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Editorial

Nutritional excess in cystic fibrosis: the skinny on obesity

Nutritional status, assessed by weight or body mass index (BMI), has long been recognized as an important predictor of lung function (FEV_1) and mortality in patients with cystic fibrosis (CF) [1,2]. Patients are often encouraged to consume a diet high in calories to offset the negative energy expenditure created by malabsorption, increased work of breathing, inflammation, and pulmonary exacerbations. Improved medical and nutritional therapies and the recent introduction of CFTR modulators have contributed to increased incidence of overnutrition in patients with CF. In fact, over the past fifteen years, the prevalence of obesity among patients with CF has been described to range from 10 to 30% [3–5]. In the 2017 Australian Patient Data Registry Report, for instance, 10.7% of patients aged 2–18 were overweight or obese while 19% of adult patients had BMIs $\geq$25 kg/m^2 [6]. These rates of overweight status and obesity are lower than the prevalence of obesity in the US adult population, 39.8% in the 2015–2016 CDC data report, but have been increasing in line with that of the general population [7]. Even though overnutrition among patients with CF is becoming more commonplace, the effect of overweight status (BMI $\geq$ 25 to $<$ 30 kg/m^2) or obesity (BMI $\geq$ 30 kg/m^2) on pulmonary and cardiovascular outcomes has not been well elucidated in this patient population. As in the general population, obesity in CF patients may increase the risk of impaired glucose tolerance, diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea. It also remains to be seen if overnutrition adversely affects outcomes in patients with CF undergoing lung transplantation [1].

In their paper, "Prevalence and factors associated with overweight and obesity in adults with cystic fibrosis: a single–center analysis," Harindhanavudhi et al. describe the prevalence of nutritional excess and the associated perturbations in cardiovascular and metabolic parameters among adults with CF seen at the University of Minnesota CF Center [8]. Out of 484 adults enrolled in the study, only 5.2% were underweight, suggesting that prevalence of malnutrition in their patient cohort was rather low. Interestingly, despite 85% of patients in this study having pancreatic insufficiency (PI), overnutrition affected >30% of the patient cohort (25.6% overweight, 6.6% obese). Also unexpectedly, 56% of patients with BMI $\geq$ 25 had severe CFTR mutations. Among those with more severe mutations, overnutrition was more likely to affect those who were older and male. These findings underscore that patients previously at high risk of malnutrition, such as those with severe mutations and PI, are now at risk of becoming overweight or obese, with a likely increase in associated comorbidities. This trend is especially striking, since the CF population is aging and may inherently be at increased risk of cardiovascular complications even in the absence of obesity [9].

Since the study enrolled patients from 2015 to 2017, it is possible that it underestimates the true prevalence of overnutrition attributable to the increasingly widespread use of CFTR-targeted therapy since 2015 [1]. Ivacaftor use, for instance, has been shown to significantly increase weight, weight-for-age Z scores and BMI in patients six years or older compared to placebo [10]. Similar findings have been reported in younger children and in those children on combined lumacator/ivacaftor therapy, as well as in adults [11]. Proposed mechanisms of weight gain from this class of medications include reduced energy expenditure through reduction in work of breathing, improved appetite with improved sense of smell and taste, decreased malabsorption, and diminished gut inflammation. Further longitudinal data are needed to fully describe the changes in BMI and body composition that occur on these medications [12]. The triple combination therapy of elexacaftor/ivacaftor/tezacaftor, commonly termed highly effective modulator therapy, was just made available in October of 2019 and may further enhance these effects on energy balance [13,14].

The authors of the study from Minnesota also examined cardiovascular risk factors in this patient cohort. They found that overweight or obese patients with CF were more likely to have hypertension and statistically higher lipid levels (total cholesterol, LDL-C, and triglycerides) compared to normal weight or underweight groups. However, their absolute cholesterol profiles were still in the normal range. This is in line with other studies, where patients with overweight or obesity were also more likely to have hypertension and exhibit variable lipid values [3]. High blood pressure and rising cholesterol are especially of concern in this aging patient population, which already exhibits additional cardiovascular risk factors such as inflammation and diabetes, and may be especially problematic for those who ultimately undergo lung transplantation. While no cardiovascular deaths have been reported in patients with CF thus far, vigilance towards screening and treating cardiovascular risk factors is paramount, as patients are living longer and are at risk of developing the metabolic and cardiovascular comorbidities of obesity seen in the general population.

In the University of Minnesota Cohort, CF patients who were overweight or obese had higher FEV_1 when compared to normal weight and underweight groups and had fewer pulmonary exacerbations. This is interesting, as the well-known correlation between BMI/weight and lung function has not held up consistently in other studies once the BMI rose above normal. For instance, while Kastner-Cole reported positive association between BMI and FEV_1 in children with CF through the entire range of BMI z-scores, no significant favorable effect on FEV_1 was seen in adults with BMIs >23 kg/m^2 [15]. Further studies are needed to explore the multiple

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confounders in these findings and to set BMI targets for adults and children, to help achieve optimal nutritional status and maximize lung function while decreasing hospitalizations and mortality.

A helpful, algorithm-based guide for nutritional screening and assessment was published in the 2019 "Nutritional Guidelines for CF in Australia and New Zealand" [16]. These guidelines cover nutritional and lifestyle modifications for all BMI categories, including for those patients with energy excess. The authors recommend dietary and activity assessment, as well as consideration of medical and psychosocial factors contributing to overweight or obese status in patients with CF, who have a BMI of $\geq$27 kg/m^2, or who experience unintentional weight gain of >5 kg from a previously acceptable BMI in a year's time. Since currently there are no study data on the safest and most effective lifestyle modifications in patients with CF who are overweight or obese, recommendations may have to be extrapolated from those for the general population pending ongoing research [1]. Unfortunately, no medical therapy has been approved to treat energy excess in patients with CF [1]. However, one of the authors' institutions (Washington University) has some experience with using phentermine and glucagon-like peptide-1 (GLP-1) receptor agonist medication classes to help patients with CF, with and without diabetes, lose weight.

GLP-1 is an incretin hormone secreted by the intestinal cells that has multiple actions. GLP-1 receptor agonist agents are used to treat diabetes through improving glucose-dependent insulin release while decreasing glucagon levels. They can also be used to treat obesity, as they slow down gastric emptying, potentiate satiety, and decrease appetite through a centrally acting mechanism. This class of agents (liraglutide, semaglutide) has been shown to have beneficial effects on glycemic control, weight, blood pressure, cholesterol levels, inflammation, nonfatal cardiovascular infarction, nonfatal stroke, and cardiovascular mortality in patients with diabetes [17]. When used for weight loss, GLP-1 RA liraglutide (brand name: Saxenda) has been shown to achieve at least a 5% weight loss in 56% of patients after one year (as opposed to 25% of in the placebo group patients) [18]. Incretin-based therapies may thus have favorable effects on glycemic control and weight loss in patients with CF, although data on this topic are lacking.

Some studies have shown that patients with CF, especially those with dysglycemia/CF-related diabetes, may exhibit abnormalities in incretin secretion and/or action, and that infusion of an incretin, exenatide, can correct postprandial hyperglycemia in CF patients with impaired glucose tolerance. No data exist, however, on the effects of GLP-1 receptor agonists on weight and body composition in patients with CF, who are overweight or obese [19,20]. Liraglutide has now been approved for use in children and adolescents (without CF) and may be a treatment option for diabetes and energy excess in some patients with CF [21]. As GLP-1 receptors are hypothesized to be present in the lungs, further studies are needed to evaluate the effect of GLP-1 receptor agonists on lung function. Interestingly, one study using a mouse model of chronic obstructive pulmonary disease (COPD) showed that GLP-1 receptor agonist use improved survival and lung function in these animals, suggesting that beneficial effects of this medication on lung function may be possible and should be further evaluated in clinical trial setting [22]. This class of medications also has GI side effects, to which patients with CF may be especially vulnerable. Because GLP-1 receptor agonists can be associated with pancreatitis, their use should be avoided in patients with intact pancreatic exocrine function.

In summary, overnutrition is a widely emerging phenomenon in patients with CF. It is likely multifactorial in etiology, now becoming more prevalent due to earlier diagnosis of CF and earlier diagnosis of pancreatic insufficiency through increased adoption of newborn screening programs globally, improved medical and nutritional therapies, CFTR targeted agents, and environmental factors that are contributing to the rise of obesity in the general population. Obesity can be associated with cardiopulmonary and metabolic abnormalities. It has been consistently associated with increased prevalence of hypertension and cholesterol abnormalities in patients with CF, while findings regarding effect of obesity on lung function have not been consistent. More effort and guidance are needed to assess patients' nutritional goals and status at every visit, and to adjust recommended caloric intake and exercise regimen accordingly. Individualized recommendations, as opposed to blanket recommendations of high calorie diets, should be provided and reassessed over time. In addition, longitudinal studies are needed to describe the natural history of cardiovascular disease in the aging CF population, the effects of weight loss medications on lung function and mortality, and the effects of these therapies on body composition, insulin sensitivity and glucose tolerance.

Declaration of Competing Interest

There are no conflicts to declare.

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