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Expanding Therapeutic Horizons: GLP-1 Receptor Agonists and SGLT2 Inhibitors in Overweight and Obese CFRD Adults

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Abstract

Background: Cystic Fibrosis-Related Diabetes (CFRD) affects up to 50% of adults with cystic fibrosis and has traditionally been managed with insulin monotherapy according to current guidelines. However, the era of highly effective Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulator therapies has transformed the clinical landscape, improving survival while dramatically increasing the prevalence of overweight and obesity in this population. This fundamental demographic shift from historically underweight patients to increasingly overweight and obese adults challenges conventional CFRD management paradigms and necessitates novel therapeutic approaches focused on concurrent weight management.

Objective: This mini-review examines emerging evidence for novel antidiabetic therapies with weight management benefits, specifically GLP-1 receptor agonists and SGLT2 inhibitors, in overweight and obese adults with CFRD, synthesizing recent case series data with contemporary obesity research to evaluate therapeutic potential for this evolving patient population.

Key findings: Recent case series demonstrate substantial weight reduction outcomes with GLP-1 receptor agonists in overweight and obese CFRD patients, including significant weight loss (median -7.2 kg, BMI reductions up to 8.1 kg/m2), improved glycemic control with a 31.5% reduction in insulin requirements, and unexpected pulmonary function improvements in 73% of patients. Sodium-Glucose Cotransporter 2 (SGLT2) inhibitor case series similarly show modest but meaningful weight reduction alongside glycemic management with additional cardiovascular and renal protective effects. Both therapeutic classes demonstrate acceptable safety profiles while addressing the critical need for weight management in this transformed patient population.

Implications: The emergence of overweight and obesity as dominant concerns in adult CFRD patients necessitates a fundamental paradigm shift from traditional weight-promoting approaches toward comprehensive weight management strategies. The convergence of improved CF survival, the obesity epidemic, and effective weight-reducing therapeutic options demands personalized, multi-drug approaches. Randomized controlled trials focusing specifically on weight management outcomes in obese CFRD adults are urgently needed to establish evidence-based protocols for this evolving demographic.

Keywords: Cystic fibrosis-related diabetes; Obesity; Overweight; Weight management; GLP-1 receptor agonists; SGLT2 inhibitors; CFTR modulators; Weight reduction

Introduction

Cystic Fibrosis-Related Diabetes (CFRD) represents the most common comorbidity in cystic fibrosis, with prevalence increasing substantially as patients survive into adulthood. Current epidemiological data indicate that approximately 19% of adolescents and up to 50% of adults with cystic fibrosis develop CFRD, making it a critical clinical concern that significantly impacts morbidity and mortality [1,2]. Unlike type 1 or type 2 diabetes, CFRD presents a unique pathophysiological profile characterized primarily by insulin insufficiency due to progressive pancreatic beta-cell destruction, complicated by intermittent insulin resistance during periods of acute illness, steroid therapy, or physiological stress [1,3].

Historically, CFRD has been associated with accelerated decline in pulmonary function, compromised nutritional status, increased frequency of pulmonary exacerbations, and reduced survival, particularly affecting women disproportionately [1,4]. Traditional management approaches, as outlined in the 2010 clinical care guidelines jointly developed by the cystic fibrosis foundation and American diabetes association, have focused exclusively on insulin therapy, reflecting the historical context of underweight or normal-weight patients with primarily insulin-deficient diabetes [1].

However, the therapeutic landscape has undergone a dramatic transformation with the introduction of highly effective CFTR modulator therapies, particularly the triple combination elexacaftor/tezacaftor/ivacaftor [5]. These breakthrough treatments have

revolutionized CF care by addressing the underlying molecular defect, resulting in significant improvements in lung function, a reduction in pulmonary exacerbations, enhanced quality of life, and extended survival projections [5,6]. Paradoxically, these life-saving therapies have introduced new clinical challenges, most notably a shift toward overweight and obesity in a population historically characterized by malnutrition and growth failure [7,8].

This demographic evolution presents unprecedented challenges for CFRD management. The traditional insulin-centric approach, designed for underweight patients requiring aggressive nutritional support, may prove inadequate or potentially counterproductive in overweight and obese CFRD patients who require weight management alongside glycemic control. Furthermore, emerging evidence suggests that novel antidiabetic therapies, specifically GLP-1 receptor agonists and SGLT2 inhibitors, may offer unique advantages in this evolving patient population, providing not only superior glycemic control but also weight reduction and potentially unexpected pulmonary benefits. This mini-review synthesizes current evidence from recent case series and contemporary research to evaluate the therapeutic potential of these novel agents and examine their implications for clinical practice in the era of CFTR modulators.

Literature Review

GLP-1 receptor agonist evidence in CFRD

The exploration of GLP-1 receptor agonists in CFRD management represents a paradigm shift from traditional insulin monotherapy toward novel incretin-based approaches. Early case series investigating glucagon-like peptide-1 receptor agonist treatment in CFRD patients complicated by obesity demonstrated encouraging preliminary results, establishing the foundation for expanded investigation of this therapeutic class [9].

The most comprehensive evidence to date comes from Park, et al., case series, which represents the largest published experience with GLP-1 agonist therapy in individuals with cystic fibrosis [10]. This study included 11 patients (3 males, 7 females; age range 24-47 years; BMI range 25.7-43.7 kg/m2) treated with GLP-1 agonists for variable durations ranging from 1 to 50 months. The therapeutic agents employed included semaglutide in 9 patients and tirzepatide in 2 patients, reflecting real-world prescribing patterns and the emergence of dual incretin receptor agonists in clinical practice [10].

Clinical outcomes demonstrated remarkable consistency across multiple domains [10]. All patients experienced significant weight reduction, with a median weight loss of 7.2 kg and BMI reductions ranging from 0.9 to 8.1 kg/m2. Perhaps more striking were the unexpected pulmonary function improvements observed in 73% of patients (8 of 11), with changes in percent predicted forced expiratory volume in 1 second (ppFEV1) ranging from -5 to +18 percentage points. Similarly, 82% of patients (9 of 11) demonstrated improvements in percent predicted forced vital capacity (ppFVC), with changes ranging from +1 to +26 percentage points [10].

Among the 7 patients with established CFRD, glycemic outcomes proved equally impressive [10]. All patients achieved substantial reductions in insulin requirements, with a mean 31.5% decrease in total daily insulin dose. Continuous glucose monitoring data revealed improved glucose time-in-range for most patients, with an average 11% increase from baseline values. These findings suggest that GLP-1 receptor agonists may provide superior glycemic control while simultaneously addressing the obesity component increasingly prevalent in CFRD patients.

The safety profile generally proved acceptable, though gastrointestinal adverse events remained the primary limitation [10]. Four patients discontinued therapy: Two due to severe nausea and vomiting, one due to perceived lack of benefit, and one due to insurance coverage changes. These discontinuation rates align with broader GLP-1 agonist experience in other populations, suggesting that CF-specific factors do not substantially increase intolerance rates [11].

The mechanistic rationale for GLP-1 agonist efficacy in CFRD extends beyond simple weight reduction [12]. Emerging evidence indicates that people with cystic fibrosis may have underlying dysfunction in the incretin hormone axis, potentially contributing to the development and progression of CFRD. GLP-1 receptor agonists may address these deficits while providing additional benefits including delayed gastric emptying, which could theoretically improve nutrient absorption, and potential anti-inflammatory effects that might benefit both pulmonary and metabolic outcomes.

Recent investigations into dual incretin receptor agonists, particularly tirzepatide, suggest even greater therapeutic potential [13]. Tirzepatide's combined GLP-1 and Glucose-dependent Insulinotropic Polypeptide (GIP) receptor agonism provides enhanced weight loss and glycemic control compared to selective GLP-1 agonists in type 2 diabetes populations [13]. While experience in CFRD remains limited, the superior efficacy profile observed in other populations warrants further investigation in overweight and obese CFRD patients.

SGLT2 inhibitor evidence in CFRD

Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors represent another novel therapeutic approach for the management of CFRD, offering unique mechanisms of action that complement incretin-based therapies. Case series investigating SGLT2 inhibitor therapy in overweight and obese patients with CFRD have demonstrated promising outcomes, although the evidence base remains more limited compared to that of GLP-1 receptor agonists [14,15].

The mechanistic rationale for using SGLT2 inhibitors in CFRD is compelling [16]. These agents work by inhibiting glucose reabsorption in the proximal renal tubules, thereby promoting urinary glucose excretion that is independent of insulin pathways. This insulin-independent mechanism makes SGLT2 inhibitors particularly attractive for patients with CFRD who have underlying insulin insufficiency. Additionally, SGLT2 inhibitors provide modest weight reduction through caloric loss *via* glucosuria, potentially addressing the obesity component increasingly prevalent in CFRD patients [16].

Clinical case series have demonstrated efficacy in glycemic control, with patients achieving improved hemoglobin A1c levels and reduced insulin requirements [14]. The weight loss effects, while generally modest (typically 2 kg-4 kg), provide additional benefit for overweight patients. Perhaps more importantly, SGLT2 inhibitors offer potential cardiovascular and renal protective effects that may prove particularly valuable as the CFRD population ages and develops traditional diabetes complications [16].

Safety considerations for SGLT2 inhibitors in patients with CFRD require careful attention to CF-specific factors. The increased risk of dehydration and electrolyte abnormalities associated with SGLT2 inhibitors may be particularly concerning in CF patients who already

face increased salt losses through sweat and may have underlying renal dysfunction. Additionally, the risk of diabetic ketoacidosis, while rare, requires consideration in patients with underlying insulin insufficiency.

Gastrointestinal considerations also merit attention, as SGLT2 inhibitors may interact with the complex intestinal manifestations of cystic fibrosis, including distal intestinal obstruction syndrome and altered gut microbiome. However, preliminary case series suggest that these theoretical concerns may not translate into clinically significant problems when appropriate monitoring protocols are followed.

The emergence of combination SGLT2 inhibitor and GLP-1 receptor agonist therapy represents an intriguing possibility for CFRD management. Such combinations have demonstrated synergistic effects in type 2 diabetes populations, providing complementary mechanisms for glycemic control and weight management. While experience in CFRD remains anecdotal, the theoretical advantages warrant systematic investigation.

Discussion

Therapeutic paradigm shift in CFRD management

The integration of GLP-1 receptor agonists and SGLT2 inhibitors into CFRD management represents a fundamental paradigm shift from the traditional insulin-centric approach toward comprehensive, multi-drug strategies that address the evolving complexity of this patient population. This transformation parallels the evolution of type 2 diabetes management over the past two decades, where therapeutic approaches expanded from insulin and metformin monotherapy to sophisticated combination regimens targeting multiple pathophysiological pathways.

However, CFRD presents unique considerations that require thoughtful adaptation of general diabetes management principles [1,3]. Unlike type 2 diabetes, where insulin resistance predominates, CFRD primarily involves insulin insufficiency with variable insulin resistance, necessitating careful consideration of agent selection and dosing strategies. The historical emphasis on aggressive nutritional support and weight gain in CF patients conflicts with contemporary approaches to obesity management, necessitating individualized therapeutic decisions based on patient phenotype and nutritional status [8].

The emerging evidence suggests that novel antidiabetic agents may offer advantages beyond glycemic control that are particularly relevant to CF patients. The unexpected improvements in pulmonary function observed with GLP-1 agonist therapy suggest potential pleiotropic effects that warrant further investigation. These findings challenge traditional compartmentalized approaches to CF care and suggest that metabolic interventions may provide broader systemic benefits. This paradigm shift requires enhanced collaboration between CF care teams and endocrinologists, as well as updated clinical protocols that integrate novel therapeutic approaches while maintaining the comprehensive, multidisciplinary care model that characterizes optimal CF management.

CFTR modulator era: Redefining patient phenotypes and therapeutic needs

The introduction of highly effective CFTR modulator therapies has fundamentally altered the clinical trajectory of cystic fibrosis, creating new therapeutic opportunities while simultaneously generating unprecedented challenges for CFRD management [12,17]. Recent longitudinal studies demonstrate that CFTR modulator therapy may improve glucose metabolism through multiple mechanisms, including enhanced insulin secretion, reduced systemic inflammation, and improved incretin hormone function [17-19].

Cohen, et al., study provided compelling evidence that long-term CFTR modulator therapy consistently improves glucose metabolism in adolescents and adults with cystic fibrosis [18]. Their analysis of 15 patients receiving CFTR modulator treatment for a mean duration of 28 months demonstrated significant improvements in 120-minute oral glucose tolerance test values, with improvements in glycemic status observed in 40% of patients. These findings suggest that CFTR restoration may partially reverse the underlying pathophysiology contributing to CFRD development, potentially delaying disease progression or reducing severity [18,20].

However, the beneficial metabolic effects of CFTR modulators are counterbalanced by their propensity to promote weight gain and, in some cases, progression to overweight and obesity [7,8]. This demographic shift creates a new patient phenotype that requires different therapeutic approaches compared to the historically underweight population with CFRD. The traditional focus on preventing weight loss and promoting caloric intake may prove counterproductive in overweight patients who require weight management alongside glycemic control [8].

Furthermore, the improved survival associated with CFTR modulator therapy means that CFRD patients will live longer and potentially develop traditional diabetes complications, including cardiovascular disease, nephropathy, and retinopathy, which were previously rare in this population due to shortened life expectancy. This evolution necessitates the adoption of comprehensive diabetes management strategies that include cardiovascular risk reduction and renal protection, areas where SGLT2 inhibitors and GLP-1 receptor agonists have demonstrated particular efficacy in other populations.

Combination therapy, potential, and personalized medicine approaches

The complementary mechanisms of action exhibited by GLP-1 receptor agonists and SGLT2 inhibitors suggest substantial potential for combination therapy approaches in CFRD management [11,16]. GLP-1 agonists primarily enhance insulin secretion, slow gastric emptying, and promote satiety, while SGLT2 inhibitors provide insulin-independent glucose lowering with additional cardiovascular and renal protective effects. This mechanistic complementarity has proven synergistic in type 2 diabetes populations and may offer similar advantages in CFRD patients [11,16].

Emerging evidence from cardiovascular outcome trials suggests that combination therapy may provide additive benefits for major adverse cardiovascular events. This consideration becomes increasingly relevant as CFRD patients survive into older age groups, where cardiovascular disease becomes more prevalent [11,16]. Additionally, the weight loss effects of both drug classes may prove particularly valuable for overweight and obese CFRD patients who require both glycemic control and weight management [10,13].

The concept of personalized medicine becomes particularly relevant in CFRD management, where patient phenotypes may vary substantially based on the response to CFTR modulators, nutritional

status, comorbidities, and disease severity. Future therapeutic approaches may require individualized protocols that consider factors such as baseline BMI, insulin requirements, pulmonary function, and CFTR modulator response when selecting optimal drug combinations and dosing strategies.

Research gaps and future directions

Despite encouraging preliminary evidence, substantial research gaps remain that limit widespread adoption of novel antidiabetic agents in CFRD management. The current evidence base relies primarily on small case series and retrospective analyses, which, while valuable for initial safety and efficacy assessment, cannot provide the robust evidence required for evidence-based clinical practice guidelines. Randomized controlled trials specifically designed for populations with CFRD are urgently needed to establish optimal drug selection, dosing protocols, and long-term safety profiles.

Additionally, health economic evaluations are needed to assess the cost-effectiveness of novel therapeutic approaches compared to traditional insulin-based management. Such analyses will be crucial for healthcare policy decisions and insurance coverage determinations that ultimately determine patient access to these potentially beneficial therapies.

Conclusion

The management of cystic fibrosis-related diabetes is undergoing rapid evolution driven by the intersection of improved survival, changing patient demographics, and expanding therapeutic options. The emerging evidence for GLP-1 receptor agonists and SGLT2 inhibitors in overweight and obese patients with CFRD represents a promising departure from traditional insulin-only approaches, offering potential benefits that extend beyond glycemic control to include weight management and unexpected improvements in pulmonary function.

The paradigmatic shift toward combination therapy approaches reflects the increasing complexity of CFRD in the CFTR modulator era, where patients present with diverse phenotypes requiring individualized therapeutic strategies. The convergence of insulin insufficiency with emerging obesity trends necessitates novel approaches that address both metabolic and weight management needs while maintaining the comprehensive care principles that optimize CF outcomes.

However, the transition from case series evidence to evidence-based clinical practice requires substantial additional research, including randomized controlled trials explicitly designed for CFRD populations, long-term safety studies, and health economic evaluations. Furthermore, clinical practice guidelines require urgent updating to address the evolving patient demographics and therapeutic landscape characteristic of contemporary CF care.

The future of CFRD management lies in personalized, multi-drug approaches that leverage the complementary mechanisms of novel antidiabetic agents while maintaining focus on the unique pathophysiological and clinical characteristics that distinguish CFRD from other forms of diabetes. As this therapeutic evolution continues, close collaboration between CF care teams and diabetes specialists will be essential to optimize outcomes for this increasingly complex patient population.

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