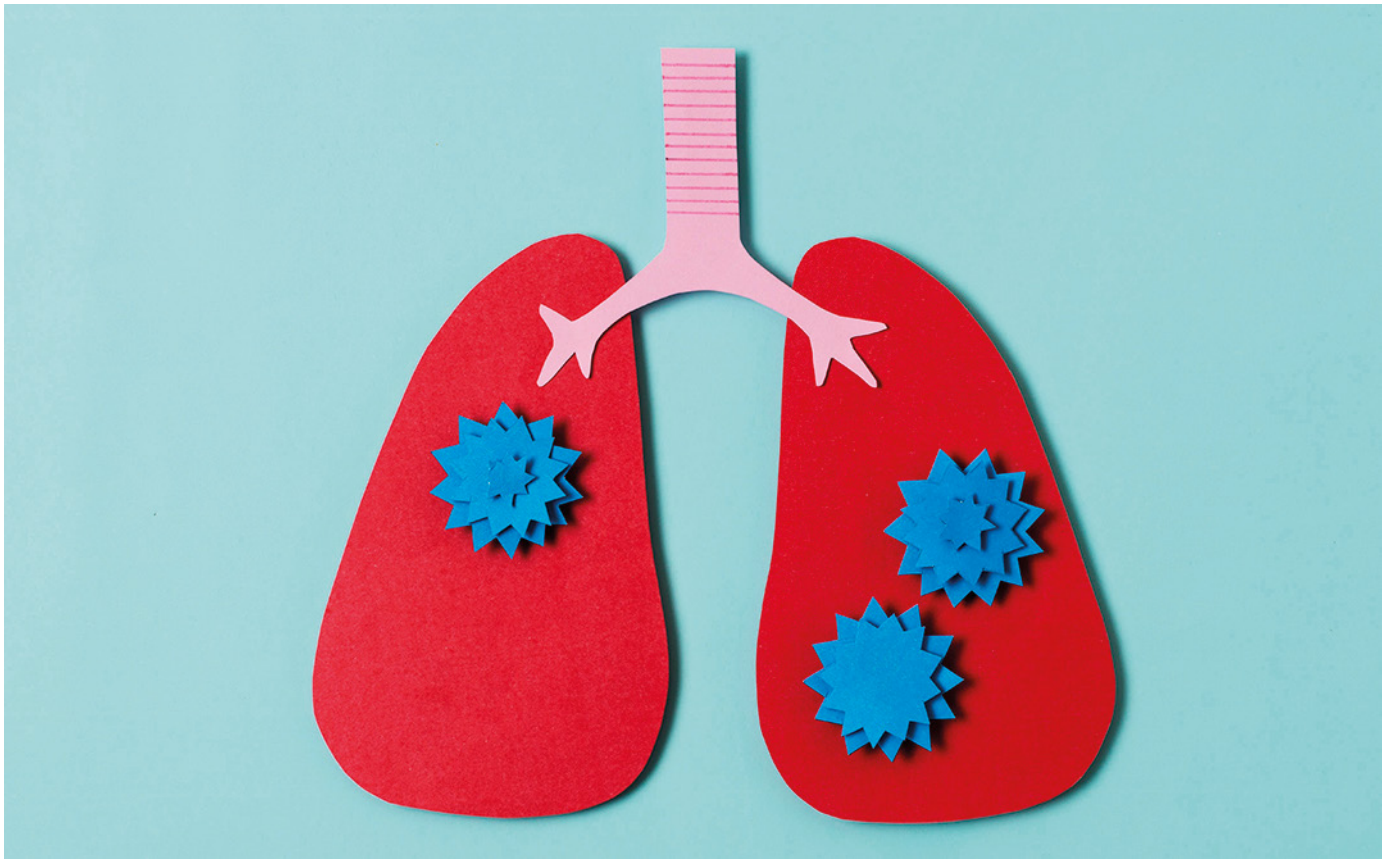
Irene Aguilera García.
PhD Student at the Universidad Autónoma de Madrid.
Department of Diabetology, Hospital Universitario Rangueil (Toulouse, France).

Noemí González Pérez de Villar.
Diabetes Unit, Department of Endocrinology and Nutrition,
Hospital Universitario La Paz (Madrid, Spain).



Glucodensities in screening for cystic fibrosis–related diabetes:

one more step toward high-precision screening

Cystic fibrosis (CF) is a genetic disease mainly known for pulmonary disease, which is the leading cause of death and complications. However, it is a multisystem disease in which, among other disorders, diabetes has a major impact on lung function, overall survival, nutritional status, and infections (1) This impact can be perceived even 2 years before the onset of diabetes, solely through early alterations in glucose metabolism (2).

For this reason, early diagnosis of diabetes in people with CF is important. Screening for cystic fibrosis–related diabetes (CFRD) is an essential part of care for affected individuals. This screening is recommended from the age of 10 years through an oral glucose tolerance test (OGTT), a 2-hour test performed after ingestion of a syrup containing 75 g of glucose. This is both a screening and diagnostic test; therefore, it should be repeated annually if the result is normal or not compatible with diabetes, but shows glucose abnormalities.3 Table 1 shows the diagnostic categories according to the OGTT result:

	FASTING GLUCOSE	GLUCOSE AFTER 1 HOUR	GLUCOSE AFTER 2 HOURS
Normal glucose tolerance.	< 100 mg/dL.	< 200 mg/dL.	< 140 mg/dL.
Indeterminate.	< 126 mg/dL.	≥ 200 mg/dL.	< 140 mg/dL.
Impaired glucose tolerance.	< 126 mg/dL.	—	≥ 140 mg/dL.
CFRD with normal fasting glucose.	< 126 mg/dL.	—	≥ 200 mg/dL.
CFRD with impaired fasting glucose.	≥ 126 mg/dL.	—	≥ 200 mg/dL.

TABLE 1. Diagnostic categories of glucose tolerance in people with CF based on oral glucose tolerance test results, with measurements at baseline, 1 hour, and 2 hours.

Because it is an uncomfortable test—among other reasons, due to nausea, an additional medical appointment, and so on—and time-consuming, in people with a significant disease burden and multiple complementary tests, such as spirometry, blood tests, and others, adherence to recommendations in adults is very low.4 Therefore, there is growing interest in developing other screening methods, although the preferences of patients with CF have not been studied so far.

The first method studied was glycated hemoglobin (HbA1c), which is generally less interpretable in people with CF because of several processes: initially, CFRD presents as postprandial hyperglycemic peaks, meaning that average glucose data represent it poorly, and people with CF may have altered total hemoglobin due to anemia or chronic inflammation. Therefore, HbA1c is usually < 6.5% when the OGTT is compatible with CFRD and is not usually a useful diagnostic method. However, a research group from Canada studied the HbA1c threshold from which the probability that the OGTT could diagnose CFRD increases, obtaining a result of 5.5%. This group proposes annual screening with HbA1c, using the cut-off point of 5.5%, above which the OGTT should be performed.5 This method is already part of Canadian clinical practice guidelines. Other studies have proposed cut-off points between 5.4% and 6%, most commonly 5.5%.

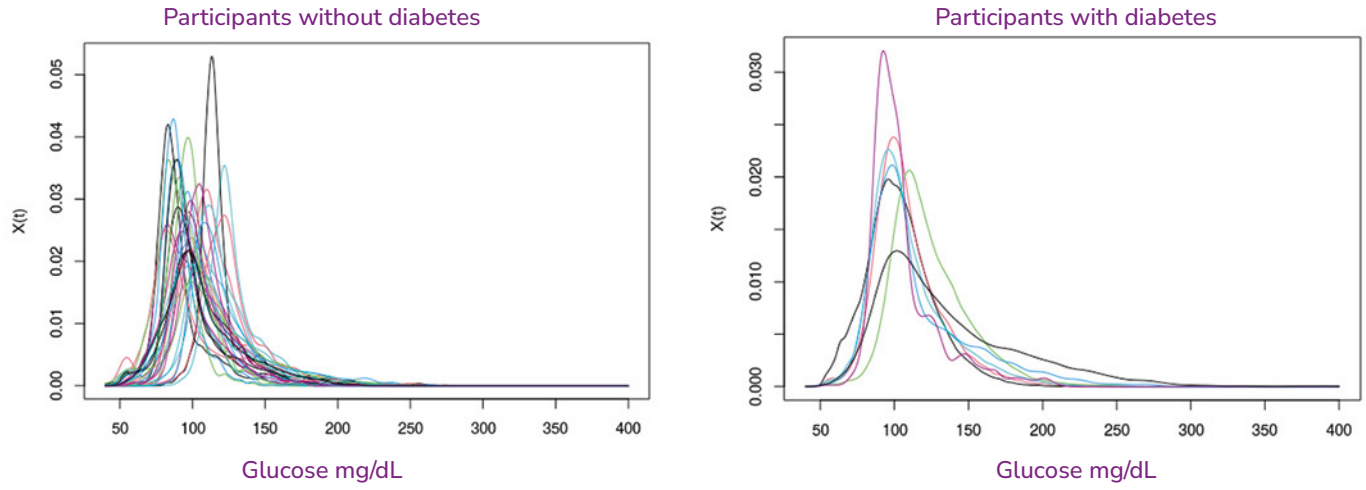
Later, other research groups studied the ability of continuous glucose monitoring (CGM), with different sensors lasting between 3 and 14 days, to diagnose CFRD without an OGTT. Results have differed depending on the study and the population analyzed—children, adolescents, or adults—with very broad discriminatory capacities for diabetes, but with promising results in adults.6

RESULTS

Our team from the Diabetes, Cystic Fibrosis, and Clinical Nutrition Units conducted a study between 2022 and 2024 in adults with CF without a previous diagnosis of CFRD.7 Our study consisted of performing an OGTT according to official recommendations, together with HbA1c measurement. After the OGTT, patients who agreed to participate in »

THIS IS BOTH A SCREENING AND DIAGNOSTIC TEST; THEREFORE, IT SHOULD BE REPEATED ANNUALLY IF THE RESULT IS NORMAL OR NOT COMPATIBLE WITH DIABETES

FIGURE 1.



» the study completed a questionnaire on screening preferences and wore a FreeStyle Libre 2 glucose sensor for 14 days. In total, 40 people with CF participated, 39 of whom completed all the parameters needed for statistical analysis.

The questionnaire was simple, with three main questions:

1. Whether they underwent the annual OGTT without discomfort or preferred another method.

2. Whether they preferred to continue screening with an annual OGTT or switch to a simple HbA1c measurement, taking into account that they would have to undergo the OGTT on another day if HbA1c exceeded a given threshold.

3. Whether, upon learning of any alteration in glucose metabolism, they would like to wear a sensor to find out what was happening.

The questionnaire results were not surprising: most people stated that the OGTT was very uncomfortable, that they preferred a simplified method—even if it required two steps—and that they would like to wear a sensor. This is the first study to directly examine patient preferences regarding screening.

Regarding analytical results, patients were classified according to OGTT results into 3 groups: normal glucose tolerance, impaired glucose tolerance—some abnormality such as indeterminate or impaired tolerance—and CFRD. Both HbA1c and some CGM parameters—including mean glucose, estimated HbA1c, and time spent > 140 mg/dL—could distinguish among the 3 groups using the simplest statistical tests in our study patient group. However, the classic sensor data that measure glycemic variability, such as the coefficient of variation, could not make this distinction.

Later, we conducted another simplified classification of participants: with or without diabetes according to OGTT results. When attempting to establish a cut-off point for the previously described parameters, we realized that HbA1c was not very sensitive for use as a first screening step—with an ideal cut-off point in our population of 5.4%—but that sensor data such as time spent > 140 mg/dL and 180 mg/dL of 20% and 6%, respectively, could be proposed. In other words, if a sensor is placed on a person with CF without previous diabetes and the results are below these percentages, the probability that they have diabetes is very low. This is consistent with other similar studies conducted in adults with CF, but our results were still not sensitive enough to propose them as a screening alternative.

Therefore, we took one final measurement using the sensor data. This measure is glucodensities, which are a graphical representation of the analysis of glucose distribution during the sensor's lifetime. Each glucose-level point is represented with a density proportional to the time spent at that glucose level, with the curve being higher if more time is spent at that glucose level and wider at its base if glycemic variability is greater. This measure has previously shown a relationship with HbA1c, insulin resistance, and glucose variability.

In our case, the representation of each participant's glucodensities can be seen in Figure 1, organized into a group without diabetes and another group with diabetes. The difference between the 2 groups was statistically significant. We can see that people with diabetes on the OGTT have densities concentrated at higher glucose levels and a wider curve base, representing more important glycemic variability. In addition, in the group without diabetes, we can observe that there are participants with higher glucodensities, which could explain why the impact of diabetes on CF complications may appear even 2 years before the diagnosis of CFRD. D

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CONCLUSIONS

Screening for CFRD is important in the care of people with CF, with early diagnosis and treatment of diabetes having a positive impact on mortality and lung function. However, diagnosis is often delayed because of nonadherence to screening recommendations due to an uncomfortable methodology. In our study, patients' preference for simplified screening was confirmed.

For this screening, HbA1c appears promising from a clinical standpoint because of its measurement simplicity and cost-effectiveness. The implementation of HbA1c in a two-step CFRD screening strategy would increase patient participation and, therefore, diagnoses. Although possible inaccuracy of HbA1c in CF must be assumed for different reasons, the number of glucose tolerance tests would decrease and, with it, the disease burden.

Finally, continuous glucose monitoring with sensors is more precise than HbA1c and provides real-life data. Measurements of different hyperglycemia levels can distinguish CFRD well, but glucodensities have shown superiority over the classic measures provided by sensors. In the coming years, it would be interesting to study whether these glucodensities can predict the future onset of diabetes, which would allow an early response to improve life expectancy and the other complications of people with CF.

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