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Potential Role for the Use of Gliptins in Cystic Fibrosis-related Diabetes

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Cystic fibrosis (CF) is the most common inherited disease among Caucasians and is often lethal. CF-related diabetes (CFRD) is now the most common comorbidity in those with CF as the life expectancy of people with CF continues to improve. This condition is associated with high morbidity and mortality, and the prevalence appears to increase with age, affecting about 2% of children, 20% of adolescents, and about 40% to 50% of adults, with a higher prevalence seen in women (1).

CFRD primarily affects those with pancreatic insufficiency who develop reduced β-cell secretory capacity compared to those without (2). Although the genetic and etiological factors that contribute to CF have largely been established, the treatment options for CFRD remain limited with subcutaneous insulin being the mainstay for treatment. This treatment option, however, can be burdensome, often requiring both intense dosing and monitoring, along with a high risk for hypoglycemia.

The earliest insulin defect seen in CF is loss of first-phase insulin response, followed by a progressively decreasing total insulin response to an oral glucose load (3). In addition, there appears to be an element of dysregulated glucagon secretion from α-cells. An inadequate glucagon response to arginine and to hypoglycemia has been reported along with low total glucagon levels. Further, impaired glucagon suppression following an oral glucose tolerance test has been shown (4) and thought to contribute to the development of glucose intolerance.

The incretin axis is another hormonal system thought to contribute to the development of CFRD. Studies have shown that people with CFRD have lower levels of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide1 (GLP-1) than those without diabetes (5). These hormones normally enhance glucose-dependent insulin secretion following food ingestion as well as glucagon suppression. In CFRD, lower levels of these hormone levels are thought to contribute to impairment of both insulin secretion and glucagon suppression (2, 5).

Both GIP and GLP-1 are rapidly degraded by the aminopeptidase protease dipeptidyl peptidase-4 (DPP-4) (6). Hence the current clinical trial by Kelly et al (7), evaluating the benefits of sitagliptin (a DPP-4 inhibitor) use in a population of pancreatic insufficient (PI)-CF patients, with the goal of achieving a therapeutic benefit derived mainly from increased incretin hormones concentrations and their normal physiologic actions. Here, the investigators aimed to test whether the use of oral sitagliptin may improve insulin secretion in PI-CF with abnormal glucose tolerance (AGT) including those with early CFRD. They designed a 6-month randomized, placebo-controlled, double-blind clinical trial and examined the effects of oral sitagliptin on incretin and islet hormone secretion in relation to a mixed-meal tolerance test. In addition, they examined measures of insulin secretory rates, glucagon suppression, glycemia, as well as glucose-potentiated arginine test-derived measures of β- and α-cell function. Twenty-six adults with PI-CF and AGT were

randomized to either 100 mg of oral sitagliptin daily or placebo. After 6 months of treatment, those who received sitagliptin showed more robust postprandial concentrations of intact GLP-1 and GIP, partially restored insulin secretory dynamics, and a modest enhancement of glucagon suppression. In addition, glucose-potentiated arginine test derived responses for glucagon were lower in the sitagliptin arm. There were no improvements, however, in glucose tolerance or β-cell sensitivity to glucose, including second-phase insulin secretion.

A similar recent, yet smaller, randomized placebo-controlled trial (with a crossover design) was conducted in 6 subjects ages 10 to 25 years with PI-CF and AGT using a low dose of a GLP-1 agonist, Exenatide (8). This study showed improvements in postprandial glucose excursions, primarily because of slower gastric emptying rather than to increased insulin secretion. Here, however, measures of gastric emptying were not examined in the study by Kelly et al (7), although DPP-4 inhibitors, generally, have lesser effects on gastric emptying and this may perhaps be contributing to the lack of improvement in glucose tolerance.

This study has several strengths. Because of the frequency of gastroparesis in CFRD (5), a concern for tolerability of these drugs in this population arises. However, this study demonstrates that the use of sitagliptin for 6 months was safe and tolerable in this population. In addition, the randomized, double-blind design and a high participant retention and adherence rates were also strengths to be considered. Further, this study uses gold-standard and complex methods for assessing islet β- and α-cell function. Finally, the earlier phased secretion of insulin and greater glucose-dependent glucagon suppression in the sitagliptin arm suggest an improvement of islet β- and α-cell function, which is indeed promising.

There were a few caveats to this study. This study used glycated hemoglobin levels as a measure of glycemia and improvements in this measure were not seen. This may not have been an appropriate outcome measure in a population with AGT and early CFRD. Therefore, continuous glucose monitoring data could have provided more extensive information regarding the potential glycemic effect of sitagliptin in this cohort. Further, this study was unable to assess the potential insulinotropic effects of GLP-1 and GIP. However, the investigators report a separate ongoing study that should be able to address this question (ClinicalTrials.gov Identifier: NCT01851694). Finally, the small number of individuals with overt CFRD and obesity did not allow for subgroup analyses; therefore, larger studies are needed.

In summary, the study by Kelly et al (7) is a very well-designed study that aimed to examine the effect of oral sitagliptin use on different measures of β- and α-cell function as well as glycemia. It showed that oral sitagliptin was safe and tolerable in this population and appeared to enhance intact incretin responses and insulin secretory dynamics. There were no changes, however, in glycated hemoglobin levels. It remains to be determined, however, if oral sitagliptin has a potential insulinotropic effect. Nonetheless, these treatment options remain attractive because of the lower treatment burden when compared with insulin along with a lower risk for hypoglycemia. Larger multicenter studies that could include additional measures of β-cell function, glycemia as well as allow for other subgroup analyses within the CF population in the future are warranted.

Additional Information

Disclosure Statement: The author has nothing to disclose.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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