Hyperglycemia in Cystic Fibrosis: Is It Diabetes, or Isn't It?

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Patient A has cystic fibrosis (CF) and is preparing to have a lung transplant. To ensure that the operation is a success, he needs to gain weight, which means waking up every morning at 4:30 AM to take a supplement.

The problem is that every time he takes the supplement, he has a hyperglycemic episode that's taking him into the diabetic range. Then, when he wakes up in the morning, he has a hypoglycemic episode, which also needs looking after.

The solution? He switched to taking Calogen, a fat-based supplement, each morning, which resulted in smaller glycemic excursions. However, it was only when he added double cream to his morning ritual that he was able to eradicate the excursions and gain the necessary weight to have his operation.

That scenario, which was presented at the recent Diabetes UK Professional Conference in Manchester, United Kingdom,[1] would sound familiar to many clinicians looking after patients with CF-related diabetes (CFRD).

Nicola Bridges, MD, a consultant pediatric endocrinologist at Chelsea and Westminster Hospital, London, United Kingdom, who opened the session, told delegates that there has been a large increase in the prevalence of CF in recent years.

Indeed, one factor in this trend is longer lifespans of patients with the disease. The UK's Cystic Fibrosis Trust calculates that median overall survival increased from 37.87 years in 2007-2009 to 47.06 years in 2013-2015,[2] which is the result of greater life expectancy due to better treatment, novel drugs, and better organization of care.

CF-Specific Diabetes

However, Dr Bridges noted that "it's been known for a very long time that people with CF have diabetes, and that that diabetes is distinct from type 1 and type 2 diabetes."

She continued, "Histologically, what's happening is that there is a loss of beta-cell numbers and a loss of insulin secretion. There also seems to be an effect of the CF mutation itself, which is evidenced by the rather interesting observation that ivacaftor [Kalydeco®; Vertex Pharmaceuticals] reverses diabetes in some individuals."

She added, "We look at it in a very different way because of the adverse effects of diabetes on the clinical status and nutritional status of people with CF."

Dr Bridges pointed out that in CF, there is a gradual fall in insulin secretion with age, resulting in a diminished and delayed insulin response to food. This is set against a relative preservation of basal insulin secretion, meaning that fasting glucose levels can be normal, even years after a diagnosis of CFRD.

Patients with CF often experience hypoglycemia after meals, despite typically having normal glucose levels on an oral glucose tolerance test (OGTT) and normal insulin sensitivity.

Dr Bridges noted that systematic screening of CF patients, alongside a greater awareness of CFRD, has led to an increase in the prevalence of the condition, resulting in more and more patients undergoing OGTT.

"One of the practical problems is doing very large numbers of OGTTs in people and adding it onto their annual review, which is a very intensive day of lung function and other testing," she said.

"Getting them to come fasted is quite difficult. But the main issue with the OGTT is that the cut-offs for treatment of diabetes related to type 2 don't seem to apply to CF, and an OGTT does not give us a clear idea of who benefits from treatment with insulin."

When Should Screening Begin?

One issue with screening is when to start it, as it has been shown that even young children with CF can have CFRD. Another problem is that the clinical status of patients with CF, which can change quite often, can have an effect on glucose status.

Patients with CFRD experience microvascular complications.

This is aside from the question of whom to treat and how. Richard Holt, MD, PhD, professor of diabetes and endocrinology, University of Southampton, United Kingdom, said in the second presentation of the session that the rationale for treating diabetes in CFRD is typically based on treating certain levels of blood glucose to prevent microvascular complications.

Although rates are lower than those seen in type 1 and type 2 diabetes, patients with CFRD experience microvascular complications[3] and increased rates of lung transplantationcompared with other CF patients.[4]

It has also been shown that even in otherwise healthy individuals, diabetes causes loss of lung elasticity and recoil and a greater rate of decline in lung function, as well as a reduced diffusion capacity due to thickening of the alveolar epithelium and increased rates of infection.

"I guess among people with type 1 and type 2 diabetes, these effects on their lungs are not their major problem, but in the situation where someone has CF, these can then compound all of the effects that they have as a result of their CF, and therefore there is the accumulation of effects," Dr Holt commented.

He said that, taking into account the impact of blood glucose on lung function, treatment should be started at levels lower than would be expected to prevent microvascular complications, "and probably starts at around a blood glucose [level] of 8 mmol/L in the postprandial state."

"So this would suggest that perhaps we shouldn't be waiting until people have the more traditional levels of glycemic control, but we should be looking to start treatment at a somewhat earlier period," he noted.

The issue is that assessing glucose control via A1c levels can be unreliable owing to increases in red blood cell turnover, whereas fasting glucose levels "can be falsely reassuring."

Nevertheless, Dr Holt said, on the basis of previous work by Moran and colleagues,[5] treatment should be started if glucose levels are greater than 11 mmol/L or A1c levels are greater than 7.0%, and considered at glucose levels greater than 8 mmol/L if there is evidence of declining lung function or weight loss.

Because the underlying pathology of CFRD is predominantly a beta-cell secretory defect, sulfonylureas have some effect. However, Dr Holt emphasized that there is no evidence for other agents, and although guidelines recommend the use of insulin, there is no evidence for any particular type or regimen.

There is hope, however, that CF transmembrane conductance regulator (CTFR) modulators, such as ivacaftor, could be beneficial, because CTFR has been shown to regulate insulin secretion and mutation of the CTFR gene reduces insulin exocytosis.

Dietary management of CFRD also plays a central role, with up to 1.5 times the daily recommended calorie intake and no restrictions on the type of fat, which should comprise up to 40% of the total calories.

However, the particularities of patients with CF means that there are several complications that arise in CFRD.

Carefully Considering the Burden on Already Fragile Lungs

In the final presentation of the session, Rachel Rowe, MD, consultant diabetologist, University Hospital of South Manchester NHS Trust, United Kingdom, highlighted that glucose concentrations in the lung, which are linearly related to those in the blood, have a "massive difference" on the growth rate of Pseudomonas aeruginosa, one of the main pathogens in CF.

"This is a little bit akin to the story with gestational diabetes, where you've got effects on the fetus at lower levels than we classically make a diagnosis in diabetes, and here effects on the lung that are specific to CFRD," Dr Rowe said.

This means that glucose levels, which may rise even in those without CFRD, can have an impact on infection rates and nutrition, making the case for the monitoring of glucose levels for feeds and supplements.

CFRD patients are difficult to treat and require close monitoring to determine when to start treatment.

CFRD can also be an issue in patients who are due to undergo lung transplant, because it is associated with worse outcomes. Therefore, CFRD management is important so that A1c levels can be kept in check while target weights are achieved.

Another potential problem is that prednisolone has altered kinetics in CF and may be malabsorbed, so glucose levels should be monitored before and 9 hours after administration.

In the discussions after the presentations, all of the speakers emphasized that CFRD patients are difficult to treat and require close monitoring to determine when to start treatment.

For session cochair Helen Atkins, DSN, advanced nurse practitioner-diabetes at the University Hospitals of Leicester NHS Trust, Leicester, United Kingdom, this underlines the importance of multidisciplinary care.

She told Medscape that "Ultimately, with CFRD, the aim is to get the diabetes team and the respiratory side, the dietetic side, and the psychology side to have that multidisciplinary approach to managing patients."

Patients "are few and far between, but because we're seeing that increase, we're starting to try and push for that sort of ideal model for those patients."

Guidelines: To Change or Not to Change?

Ms Atkins also believes that although a great deal of progress has been made in recent years in understanding CFRD and how it should be managed, there are some outstanding research priorities.

"For us, it's the criteria of when people are diagnosed and start treatment," she said, adding, "Obviously, at the moment, we've still got the [World Health Organization] criteria," but by the time these patients get to WHO, they "are already presenting with complications."

"So, as Rachel, Richard, and Nicola have said, we should be treating them in the prediabetes stage, which would be the normal population. We need clearer guidance to say we're looking at a diagnosis of CFRD probably to a lower A1c level, but the jury's out."

However, Antoinette Moran, MD, professor and division chief of pediatric endocrinology and diabetes at University of Minnesota, Minneapolis, Minnesota, who was lead author on the 2010 Clinical Care Guidelines for Cystic Fibrosis-Related Diabetes,[5] disagrees that a change in the guidelines is necessary.

Approached for comment, she said, "The only accepted criteria for starting insulin is when a definitive diagnosis of diabetes has been made."

She continued, "When CFRD has been diagnosed by the criteria outlined in the CFRD consensus guidelines, there is good evidence that starting insulin improves prognosis. A number of people have now shown that almost all CF patients have intermittent high postprandial glucose levels when you measure them with continuous glucose monitoring at home, but this is not a valid method of diagnosing diabetes."

"There are no outcome data available to say that these patients should be treated with insulin. Same for impaired glucose tolerance."

Nevertheless, Dr Moran told Medscape that studies are taking place that could warrant a change in the guidelines, once their results are available.

She also shared the optimism of the presenters that CFTR modulators could benefit patients with CFRD, saying, "They offer the potential to perhaps prevent diabetes in the first place, if started early enough and if they are effective."

References

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