevent build-up of thick mucus in the respiratory system.

Pulmonary physiotherapy is important for airway clearance, which reduces chest infections and reduces airflow obstruction [67]. Commonly used airway clearance methods include active cycle of breathing techniques, autogenic drainage, chest physiotherapy and different techniques involving positive expiratory pressure (PEP) [67]. As described in the preceding section, specialized dieticians optimize caloric intake and enzyme/vitamin supplementation. Together, health care providers constantly monitor the progression of the disease and provide support to improve the quality of life of patients with CF.

1.6.1 CFRD Screening via Oral Glucose Tolerance Test (OGTT)

In addition to their routine clinical visits, patients are strongly encouraged to undergo CFRD screening every 12 months from 10 years of age onward [53]. These screenings consist of a 2-h oral glucose tolerance test (OGTT). Patients arrive after an overnight fast and ingest a standardized dextrose load (1.75 g/kg, to a maximum of 75g). In clinical settings, glucose sampling is performed before and 2 hours after ingestion of the dextrose load. A fasting glucose level $\geq$ 7.0 mmol/L and/or a 2-h OGTT glucose level $\geq$ 11.1 mmol/L are used to diagnose CFRD. In research settings, such as for patients in the Montréal CF Cohort (MCFC), glucose sampling is performed before ingestion of the dextrose load, and then 2 hours later. The glucose values from these two points are then used to classify patients into glucose tolerance groups: normal glucose tolerance (NGT), impaired

glucose tolerance (IGT), indeterminate glucose tolerance (INDET), and CFRD [53]. The classification values can be found in Table 1.1. Patients who are classified as *de novo* CFRD have a follow-up OGTT to confirm the CFRD diagnosis. For research purposes, intermediate time-points with 30-min sampling time can be added [49, 68]. It is important to highlight that other diagnosis methods, such as fasting plasma glycose of glycosylated hemoglobin (HbA1c), frequently used to diagnose type 2 diabetes are less reliable for patients living with CF [69].

Table 1.1 Glucose Tolerance Classification [53]

	Fasting Glucose (mmol/L)	**2-h Glucose (mmol/L)**
NGT	**< 7.0**	**< 7.8**
IGT	**< 7.0**	**≥ 7.8 but < 11.1**
INDET	**< 7.0**	**< 7.8 but ≥ 11.1 at 1-h**
CFRD	**≥ 7.0**	**≥ 11.1**

Abbreviations: NGT, normal glucose tolerance; IGT, impaired glucose tolerance; INDET, indeterminate glucose tolerance; CFRD, cystic fibrosis-related diabetes

1.6.2 Respiratory Therapies and CFTR Modulators

Outside of the clinic, patients with CF are generally prescribed several medication and treatments to maximize lung function and reduce the occurrence of exacerbations. In order to dilate

respiratory airways and reduce bacterial infection, patients with CF are often administered inhaled broncho-dilators, corticosteroids, and antibiotics [70].

Pulmonary exacerbations are intermittent episodes of acute worsening of pulmonary symptoms. There are several definitions of pulmonary exacerbations. The European Consensus Group defines a pulmonary exacerbation as follows. An exacerbation is the need for additional antibiotic treatment as indicated by a recent change in at least two of the following: change in sputum volume or color, increased cough, increased malaise, fatigue or lethargy; anorexia or weight loss; decrease in lung function by >10% or radiographic changes; increased dyspnea [71]. Depending on infection severity and type, either an oral or intravenous (IV) route is chosen for antibiotic treatment. Patients with very weak lung function, such as an FEV_1 at or below 30%, are often referred for lung transplantation evaluation [29].

In addition to respiratory therapies, nutritional optimization and enzyme supplementation, an increasingly emerging medication includes CFTR modulators. Although there are only a few patients in the MCFC that are using CFTR modulators, these medications have shown promise in improving quality of life and overall health, at least in CF patients with selected mutation types [72, 73]. Altogether, the complex and specialized care plans for patients with CF have contributed to observed increases in lung function, nutritional status, and lifespan. However, this increased survival is followed by other emerging CF-related complications, such as CFRD, as well as an emerging group of overweight and obese patients with CF [68].

1.7 Obesity in the General Population

In recent decades, obesity has become the most prevalent nutritional problem in the world, replacing undernutrition and infectious diseases as the major contributor to ill health and mortality

[74]. Between 2015 and 2016, the prevalence of obesity in the United States was 39.8% in adults and 18.5% in youth [75]. The increasing trend in obesity is mainly due to a combination of genetic susceptibility, increased availability in high-energy foods, and decreased physical activity (ie. increased use of cars and sedentary leisure activities) [76]. However, the rapid increase in prevalence suggests that behavioral and environmental factors have a stronger influence rather than biological changes [77].

Obesity is defined as a state of body energy stores (body fat) that exceeds physiologic needs, and consequentially may begin to adversely affect health [76]. The most widely used measurement for assessing obesity is BMI, where a BMI below 18.5 kg/m^2 is underweight, 18.5-24.9 kg/m^2 is normal, 25-29.9 kg/m^2 is overweight, 30-39.9 kg/m^2 is obese, and 40 kg/m^2 and above is severe obesity [78]. However, BMI only estimates total body mass relative to height, without discriminating between muscle mass, bone density, and body fat. Thus, waist circumference is typically used to specifically monitor abdominal obesity and the associated health risks. Monitoring abdominal obesity in addition to total body fat is equally important since excess fat around the waist and upper body is associated with greater health risk than excess fat in the hip and thigh areas [79]. Furthermore, abdominal obesity is more strongly associated with increased metabolic and cardiovascular disease risk, as well as decreased lung function [80].

Obesity can cause or exacerbate several health complications, such as hypertension, dyslipidemia, insulin resistance, glucose intolerance and hyperglycemia [4, 77, 81]. These cardiometabolic complications can lead to the development of type 2 diabetes, cardiovascular disease, increased incidence of certain cancers, obstructive sleep apnea, osteoarthritis, and an increased risk of early mortality [76]. Early detection and intervention is essential to prevent serious health complications in obese individuals. Intervention measures often include lifestyle changes (weight loss, food

quality, regular physical activity and smoking cessation), anti-hypertensive medications, and anti-dyslipidemic medications [76].

1.7.1 Diabetes in the General Population

Diabetes mellitus describes metabolic disorders characterized by chronic hyperglycemia due to defective insulin secretion, insulin action, or both. The prevalence of diabetes is increasing rapidly globally, with 285 million adults having any form of diabetes in 2010 [82]. Diabetes is diagnosed based on any of the following criteria: a fasting plasma glucose of $\geq$ 7.0 mmol/L, a 2-h OGTT plasma glucose of $\geq$ 11.1 mmol/L, a random plasma glucose $\geq$ 11.1 mmol/L at any time of the day, or a glycated hemoglobin (HbA1c) of $\geq$ 6.5% (in adults). In the presence of symptoms of hyperglycemia (e.g. frequent urination, increased thirst, fatigue, blurred vision), a single test result is enough to make the diagnosis of diabetes. In the absence of symptoms of hyperglycemia, a repeat confirmatory laboratory test (fasting, 2-h OGTT, or HbA1c) must be done on another day [83]. There are two main types of diabetes: type 1 (T1D) and type 2 (T2D) diabetes. T1D is characterized by the complete absence of insulin secretion, as well as an autoimmune destruction of the pancreatic beta-cells. Meanwhile, T2D is characterized by the combination of peripheral and hepatic insulin resistance with beta-cell failure [39].

Clinical characteristics of T1D generally includes a low to normal body mass, low or absent plasma insulin, high plasma glucagon and glucose, and normal insulin sensitivity. The age of onset for T1D is typically less than 20 years of age; some adults develop a later onset form (late onset diabetes of the young, or LADA) [83]. People with T2D are typically diagnosed after 30 years of age. Furthermore, T2D is generally clinically characterized with obesity, fasting hyperinsulinemia, high plasma glucagon and glucose, and reduced insulin sensitivity [83]. Persons living with T1D are treated with subcutaneous insulin. Persons living with T2D undergo intensive lifestyle

counseling in which weight loss, food quality and regular physical activity are central and will remain key along the course of the disease. If these measures are insufficient, Metformin is the first line pharmacological treatment for the vast majority of patients because of its safety, low cost and possible heart benefits. Metformin lowers your glucose production from the liver and improves your body's response to insulin so that it uses insulin more effectively [83]. If Metformin is insufficient, other oral treatments (sulfonylurea, DPP-4 inhibitors, alpha-glucosidase inhibitors and SGLT-2 inhibitors) or injectable treatments (GLP-1 receptor analog and insulin) are added sequentially. Oral anti-diabetic medications are chosen based upon an individual's cardiovascular risk factors, renal function, and health insurance plans. In overweight and obese patients living with T2D, bariatric surgery may also be considered [39, 82, 83].

Individuals with T1D or T2D often develop microvascular and macrovascular complications. As mentioned previously, microvascular complications include retinopathy, nephropathy, and peripheral neuropathy [84]. Although microvascular complications develop in T1D, T2D and CFRD, macrovascular complications, such as atherosclerosis and cardiovascular disease, have only been documented in T1D and T2D. Atherosclerosis, plaque formation from foam cells (liquid laden macrophages) and plaque rupture triggering an inflammatory cascade in arterial walls, is the main pathological mechanism in macrovascular disease. Furthermore, platelet adhesion, hypercoagulability and impaired fibrinolysis commonly occur in T2D, increasing the risk of vascular occlusion and cardiovascular events [84]. Although the exact mechanisms are not well characterized, people who develop diabetes are at increased risk of developing cardiovascular disease (CVD). CVD is the primary cause of death in people with either T1D or T2D, and accounts for the greatest component of health care expenditures in patients with diabetes [85]. Diabetes significantly increases the risk of coronary heart and artery disease, strokes, and cerebrovascular

disease. Treatment of diabetes is imperative to reduce cardiovascular risk. Other important cardioprotective strategies include lifestyle measures (weight loss, food quality, regular physical activity and smoking cessation), anti-hypertensive medications, anti-dyslipidemic medications, and acetylsalicylic acid to reduce risk of platelet adhesion [83].

1.8 Obesity in CF

In parallel to rising prevalence of obesity in the general population, a small, but significant, group of patients with CF have become overweight and obese in recent years. A large Canadian study reported that 22% of their subjects with CF were overweight or obese [5], while another study investigating 226 children with CF found that 15% were overweight and 8% were obese [4]. With improvements in pulmonary management and the introduction of CFTR modulators (which also induce weight gain), some patients with CF no longer require the same level of high calorie, high fat dietary supplementation adopted in the 1980s to overcome the malnutrition associated with CF [4, 5]. The majority (50-80%) of overweight/obese patients with CF are pancreatic sufficient, suggesting this sub-group of subjects with CF may not need enzyme supplementation, as well as repeated advice about energy-dense nutritional intake [2, 5].

In the general population, obesity is associated with poor lung function. However, in the CF population, multiple publications have shown that a higher BMI is closely associated with better FEV_1 [5, 86, 87]. A cross-sectional study by Moriconi et al. found that underweight and normal-weight adult patients with CF had increased central (abdominal) fat accumulation compared to non-CF controls [88]. As central fat accumulation is associated with impaired lung function, this could contribute to the fact that underweight and normal-weight patients tend to have a lower FEV_1 than overweight patients with CF.

Several publications have shown that patients who develop CFRD are more likely to be underweight than overweight [59, 89]. It would be clinically important to see if after a certain point, there is a reversal of the beneficial effects of a high BMI. If a patient with CF developed features of metabolic syndrome, the increased insulin resistance might make the beta-cells work harder or worsen beta-cell dysfunction by increasing metabolic demand. Furthermore, hyperglycemia (> 8 mmol/L) favors bacterial growth in the lungs [52]. Therefore, dysglycemia can directly contribute to worsening lung function. It is unclear whether obesity has the same cardiometabolic risk in patients with CF as in the general population.

2 Preface for Chapter 3

In chapter 3, we are using a large and well-characterized, long-standing, prospective observational cohort to investigate whether the cardiometabolic risks associated with obesity in the general population can also be found in the CF population. To begin with, we attempt to characterize adult patients with CF who are overweight/obese in the Montreal Cystic Fibrosis Cohort (MCFC) and to compare the cardiometabolic profile and lung function status between various BMI categories (underweight, normal and overweight/obese). Furthermore, we investigate the impact of significant weight change (> 10% weight gain or loss) over 3.5 years in the same patients. We hypothesize that overweight/obese CF patients, as well as those who gained weight, would have better, or improved, pulmonary function but less favorable cardiometabolic profiles than their respective counterparts.

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3 Overweight, Obesity and Significant Weight Gain in Adult Patients with Cystic Fibrosis Association with Lung Function and Cardiometabolic Risk Factors

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3.1 Abstract

Background: For patients with cystic fibrosis (CF), maintaining a normal BMI is associated with better pulmonary function (FEV1) and survival. Given therapy improvements, some patients are now overweight, obese or present rapid weight gain. However, the impact of being overweight on clinical outcomes (e.g. FEV1 & metabolic complications) remains unknown.

Methods: Baseline data from 290 adult CF patients and observational follow-up (3.5 years; n=158) were collected. BMI categories: underweight (UW < 18.5 kg/m^2), normal (NW 18.5-26.9 kg/m^2), and overweight/obese (OW ≥ 27 kg/m^2). Follow-up data (weight change over time): weight loss (WL > 10%), stable (WS), and weight gain (WG > 10%). BMI categories and follow-up data were compared to FEV1 and cardiometabolic parameters: glucose tolerance, estimated insulin resistance (IR), blood pressure (BP), and lipid profile.

Results: For BMI categories, 35 patients (12.1%) were UW, 235 (81.0%) NW, and 20 (6.9%) OW. Compared to UW and NW patients, OW patients are older ($p < 0.001$), had less pancreatic insufficiency ($p = 0.009$), a higher systolic BP ($p = 0.004$), higher LDL ($p < 0.001$), and higher IR ($p < 0.001$). Compared to UW patients, OW patients had a better FEV1 ($p < 0.001$).

For weight change, WL was observed in 7 patients (4.4%), WS in 134 (84.8%) and WG in 17 patients (10.8%). Compared to WL and WS patients, WG patients had a 5% increase in FEV1 accompanied by higher IR ($p = 0.017$) and triglycerides ($p < 0.001$). No differences were observed for glucose tolerance for neither BMI nor weight change.

Conclusion: A higher weight or weight gain over time are associated with a better FEV_1 but also some unfavorable cardiometabolic trends.

3.2 Introduction

Cystic fibrosis (CF) is the most common genetically lethal disease in Caucasian people, caused by mutation in the gene encoding the CF transmembrane conductance regulator (*CFTR*) protein [1]. The mutated chloride channel leads to thick mucus secretions in various glands and organs. The viscous mucus secretions in the lungs lead to airway obstruction increasing the risk of infection, pulmonary exacerbation and respiratory failure [2]. In the pancreas, thick mucus can lead to exocrine and endocrine insufficiency [1].

In patients with CF, malnutrition is mainly caused by a combination of nutrient malabsorption secondary to exocrine pancreatic insufficiency and increased energy expenditure mainly related to breathing efforts [3]. Malnutrition is associated with lower pulmonary function and increased early mortality [4]. Thus, measures to improve nutrient intake (diet high in energy and fat) and absorption (pancreatic enzyme replacement therapy) are central for patient care and have contributed to observed increases in pulmonary function and lifespan. In Canada, the estimated median life expectancy has risen from 33 years in 2001 to 52.3 years in 2017 [5]. However, increased survival is associated with other emerging CF-related complications, such as diabetes [6]. In parallel, the mean Body Mass Index (BMI) of CF adults has risen from 21.6 kg/m^2 in 2002 to 22.5 kg/m^2 in 2017 [5]. In the general population, the emergence of overweight, obesity and significant weight gain increases the risk of cardiometabolic complications (e.g. insulin resistance, glucose intolerance, hypertension, dyslipidemia, etc.) [7, 8]. In CF patients, some publications [9] have shown a clear association between higher BMI and better pulmonary function as assessed by FEV_1 (Forced Expiratory Volume in one second). However, the impact of being overweight, as well as rapid weight gain, on both pulmonary function and the risk of cardiometabolic

complications remains unknown. In the context of longer survival, and increased prevalence of overweight, it is thus important to assess these parameters.

The aim of this observational study was to characterize adult patients with CF who are overweight/obese in the Montreal Cystic Fibrosis Cohort (MCFC) and to compare the cardiometabolic profile and lung function status between various BMI categories (underweight, normal and overweight/obese). Another objective was to determine the impact of significant weight change (>10% weight gain or loss) in adult patients with CF over a three-year period on the same clinical parameters. We hypothesized that overweight/obese CF patients, as well as those who gained weight, would have better, or improved, pulmonary function but less favorable cardiometabolic profiles than their respective counterparts.

3.3 Materials and methods

3.3.1 Subjects

Data was collected from the Montreal Cystic Fibrosis Cohort, an ongoing systematic diabetes screening program [6, 10, 11].

Included in this analysis were adult patients (≥ 18 years) with CF who had BMI data available for their first visit without a diagnosis of CF-Related Diabetes (CFRD). Inclusion and exclusion criteria have been previously described [10]. In summary, the main exclusion criteria were pregnancy, previous pulmonary transplantation, and the use of modulator therapies. In the case of recent exacerbations or the use of medications that could interfere with glucose metabolism (e.g. intravenous antibiotics, oral or intravenous steroids, growth hormone treatment), inclusion was postponed until medical condition was stable for at least one month without the use of

contraindicated medication. The protocol was approved by the Research Ethics Committee of the Centre Hospitalier de l'Université de Montréal and of the Institut de Recherches Cliniques de Montréal. Informed consent forms were reviewed and signed by all subjects.

3.3.2 Clinical and biological data

All measures were taken on the same day at the time of diabetes screening.

3.3.2a Pulmonary function and anthropometry

Pulmonary function was determined using spirometry with predicted FEV_1 % (Medgraphic).

Body weight (kg) was measured using an electronic scale (Tanita Corporation Arlington heights, IL, USA). Standing height (cm) was measured using a wall stadiometer. BMI was calculated by dividing weight in kilograms by height in meters squared (kg/m^2).

3.3.2b Metabolic parameters

To assess glucose tolerance, a 2–hour Oral Glucose Tolerance Test (OGTT) was undertaken in standardized condition as previously described [10]. Blood samples were then taken at 0, 30, 60, 90, and 120 min in order to measure plasma glucose and insulin levels. Plasma glucose levels were measured immediately after the OGTT with a Glucose Analyzer (YSI 2900, YSI Inc.). Insulin samples were frozen at -80 °C and later measured in duplicate using human insulin RIA (Linco Research, Inc.).

Using OGTT plasma glucose and insulin values, insulin secretion and sensitivity values were estimated. Insulin sensitivity index (ISI) was estimated using the Stumvoll index [12]. Insulin area under the curve (AUC) was used to estimate the 1st phase (AUC from 0 to 30 min) of insulin secretion, which represents an index of early insulin secretion [11].

Using OGTT fasting samples, HbA1c levels and lipid profiles (total cholesterol, LDL, HDL-cholesterol, and triglycerides) were measured using enzymatic reaction (ADVIA1650, Bayer Health Care Diagnostics) [13].

Blood pressure (BP) and pulse were measured the day of the OGTT using a blood pressure monitor stand. Patients had been sitting down for at least 10 minutes prior.

3.3.2c Other CF-related characteristics and genotype

Information from medical charts extracted for this analysis, on day of the study visit, included: age, sex, CF-related genotype, and chronic bacterial colonization. Exocrine pancreatic insufficiency was determined by current enzyme supplementation. Chronic bacterial colonization was defined as follows: 50% or more of samples being positive for specific bacteria in the preceding 12 months [14]. Genotype was classified into three groups based on CFTR expression and function: homozygous for the delta F508 mutation, heterozygous for the delta F508 mutation, and other mutations neither homozygous nor heterozygous for the delta F508 mutation.

3.3.3 Patient categorization

For this analysis, patients were categorized into three BMI categories: underweight (UW: < 18.5 kg/m^2), normal (NW: 18.5 kg/m^2 to < 27 kg/m^2), and overweight/obese (OW: ≥ 27 kg/m^2) [15]. Values for the UW group and the lower limit of the NW group are in accordance with the BMI Nomogram from Health Canada [15]. The upper limit for NW subjects was 26.9 kg/m2 since there is less controversy in the general population regarding a significant increased risk of having a worse cardiometabolic profile above this threshold [16]. Since it is already known that a higher normal BMI is associated with better pulmonary function in CF patients [9], this higher BMI threshold will help to determine if FEV_1 continues to improve in a higher BMI category.

Patients were assigned a glucose tolerance group based on OGTT fasting and 2h glucose values. Subjects with a fasting plasma glucose ≤ 7.0 mmol/L (126.1 mg/dL) and a 2h plasma glucose ≤ 7.7 mmol/L (138.7 mg/dL) were placed in the Normal Glucose Tolerance (NGT) group. The abnormal glucose tolerance (AGT) group consisted of patients with either indeterminate glucose tolerance (INDET) or impaired glucose tolerance (IGT). INDET is defined as having a fasting plasma glucose ≤ 7.0 mmol/L and a 2h plasma glucose ≤ 7.7 mmol/L, but a 1h plasma glucose ≥ 11.1 mmol/L (200.0 mg/dL). IGT is defined as having a fasting plasma glucose ≤ 7.0 mmol/L and a 2h plasma glucose > 7.7 mmol/L, but < 11.1 mmol/L. Finally, de novo CFRD subjects had a fasting plasma glucose > 7.0 mmol/L or a 2h plasma glucose ≥ 11.1 mmol/L.

Patients with 2 to 4-year follow-up data were categorized into three weight change groups based on the difference in weight between the initial (baseline) and follow-up visits: weight loss (WL: ≥ 10% weight loss), stable weight (WS within -10 and + 10% weight change), and weight gain (WG: ≥ 10% weight gain).

3.3.4 Statistical analyses

Descriptive statistics were computed for all variables of interest. Data are given as mean ± SD. For continuous variables, differences between BMI categories were calculated using one-way ANOVA. When significant differences were found, a Tukey post hoc test was used to determine which groups were significantly different. For categorical variables, such as sex, genotype, and pancreatic enzyme supplementation, the difference between groups was determined using χ^2 logistic regression.

For weight change prospective analysis, paired T-tests were run for each weight change group to compare the change in certain characteristics (FEV_1, BP, lipid profiles, etc) between the baseline

and follow-up visits. The change in those characteristics was also calculated by subtracting the baseline value from the follow-up value. One-way ANOVAs were run to compare the change in characteristics between the three weight change groups. Significance was accepted when $P \leq 0.05$. The SPSS program for Windows was used for all statistical analyses (version 25 by IBM, Chicago, USA). AUC for glucose and insulin was calculated using GraphPad Prism (GraphPad Software Inc; CA, USA).

3.4 Results

3.4.1 Characteristics comparison between BMI categories

Of the 290 adult CF patients, 131 (45.2%) were female and 159 (54.8%) were male. There were 35 (12.1%) UW patients, 235 (81.0%) NW patients, and 20 (6.9%) OW patients (Table 3.1). For overall patients, mean age was 25.5 ± 7.9 years old and mean BMI was 21.7 ± 2.9 kg/m^2. OW patients were older, being 34.0 ± 8.5 years old, while UW and NW patients were 22.7 ± 4.9 and 25.2 ± 7.8 years old, respectively ($p < 0.001$). Only 55% of OW subjects were pancreatic insufficient, while over 80% of NW & UW patients were pancreatic insufficient ($p = 0.009$).

In terms of lung function, OW patients had an FEV_1 of 82.8 ± 19.6% while UW subjects had an FEV_1 of 56.2 ± 18.4% ($p < 0.001$). There was no difference of FEV_1 between OW and NW ($p = 0.215$). Patients who were OW had a higher diastolic BP compared to UW subjects ($p = 0.013$), and a higher systolic BP compared to patients in the UW and NW groups ($p = 0.004$). Percentage of patients in the homozygous and heterozygous for the delta F508 mutation groups, chronic bacterial colonization and number of infections were similar between all BMI categories, as well as the glucose tolerance status ($p = 0.474$), sex repartition ($p = 0.142$) and CFTR mutations ($p =$

0.292). Although, there were more OW men (70%) than OW females (30%) and one half of OW patients presented with abnormal glucose tolerance.

Total cholesterol and LDL-cholesterol levels were different between BMI categories ($p < 0.001$), with highest levels in OW patients. However, triglyceride and HDL levels were similar across all BMI categories (Table 3.1). There were no significant differences in glucose levels or excursions during the OGTT between BMI categories (Table 3.1 & Fig. 3.1). Insulin secretion was different between BMI categories for time 0, 30, 60 and 90 min of the OGTT ($p \leq 0.039$), but was not significantly different for the 2h OGTT value (Fig. 3.2). The OW group had a significantly more elevated 1st phase insulin secretion response ($p < 0.001$) and total insulin secretion ($p = 0.002$), and exhibited a lower ISI ($p < 0.001$) compared to the other two groups (Table 3.1).

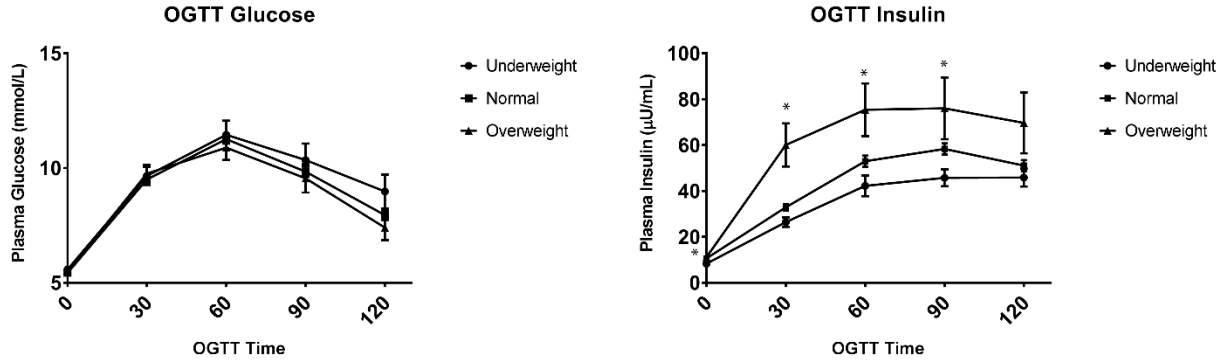

Fig. 3.1. (Left) Plasma glucose (mmol/L) during 2-h OGTT based on BMI.
The black dot (●) represents underweight patients, the black square (■) represents patients with a normal BMI, and the black triangle (▲) represents overweight patients. Values are presented as mean ± SEM. *: p value is significant

Fig. 3.2. (Right) Insulin secretion (µU/mL) during 2-h OGTT based on BMI.
The black dot (●) represents underweight patients, the black square (■) represents patients with a normal BMI, and the black triangle (▲) represents overweight patients. Values are presented as mean ± SEM. *: p value is significant

Table 3.1. Physical and biochemical characteristics of adult patients with CF at baseline for BMI category analysis (Mean ± SDs)

	Total n = 290	Underweight (< 18.5 kg/m^2) n = 35 (12.1%)	Normal (18.5 to 26.9 kg/m^2) n = 235 (81.0%)	Overweight/Obese (≥ 27.0 kg/m^2) n = 20 (6.9%)	P Value
FEV_1 (%)	73.0 ± 21.9	56.2 ± 18.4^a	74.6 ± 21.4^b	82.8 ± 19.6^b	**0.000**
Sex					
Female (%)	45.2	57.1	44.7	30.0	0.142*
Male (%)	54.8	42.9	55.3	70.0	
Age (years)	25.5 ± 7.9	22.7 ± 4.9^a	25.2 ± 7.8^a	34.0 ± 8.5^b	**0.000**
BMI (kg/m²)	21.7 ± 2.9	17.4 ± 1.1^a	21.8 ± 2.0^b	28.1 ± 1.0^c	**0.000**
Body Fat (%)	18.6 ± 7.8	11.4 ± 4.7^a	18.8 ± 7.2^b	29.2 ± 6.3^c	**0.000**
Pancreatic Enzyme (% Yes)	79.9	88.6	80.8	55.0	**0.009***
Systolic BP (mmHg)	112.8 ± 11.3	107.5 ± 9.1^a	113.0 ± 11.4^a	121.7 ± 8.6^b	**0.004**
Diastolic BP (mmHg)	68.4 ± 9.5	64.9 ± 8.6^a	68.4 ± 9.6^b	75.6 ± 6.5^c	**0.013**
HbA1c (%)	5.70 ± 0.60	5.80 ± 0.60	5.70 ± 0.60	5.70 ± 0.30	0.448
WBC (x10^9/L)	7.62 ± 2.30	8.83 ± 2.45^a	7.53 ± 2.29^b	6.73 ± 1.52^b	**0.002**
S. Aureus (n infections)	0.49 ± 0.50	0.43 ± 0.50	0.50 ± 0.50	0.45 ± 0.51	0.659
P. Aeruginosa (n infections)	0.62 ± 0.49	0.69 ± 0.47	0.62 ± 0.49	0.50 ± 0.51	0.395
Cholesterol (mmol/L)	3.50 ± 0.92	3.22 ± 0.79^a	3.47 ± 0.92^a	4.34 ± 0.76^b	**0.000**
HDL (mmol/L)	1.19 ± 0.32	1.25 ± 0.37	1.18 ± 0.32	1.19 ± 0.26	0.562
LDL (mmol/L)	1.80 ± 0.73	1.51 ± 0.55^a	1.78 ± 0.71^b	2.49 ± 0.78^c	**0.000**
Chol/ HDL Chol	2.95 ± 0.74	2.56 ± 0.54^a	2.93 ± 0.70^a	3.90 ± 0.66^b	**0.000**
Triglycerides (mmol/L)	1.15 ± 0.75	1.01 ± 0.40	1.15 ± 0.79	1.44 ± 0.71	0.121
Fasting Plasma Glucose (mmol/L)	5.45 ± 0.79	5.58 ± 0.96	5.43 ± 0.79	5.47 ± 0.46	0.601
Plasma Glucose (AUC)	1124.9 ± 287.1	1184.8 ± 358.8	1117.7 ± 281.3	1111.8 ± 218.7	0.479
Fasting Plasma Insulin (µU/mL)	10.35 ± 5.05	8.32 ± 2.90^a	10.59 ± 5.31^b	11.14 ± 4.16^c	**0.039**
1st Phase Insulin Secretion (AUC)	657.2 ± 369.5	527.2 ± 186.4^a	643.2 ± 334.7^a	1022.0 ± 662.2^b	**0.000**
Total Insulin Secretion (AUC)	5278.0 ± 3105.7	4394.9 ± 1733.1^a	5201.2 ± 2970.5^a	7622.0 ± 4984.5^b	**0.002**
Insulin Sensitivity Index	0.117 ± 0.017	0.129 ± 0.016^a	0.117 ± 0.015^b	0.097 ± 0.014^c	**0.000**
CFTR Mutation Class					
Homozygous ΔF508 (%)	49.1	58.8	49.2	31.6	0.292*
Heterozygous ΔF508(%)	41.4	38.2	40.5	57.9	
Other (%)	9.5	3.0	10.3	10.5	
Glucose Tolerance Class					
NGT (%)	34.6	34.3	34.2	40.0	0.474*
AGT (%)	50.5	42.9	51.3	55.0	
CFRD (%)	14.9	22.8	14.5	5.0	

Abbreviations: AUC, area under the curve; FEV1, forced expiratory volume expired in 1 s; BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; Chol/HDL Chol, cholesterol divided by high-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; WBC, white blood cells; BP, blood pressure; NGT, normal glucose tolerance; AGT, abnormal glucose tolerance; CFRD, Cystic fibrosis-related diabetes; P. Aeruginosa, *Pseudomonas aeruginosa*; S. aureus, *Staphylococcus aureus*. Mean and SDs are shown (±); P value was determined using One-Way ANOVA.*: P Value was determined by chi^2. Groups that have a different letter are statistically different from each other. Values in bold represent significant P values. Significant difference when $P \leq 0.05$.

3.4.2 Weight change over time

3.4.2a Weight change groups characteristics

From the 290 included patients, only 158 had available prospective data for the weight change sub-analysis as not all patients participated in other OGTTs within the follow-up time frame. The mean duration between the baseline and follow-up visits was 3.53 ± 0.78 years. During this time period, 7 (4.4%) patients lost weight (WL group) while 134 (84.8%) kept a stable weight (WS group) and 17 (10.8%) gained weight (WG group). The only difference at baseline between groups was for the ISI, which was lower in the WL group. Interestingly, the majority of patients who lost or gained weight were in the NW group at baseline (Table 3.2).

At follow-up, surprisingly, despite lower FEV_1 in the WL group, FEV_1 was not significantly different between groups. The WG group had the lowest ISI, while the WL group had the highest ISI ($p = 0.017$). Triglyceride levels were significantly higher for the WG group (2.00 ± 1.45 mmol/L) compared to both the WS (1.09 ± 0.54 mmol/L) and WL groups (0.60 ± 0.18 mmol/L; $p < 0.001$). Across the groups, subjects had similar BP and lipid profiles (Table 3.3).

3.4.2b Evolution of weight groups over time

Per design, WL subjects had a significant reduction in BMI (-12%), while WS (+1%) patients maintained their BMI and WG (+16%) patients had significant increase in BMI. Mirroring these BMI changes, the FEV_1 decreased by 6.7% in the WL group ($p = 0.036$) and 3.5% in the WS group ($p < 0.001$), but, in contrast, increased by 5.1% in the WG group ($p = 0.036$; Table 3.4). The increase in FEV_1 in the WG group was significantly different from the FEV_1 decreases in the WL and WS groups ($p = 0.003$, Table 3.5). WL patients had a 3% cholesterol reduction over time ($p < 0.035$), while WG patients had an increase in systolic BP (+10%), cholesterol (+8%), and

triglycerides (+54%) over time ($p < 0.050$). There was also an increase in plasma insulin at 2h OGTT and plasma glucose at 60 and 90-min OGTT ($p < 0.036$), accompanied by a 15% decline in ISI ($p < 0.001$). Subjects in the WS group had an increase in plasma glucose levels at multiple OGTT time points ($p < 0.014$). ISI (-2.5%) and cholesterol (-3%) decreased over time ($p < 0.018$). Plasma glucose levels increased by 5-10% in WS subjects, while levels increased by 5-17% in WG patients. Plasma insulin only increased over time for WG patients at 2h OGTT ($p = 0.034$).

Table 3.2. Physical and biochemical characteristics of adult patients with CF at baseline for *weight change* analysis (Mean ± SDs)

	Total n = 158	Lost (>10% weight lost) n = 7 (4.4%)	Stable (<10% weight change) n = 134 (84.8%)	Gained (>10% weight gain) n = 17 (10.8%)	P Value
Sex					
Female (%)	48.7	57.1	50.0	35.3	0.469*
Male (%)	51.3	42.9	50.0	64.7	
Age (years)	25.9 ± 8.6	28.1 ± 8.8	26.32 ± 8.7	22.0 ± 6.3	0.114
BMI (kg/m²)	21.9 ± 3.0	24.1 ± 3.1	21.8 ± 3.0	21.5 ± 2.7	0.115
FEV_1 (%)	74.8 ± 19.4	73.5 ± 18.1	74.7 ± 20.0	75.5 ± 15.4	0.974
Systolic BP (mmHg)	112.8 ± 11.0	117.3 ± 16.9	113.2 ± 10.8	108.4 ± 11.1	0.399
Diastolic BP (mmHg)	68.7 ± 8.9	72.7 ± 6.7	69.3 ± 8.9	62.8 ± 8.4	0.110
Pancreatic Enzyme (% Yes)	79.6	85.7	78.9	82.4	0.871*
Insulin Sensitivity Index	0.120 ± 0.139	0.105 ± 0.020[a]	0.120 ± 0.013[b]	0.126 ± 0.014[a]	**0.007**
Fasting Plasma Glucose (mmol/L)	5.27 ± 0.45	5.28 ± 0.57	5.26 ± 0.45	5.33 ± 0.43	0.852
Cholesterol (mmol/L)	3.58 ± 0.96	3.69 ± 0.80	3.60 ± 0.97	3.41 ± 1.02	0.718
HDL (mmol/L)	1.20 ± 0.32	1.24 ± 0.15	1.21 ± 0.33	1.08 ± 0.23	0.294
LDL (mmol/L)	1.87 ± 0.76	1.92 ± 0.61	1.88 ± 0.77	1.75 ± 0.78	0.777
Triglycerides non HDL (mmol/L)	1.71 ± 7.18	1.16 ± 0.84	1.80 ± 7.82	1.27 ± 0.48	0.941
HbA1c	0.056 ± 0.004	0.056 ± 0.004	0.056 ± 0.004	0.057 ± 0.003	0.923
S. Aureus (n infections)	0.59 ± 0.49	0.33 ± 0.52	0.60 ± 0.49	0.59 ± 0.51	0.427
P. Aeruginosa (n infections)	0.66 ± 0.48	0.67 ± 0.52	0.64 ± 0.48	0.76 ± 0.44	0.606
CFTR Mutation Class					
Homozygous ΔF508 (%)	44.3	28.6	43.3	58.8	0.393*
Heterozygous ΔF508 (%)	44.9	42.8	46.3	35.3	
Other (%)	10.8	28.6	10.4	5.9	
Glucose Tolerance Class					
NGT (%)	43.7	42.8	42.5	53.0	0.411*
AGT (%)	53.2	42.8	54.5	47.0	
CFRD (%)	3.1	14.4	3.0	0.0	
BMI Categories					
Underweight (%)	8.2	14.3	6.7	17.6	0.524*
Normal (%)	83.6	71.4	85.1	76.5	
Overweight (%)	8.2	14.3	8.2	5.9	

Abbreviations : FEV_1, forced expiratory volume expired in 1 s; BMI, body mass index; BP, blood pressure; CFTR, cystic fibrosis transmembrane conductance regulator; NGT, normal glucose tolerance; AGT, abnormal glucose tolerance; CFRD, Cystic fibrosis-related diabetes; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; P. Aeruginosa, *Pseudomonas aeruginosa*; S. aureus, *Staphylococcus aureus*. Mean and SDs are shown (±); P value was determined using One-Way ANOVA.*: P Value was determined by chi^2. Groups that share the same letter are not statistically different from each other. Values in bold represent significant P values. Significant difference when $P \leq 0.05$.

Table 3.3. Physical and biochemical characteristics of adult patients with CF at follow-up according to *weight change* (Mean ± SDs).

	Total n = 158	Lost (>10% weight lost) n = 7 (4.4%)	Stable (<10% weight change) n = 134 (84.8%)	Gained (>10% weight gain) n = 17 (10.8%)	P Value
FEV_1 (%)	72.2 ± 20.9	66.8 ± 23.0	71.3 ± 21.1	81.6 ± 18.0	0.149
Age (years)	29.5 ± 8.6	31.6 ± 8.3	29.8 ± 8.8	25.8 ± 6.5	0.152
BMI (kg/m^2)	22.4 ± 3.1	21.2 ± 2.6[a]	22.1 ± 3.1[a]	25.0 ± 2.7[b]	**0.001**
Systolic BP (mmHg)	111.0 ± 11.3	103.7 ± 8.5	111.0 ± 11.4	112.5 ± 11.3	0.488
Diastolic BP (mmHg)	66.9 ± 9.1	63.7 ± 4.7	66.8 ± 9.6	68.0 ± 7.1	0.767
Pancreatic Enzyme (% Yes)	79.0	85.7	78.2	82.4	0.837*
Insulin Sensitivity Index	0.116 ± 0.014	0.124 ± 0.015[a]	0.117 ± 0.013[a]	0.107 ± 0.012[b]	**0.017**
Fasting Plasma Glucose (mmol/L)	5.35 ± 0.68	5.18 ± 0.56	5.32 ± 0.53	5.59 ± 1.39	0.256
Cholesterol (mmol/L)	3.59 ± 0.90	3.56 ± 0.99	3.55 ± 0.89	3.88 ± 0.97	0.450
HDL (mmol/L)	1.26 ± 0.33	1.29 ± 0.23	1.27 ± 0.33	1.15 ± 0.33	0.439
LDL (mmol/L)	1.80 ± 0.72	2.00 ± 0.76	1.78 ± 0.73	1.92 ± 0.61	0.672
Triglycerides non HDL (mmol/L)	1.17 ± 0.73	0.60 ± 0.18[a]	1.09 ± 0.54[a]	2.00 ± 1.45[b]	**0.000**
HbA1c (%)	5.60 ± 0.40	5.70 ± 0.60	5.60 ± 0.40	5.60 ± 0.20	0.808
S. Aureus (n infections)	0.43 ± 0.50	0.33 ± 0.58	0.41 ± 0.50	0.60 ± 0.516	0.513
P. Aeruginosa (n infections)	0.61 ± 0.65	1.20 ± 2.17	0.58 ± 0.53	0.60 ± 0.51	0.114
Glucose Tolerance Class					
NGT (%)	35.7	42.8	35.3	35.3	0.276*
AGT (%)	52.8	28.6	52.6	64.7	
CFRD (%)	11.5	28.6	12.1	0.0	

Abbreviations: FEV_1, forced expiratory volume expired in 1 s; BMI, body mass index; BP, blood pressure; NGT, normal glucose tolerance; AGT, abnormal glucose tolerance; CFRD, Cystic fibrosis-related diabetes; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; P. Aeruginosa, *Pseudomonas aeruginosa;* S. Aureus, *Staphylococcus aureus*. Mean and SDs are shown (±); P value was determined using One-Way ANOVA.*: P Value was determined by chi^2. Groups that have a different letter are statistically different from each other. Values in bold represent significant P values. Significant difference when $P \leq 0.05$.

Table 3.4. Physical and biochemical characteristics at baseline and at follow-up (mean duration of 42.3 ± 9.3 months, Mean ± SDs)

Weight Lost n = 7 (4.4%)	Base-line	Follow-up	P Value	**Stable Weight n = 134 (84.8%)**	Base-line	Follow-up	P Value	**Weight Gain n = 17 (10.8%)**	Base-line	Follow-up	P Value
BMI (kg/m²)	24.1 ± 3.1	21.2 ± 2.6	**0.000**	BMI (kg/m²)	21.8 ± 22.1	22.1 ± 3.1	**0.002**	BMI (kg/m²)	21.5 ± 2.7	25.0 ± 2.7	**0.000**
FEV_1 (%)	73.5 ± 18.1	66.8 ± 23.0	**0.036**	FEV_1 (%)	74.8 ± 19.8	71.3 ± 21.1	**0.000**	FEV_1 (%)	75.5 ± 15.4	81.6 ± 18.0	**0.036**
Body Fat (%)	26.4 ± 4.6	21.1 ± 6.2	**0.001**	Body Fat (%)	19.5 ± 7.8	20.6 ± 7.7	**0.000**	Body Fat (%)	16.5 ± 7.0	24.7 ± 7.4	**0.000**
Fat Free Mass (kg)	50.3 ± 10.1	47.2 ± 9.9	**0.000**	Fat Free Mass (kg)	48.6 ± 8.8	48.4 ± 8.9	0.170	Fat Free Mass (kg)	48.8 ± 8.1	51.1 ± 8.6	**0.000**
Systolic BP (mmHg)	117.3 ± 16.9	103.7 ± 8.5	0.106	Systolic BP (mmHg)	111.4 ± 8.9	110.1 ± 10.4	0.406	Systolic BP (mmHg)	106.7 ± 12.4	117.8 ± 11.4	**0.050**
Diastolic BP (mmHg)	72.7 ± 6.7	63.7 ± 4.7	0.077	Diastolic BP (mmHg)	68.4 ± 8.7	65.7 ± 8.9	0.060	Diastolic BP (mmHg)	62.0 ± 9.8	68.8 ± 7.0	0.221
Cholesterol (mmol/L)	3.7 ± 0.8	3.6 ± 1.0	**0.035**	Cholesterol (mmol/L)	3.6 ± 1.0	3.5 ± 0.9	**0.000**	Cholesterol (mmol/L)	3.6 ± 1.1	3.9 ± 1.0	**0.000**
Triglycerides (mmol/L)	0.78 ± 0.11	0.60 ± 0.18	0.076	Triglycerides (mmol/L)	1.9 ± 8.2	1.1 ± 0.5	0.862	Triglycerides (mmol/L)	1.3 ± 0.5	2.0 ± 1.4	**0.037**
GT0 (mmol/L)	5.3 ± 0.6	5.2 ± 0.6	0.686	GT0 (mmol/L)	5.3 ± 0.5	5.3 ± 0.5	0.198	GT0 (mmol/L)	5.3 ± 0.4	5.6 ± 1.4	0.440
GT60 (mmol/L)	10.4 ± 2.0	10.6 ± 3.3	0.856	GT60 (mmol/L)	10.5 ± 2.3	11.0 ± 2.6	**0.014**	GT60 (mmol/L)	10.3 ± 2.2	12.0 ± 2.5	**0.036**
GT120 (mmol/L)	7.7 ± 2.4	8.8 ± 3.8	0.339	GT120 (mmol/L)	7.0 ± 1.9	7.8 ± 2.5	**0.000**	GT120 (mmol/L)	6.6 ± 2.0	7.4 ± 1.9	0.105
INS0 (µU/mL)	16.2 ± 9.8	7.5 ± 2.5	0.213	INS0 (µU/mL)	9.8 ± 3.8	9.8 ± 5.8	0.976	INS0 (µU/mL)	9.7 ± 3.1	9.4 ± 4.6	0.822
INS60 (µU/mL)	79.1 ± 51.7	47.7 ± 2.5	0.387	INS60 (µU/mL)	55.8 ± 39.8	50.7 ± 28.7	0.106	INS60 (µU/mL)	54.2 ± 33.0	65.2 ± 48.0	0.409
INS120 (µU/mL)	70.7 ± 37.3	51.4 ± 19.5	0.422	INS120 (µU/mL)	57.0 ± 44.7	53.4 ± 34.0	0.377	INS120 (µU/mL)	41.8 ± 25.3	64.9 ± 41.0	**0.034**
ISI	0.105 ± 0.020	0.124 ± 0.015	0.252	ISI	0.120 ± 0.013	0.117 ± 0.013	**0.018**	ISI	0.126 ± 0.015	0.107 ± 0.013	**0.000**

Abbreviations: FEV_1, forced expiratory volume expired in 1 s; BMI, body mass index; OGTT, oral glucose tolerance test; GT, glucose OGTT time; INS, insulin OGTT time; ISI, insulin sensitivity index; BP, blood pressure. Mean and SDs are shown (±); P value was determined using Paired T-tests. Values in bold represent significant P values. Significant difference when $P \leq 0.05$.

Table 3.5. Change in physical and biochemical characteristics of adult patients with CF from baseline to follow-up (Mean ± SDs, percent variance %)

	Total n = 158	Lost (>10% weight lost) n = 7 (4.4%)	Stable (<10% weight change) n = 134 (84.8%)	Gained (>10% weight gain) n = 17 (10.8%)	P Value
BMI (kg/m²)	0.470 ± 1.576 (2.3%)	-2.971 ± 0.989[a] (-12.0%)	0.104 ± 2.041[b] (1.4%)	3.512 ± 0.919[c] (16.3%)	**0.000**
FEV_1 (%)	-2.60 ± 10.08	-6.67 ± 5.72[a]	-3.48 ± 9.69[a]	5.06 ± 9.32[b]	**0.003**
ISI	-0.005 ± 0.014 (-3.3%)	0.010 ± 0.014[a] (9.5%)	-0.003 ± 0.015[a] (-2.5%)	-0.011 ± 0.036[b] (-15.1%)	**0.001**
Fasting Plasma Glucose (mmol/L)	0.042 ± 0.810 (0.80%)	-0.106 ± 0.654 (-2.0%)	0.022 ± 0.728 (0.42%)	0.259 ± 1.347 (4.9%)	0.467
Systolic BP (mmHg)	-0.49 ± 10.81 (-1.5%)	-13.67 ± 8.39[a] (-11.6%)	-1.29 ± 9.46[a] (-1.2%)	11.17 ± 10.61[b] (10.4%)	**0.002**
Diastolic BP (mmHg)	-1.96 ± 9.68 (-2.6)	-9.00 ± 4.58[a] (-12.4%)	-2.79 ± 8.88[b] (-3.9%)	6.83 ± 11.97[c] (11.0%)	**0.029**
HbA1c (%)	0.30 ± 4.20 (5.4%)	0.30 ± 0.30 (5.4%)	0.40 ± 4.60 (7.1%)	-0.10 ± 0.30 (-1.8%)	0.926
Cholesterol (mmol/L)	0.006 ± 0.576 (0.28%)	-0.096 ± 0.434 (-2.7%)	-0.028 ± 0.590 (-2.8%)	0.318 ± 0.406 (8.3%)	0.097
Triglycerides non HDL (mmol/L)	-0.593 ± 7.613 (-31.0%)	-0.174 ± 0.102[a] (-23.1%)	-0.762 ± 0.8.194[a] (-42.1%)	0.656 ± 1.240[b] (53.8%)	**0.001**
HDL (mmol/L)	0.072 ± 0.262 (6.0%)	0.006 ± 0.189 (0.5%)	0.076 ± 0.271 (6.3%)	0.064 ± 0.214 (5.9%)	0.840
LDL (mmol/L)	-0.085 ± 0.482 (-4.5%)	-0.024 ± 0.264 (-1.3%)	-0.110 ± 0.479 (-5.9%)	0.128 ± 0.556 (7.3%)	0.256
Pancreatic Enzyme (%)	-0.6	0	-0.7	0	
Glucose Tolerance					
NGT (%)	-8	0	-7.2	-17.7	
AGT (%)	-0.4	-14.2	-1.9	17.7	
CFRD (%)	8.4	14.2	9.1	0	

Abbreviations: FEV_1, forced expiratory volume expired in 1 s; BMI, body mass index; BP, blood pressure; ISI, insulin sensitivity index. Mean and SDs are shown (±); Percent variance % = [(follow-up – baseline) / baseline] * 100. P value was determined using One-Way ANOVA. Groups that have a different letter are statistically different from each other. Values in bold represent significant P values. Significant difference when $P \leq 0.05$.

3.5 Discussion

In patients with CF, achieving and maintaining a normal BMI is a key objective associated with improved lung function and longer survival [9]. However, to what extent this weight gain also translates into an adverse cardiometabolic profile remains largely unknown. Key results of this prospective observational study are that **1.** OW patients (6.9%) exhibit a better FEV_1 (though not significant compared to NW), but also have a worse cardiometabolic profile, although most values

remain within normal values, and **2.** Patients experiencing significant weight gain (at least 10% over 3 years; 10.8% of patients) are able to gain pulmonary function but, simultaneously, exhibit worse cardiometabolic profiles. These results suggest that although achieving weight maintenance/gain improves key clinical outcomes, monitoring of cardiometabolic parameters could become important. In addition, our data confirm that NW patients have a far better pulmonary function than UW patients, with mild-intermediate metabolic profiles.

In this large sample of 290 adult CF patients, the majority had a normal nutritional status (81.0%) as defined by BMI. Still a significant subgroup of patients (12.1%) remains with poor nutritional status while, as reported by other groups [7, 9], at the other end of the BMI spectrum, a group of patients (6.9%) with overweight and obesity emerges.

In the present study, CF patients with a higher BMI had better pulmonary function, less pancreatic insufficiency, but also less favorable cardiometabolic profiles (Table 3.1). The positive relationship between BMI and pulmonary function has already been reported [9]. For example, in another large Canadian study comparable percentages of underweight (17%), adequate weight (60%) and overweight or obese (22%) patients were reported [9]. Similar to our findings, Gonzalez et al reported that OW patients had a significantly better lung function compared to UW patients, but not compared to NW patients [17]. Additionally, as in our study, others have reported associations between higher BMI and older age, lower prevalence of pancreatic insufficiency and less favorable cardiometabolic parameters, such as higher insulin levels or dyslipidemia [7, 9, 18]. It should, however, be highlighted that in both previous studies and ours, despite unfavorable trends for cardiometabolic parameters in CF patients presenting higher BMI, observed values usually remained within normal values.

To further explore the association between weight and pulmonary function and cardiometabolic risk factors, we examined the impact of significant weight change over 3.5 years. Similar to our findings, another study looking at weight and BMI change in teenagers and adults with CF found that over a one-year period, weight gain was positively associated with FEV_1, with a gain of 9.31% FEV_1, while weight loss is associated with a negative impact on lung function [19]. To our knowledge, our study is the first instance that data were examined for a period greater than one year.

While both WL and WS patients lost pulmonary function, a statistically and clinically significant 5% FEV_1 gain was observed in patients who gained 10% or more of their weight (Table 3.5). Thus, weight gain was associated with a clinically significant improvement in pulmonary function.

It has been speculated that insulin deficiency has an adverse effect on nutrition by promoting a catabolic state in CF patients [20]. Since insulin is a potent anabolic hormone, a deficiency can be linked to protein catabolism, leading to decreased diaphragm and intercostal muscle mass and strength, and thus, decreased lung function [20, 21]. Indeed, some studies suggest that early insulin introduction can be associated with improved BMI [22]. Since better pulmonary function in CF patients is the main clinical objective, mechanisms linking weight gain to improved FEV_1 should be further investigated (e.g. impact on body composition, pulmonary exacerbations, etc.).

Besides the essential improvement in lung function associated with weight gain, some adverse consequences could also emerge. In the general population, both obesity and significant weight gain are associated with adverse cardiometabolic conditions, including hypertension, type 2 diabetes, ischemic heart disease, and poor pulmonary function [7, 8]. For adult CF patients, better lung function is associated to higher BMI or weight gain; however, these patients may also exhibit

less favorable (OW patients) or unfavorable (WG patients) trends in their cardiometabolic profiles. We observed reduced estimated insulin sensitivity, higher BP, and deteriorating lipid profiles (HDL, LDL, cholesterol, triglycerides) in OW and WG patients (Tables 3.1 and 3.3). In both cases, it is essential to highlight that no patient group exhibited overtly pathologic cardiometabolic values, as their lipid profiles remained within normal range [23-25]. Still, over a longer time period, such trends suggest patients living with CF might need to be monitored for cardiometabolic parameters. Treatment thresholds as well as risks and benefits of appropriate management and intervention in patients with over-nutrition (lifestyle & pharmacological) in the context of CF remain unknown.

Interestingly, despite the very high prevalence of glycemic abnormalities in patients with CF, we observed no major differences in glucose tolerance categories between BMI categories or weight change groups. Still, we observed differences for underlying pathophysiological mechanisms with reduced estimated insulin sensitivity for both OW and WG patient groups (Tables 3.1 – 3.5). We have recently reported that in aging patients with CF, in the context of limited insulin secretion characterizing CF, emerging insulin resistance could be, over a longer period of time, a factor contributing to glucose intolerance and new cases of CF-related diabetes [26]. In addition, insulin resistance is a central, possibly causal mechanism for cardiometabolic complications [16]; thus emergence of insulin resistance may be associated with the occurrence of cardiometabolic complications.

In adult CF patients, recommended BMI goals are a BMI of at least 22 kg/m^2 for women and 23 kg/m^2 for men [27]. The present study supports these BMI goals and suggests that some FEV_1 benefits might be seen with slightly higher BMI thresholds at least up to 25; however, at the extent of some unfavorable cardiometabolic trends. The patient group likely benefiting the most from

optimizing nutritional status are underweight patients, but our data suggest that even patients with target BMI could also, with weight gain, exhibit pulmonary function benefits.

Our study had some limitations. First, this analysis used a large and well-characterized cohort implying limitations for external validity. Secondly, a longer follow-up period might be necessary to identify more clinically significant cardiometabolic trends, as some adverse effects can take years to emerge [28]. Third, well-known factors that can mitigate the relationship between weight and cardiometabolic profiles, like food quality or physical activity, [28] were not measured in this analysis. Fourth, as with any observational analysis, causality cannot be established and a higher weight or weight gain might be markers of lower disease severity and/or better therapeutic compliance.

In conclusion, CF patients who are overweight/obese or experience significant weight gain, have better pulmonary function, but also present adverse cardiometabolic risk factor trends. The clinical implication of this observation remains to be established. Meanwhile, achieving a normal BMI should remain a crucial therapeutic objective.

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Author contributions

AB, VB, and RRL designed research; AB, VB, JC, and CB conducted research; AB, VB, JC, and CB analyzed data; AB, VB, RRL, and ML wrote the paper; AB, VB and RRL had primary responsibility for final content. All authors read and approved the final manuscript.

Conflict of interest

The authors have nothing to disclose.

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3.6 Chapter 3 References

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4 General Discussion

For individuals afflicted with CF, achieving and maintaining a normal BMI is critical to safeguard lung function and improve longevity [5]. The aim of this work was to compare the cardiometabolic and clinical profiles of adult patients with CF based on their BMI (underweight, normal, or overweight/obese). We also performed prospective observational analyses in order to compare the same parameters based on whether patients lost >10%, maintained, or gained >10% of their weight. This thesis demonstrates that overweight/obese patients exhibit a better lung function, although only significant compared to underweight patients, but also have a less favorable cardiometabolic profiles, with higher triglycerides, cholesterol, insulin levels, and blood pressure compared to underweight and normal weight patients. Importantly, however, the observed cardiometabolic values often remained within normal values [101, 102]. Furthermore, we found that patients who gained significant weight over 3 years are able to gain pulmonary function but, simultaneously, exhibit worse trends for cardiometabolic profiles.

Whilst patients who lost or maintained their weight lost pulmonary function, the patients who gained weight were observed to improve their FEV_1 by 8%. There is a well-known association between weight lost and worse pulmonary function in patients with CF. There is also a mean 1-2% yearly FEV_1 decrease in patients with CF, even in those with stable nutritional statuses [105]. Thus, the weight gain was associated with stabilization and even improvement in pulmonary function. This important finding suggests that weight gain may augment preservation of lung function. Our observational data cannot imply causality, but it remains plausible. The patients with CF in this study all followed the same dietary recommendations. Our findings demonstrate that it may be important for CF dieticians to re-evaluate individual needs for high calorie, high fat diets.

To avoid excess weight gain, nutritional goals must be individualized, reflecting patients' disease severity: BMI (current and trend), caloric expenditure (e.g. intense physical activity), and comorbidities (e.g. specific advices during exacerbations). Additional prospective studies will need to examine which groups of patients will benefit the most from weight gain. While underweight patients with low FEV_1 are likely to experience the most improvement in lung function by increasing their weight, our data suggest that this can be observed even in patients with normal BMI. Improvement in lung function in adult patients with a BMI over 25 kg/m^2 might be marginal at best, however [5]. Similarly, our data, comparing BMI and FEV_1 of the WG patients with the OW patients suggest that a BMI increase over 25.0 kg/m^2 is associated with only minimal improvement in pulmonary function, but increased adverse cardiometabolic trends. Thus, while a higher BMI and weight gain are associated with better or improved lung function, cardiometabolic parameters should be closely monitored by the patients' health care team.

4.1 Future Investigations

As mentioned in the discussion of Chapter 2, further investigation into obesity in patients with CF is necessary. First, we observed that both overweight patients with CF and those who gained weight had higher insulin levels. Although it has been speculated that an increase in insulin could be associated with increased diaphragm and intercostal muscle mass and strength [50, 99], and thus lung function, the mechanisms linking weight gain to improved FEV_1 are not clear. Furthermore, whether weight gain leads to improved lung function through better absorption of key vitamins and nutritional elements or if improved lung function leads to increased weight gain due to less energy expenditure, remains uncertain. To better understand the association between lung function and BMI, and the clinical implications of our observations, the mechanisms should

be further investigated, as well as their impact on body composition, pulmonary exacerbations, and other important clinical parameters.

For this thesis, prospective observational analyses performed to investigate weight change were only done over a period of 3 years. Since both overweight/obese patients and those who gained weight had unfavorable cardiometabolic trends, further studies should be performed to investigate the cardiometabolic trends over a longer period of time (ie. 10 years). It would also be interesting to investigate the cardiometabolic profiles and clinical statuses of individuals with CF who maintain a high BMI (overweight/obese) over a long period of time.

Nutrition quality is an important issue in the general population [74] and in the future it would be important to establish if the type of calories matter in terms of body composition, as well as the impact of weight gain and/or higher BMI on cardiometabolic trends. Numerous factors including food quality, physical activity, and genetics could influence weight gain impact on adverse cardiometabolic outcomes. Though this remains to be demonstrated, a better food quality could translate in an overall healthier impact of weight gain.

In addition, beyond weight gain, body composition can impact overall health. For example, central obesity is clearly associated with increased cardiometabolic risk [80] and can also have some negative impact on lung function. Thus, a similar weight gain could translate into different outcomes if it is more fat mass (and its location) or muscle mass. A significant proportion of patients with CF have low fat-free mass, but have a fat mass and percent body fat similar to non-CF individuals [59]. It would be important to know if an increase in fat mass or percent body fat in persons with CF leads to the same consequences (e.g. risk of CVD) seen in the general population. Meanwhile, patients with CF have decreased muscle mass, which could contribute to

decreased lung function [58]. Thus, an increase in muscle mass may contribute to a positive impact on lung function. Monitoring body composition, especially fat mass and muscle mass, is therefore important for the overall health of patients with CF who gain weight.

As mentioned earlier, one of the limitations of this study was that it used a large and well-characterized cohort consisting of a francophone population base in a single region of Canada. Comparable analyses should be performed in different cohorts to see if similar observations are made. Furthermore, it would be interesting to see if similar results appear in a CF cohort that has a lower mean BMI such as ones in France [106], as well as cohorts who have patients with CF who are taking CFTR modulators. None of the patients in this study had a CFTR modulator prescription. Since CFTR modulators induce weight gain [73], it would be beneficial to see if an improvement in lung function is also seen in patients with CF who take CFTR modulators.

Finally, the clinical implication of this study remains to be established. However, the trends observed suggest patients living with CF who are overweight/obese or gain significant weight may need to be monitored for cardiometabolic parameters. Currently, though, treatment thresholds as well as risks and benefits of appropriate management and intervention in these patients in the context of CF are unknown.

5 Conclusion

Patients with CF who are overweight/obese or experience significant weight gain have better or improved pulmonary function, but also exhibit adverse cardiometabolic trends. However, until the clinical significance of this work is established, achieving and maintaining a normal BMI should remain a main priority for patients with CF and their health care team.

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