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SHORT REPORT

New criteria for impaired fasting glucose and screening for diabetes in cystic fibrosis

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ABSTRACT: Cystic fibrosis-related diabetes mellitus (CFRD) is the most frequent comorbidity in cystic fibrosis. Its clinical relevance is stressed by the association with increased mortality, and decreased pulmonary and nutritional status. An annual oral glucose tolerance test (OGTT) is recommended as a screening test for CFRD, but this is often not realised because of its time- and resource-consuming nature. Therefore, alternative approaches are welcome.

In 2003, the American Diabetes Association (ADA) lowered the cut-off point separating normal from elevated fasting plasma glucose from $<$6.1 mmol·L^{-1} to $<$5.6 mmol·L^{-1}, suggesting the performance of an OGTT only in those with impaired fasting glucose (IFG; range 5.6–6.0 mmol·L^{-1}). The current authors tested whether this approach was reliable for the early identification of patients with CFRD.

OGTTs from 1,128 patients (53% males; 47% females; median age 17.1 yrs) were available for analysis. A total of 101 (8.9%) OGTTs were classified as diabetic. The new ADA criteria for IFG increased the sensitivity to 82% (*versus* 65%) and decreased the specificity to 70% (*versus* 94%) compared with the old criteria used to identify patients with diabetic OGTTs.

In conclusion, the American Diabetes Association approach of using impaired fasting glucose as an indication for performing selective oral glucose tolerance tests is definitely unsuitable when aiming at the early identification of patients with cystic fibrosis-related diabetes mellitus, and it cannot replace annual oral glucose tolerance tests.

KEYWORDS: Cystic fibrosis, diabetes mellitus, oral glucose tolerance test, screening

The most important life-limiting factor in cystic fibrosis (CF) is the decline of pulmonary function. Numerous reports indicate glycaemic exposure as being tightly linked with impaired pulmonary function in type 2 diabetes [1], as well as in secondary diabetes, such as in patients with CF [2–4]. CF-related diabetes mellitus (CFRD) is mainly as a result of insulin deficiency due to obstruction of the pancreatic ducts by thick viscous exocrine secretions, which leads to progressive damage to both the exocrine and endocrine tissue. Pulmonary decline correlates with the extent of glucose intolerance [3], but it can be reversed to a significant degree if CFRD is diagnosed and treated early with insulin [5]. As life expectancy increases, the prevalence of CFRD is also rising. Nevertheless, both the screening for altered glucose metabolism and the preferred therapeutic approach are still controversial [2, 6]. Cost, time and resources necessary for a suitable test compete with its ability to predict future diabetes followed by therapeutic consequences.

In 1997, the American Diabetes Association (ADA) recommended the use of a fasting venous plasma glucose (FPG) test for diagnosing diabetes mellitus [7]. At the end of 2003, the ADA lowered the cut-off point separating normal from elevated FPG from $<$6.1 mmol·L^{-1} to $<$5.6 mmol·L^{-1}) [8]. Since individuals with elevated FPG are more likely to also have a diabetic 2-h plasma glucose value, these patients should then receive an oral glucose tolerance test (OGTT) to exclude the presence of diabetes [8]. Elevated FPG levels that were not within the diabetic range were referred to as ''impaired fasting glucose'' (IFG) [8].

However, in patients with CF, glucose intolerance develops gradually because of the pathological mechanism of FPG staying normal for a long period of time. To screen for CFRD, an

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annual OGTT starting at age 10 yrs is therefore recommended [4] and widely accepted, at least in Europe. Neither clinical signs [2, 4, 9] nor haemoglobin A1c [4, 6, 9] alone have proven to be reliable in the early diagnosis of CFRD. An approach using a combination of clinical signs, FPG and HbA1C was tested only in a small cohort [6]. However, that study aimed to compare different markers of disturbed glucose metabolism and not to identify CFRD as early as possible [6]. To answer the question of how many patients with impaired glucose regulation would remain undiagnosed and, therefore, untreated when using the OGTT only in patients with IFG based on the new ADA criteria, the current authors evaluated the data from an ongoing two-step prospective randomised multi-centre study on patients with CF. Patients who were identified as diabetic by an annual screening programme were asked to take part over a 2-yr period in a randomised prospective intervention study on either an oral antidiabetic drug (repaglinide) or on insulin, in order to compare the effect on glucose metabolism and clinical status.

METHODS

In patients with CF aged ⩾10 yrs, an annual OGTT following standard World Health Organization (WHO) [10] recommendations was conducted as a screening test in order to identify CFRD. Criteria for IFG are responding to the former ADA criteria for elevated FPG [7]. IFG was diagnosed using a ~10% lower level for whole blood testing compared with plasma testing according to WHO [10], who have published comparative values for diagnosis of diabetes and other categories of hyperglycaemia for whole blood and plasma. The OGTTs were performed during clinical stable conditions, including no actual changes in corticosteroid dose. The study was approved by the local ethics committees.

RESULTS

A total of 1,128 OGTTs from 1,128 patients (53% males; 47% females; median (range) age 17.1 yrs (10–64)) were available for analysis. According to WHO [10] criteria, 786 (69.7%) OGTTs displayed normal glucose tolerance (NGT), 72 (6.4%) IFG, and 169 (15.0%) impaired glucose tolerance (IGT). In total, 101 (8.9%) were classified as diabetic. Implementing the new (old) ADA criteria, 716 (968) patients were classified as having a fasting glucose within normal, 363 (111) IFG, and 49(49) within the diabetic range. Using the new ADA criteria, which suggested performing an OGTT only in patients with IFG, the percentage of required OGTTs would be reduced to 33% (fig. 1a); however, 17.8% of diabetic OGTTs that showed normal fasting glucose levels would have been missed (fig. 1b) compared with 35% using the old ADA criteria. Using the new ADA criteria for IFG, the sensitivity and specificity were 82% and 70%, respectively, compared with 65% and 94% when using the former ADA criteria. Overall, 82 patients (7.3%) were on oral corticosteroids. This is close to the data reported from an European CF registry [11]. There was no difference in sensitivity and specificity comparing the cohorts including *versus* excluding patients on oral corticosteroids (data not shown).

DISCUSSION

By using the results of a large number of patients with systematic screening for CFRD by annual OGTTs, the sensitivity and specificity of the new ADA criteria to perform an OGTT to detect CFRD could be reliably calculated. The results indicated that only 33% of OGTTs would be performed using the new ADA criteria. This would reduce the burden to patients and the need for resources in the CF centres. However, is this a relevant alleviation? OGTTs need only two blood samples (fasting and after 2 h). This must be compared with the many other diagnostic or therapeutic procedures that are performed in CF patients. The ''burden'' of these two blood samples is outweighed tremendously by the possible benefit [5, 12] of early diagnosis and treatment of CFRD. Nevertheless, even in the actual guidelines for CFRD in the USA, an annual OGTT starting at the age of 14 yrs is not mandatory, with the suggestion to ''consider it strongly only in patients with symptoms of diabetes'' [13]. Conversely, even in spite of a lower cut-off point for IFG, an unacceptable high percentage (17.8%) of patients with diabetic OGTT results would be missed by not performing OGTT as an annual screening procedure. Otherwise, the CFRD in these patients would be undetected and, therefore, these patients would remain untreated, resulting in a yet further decline in pulmonary function [5]. It is important to remember that a single diabetic OGTT result by itself is not diagnostic for CFRD, but it is an

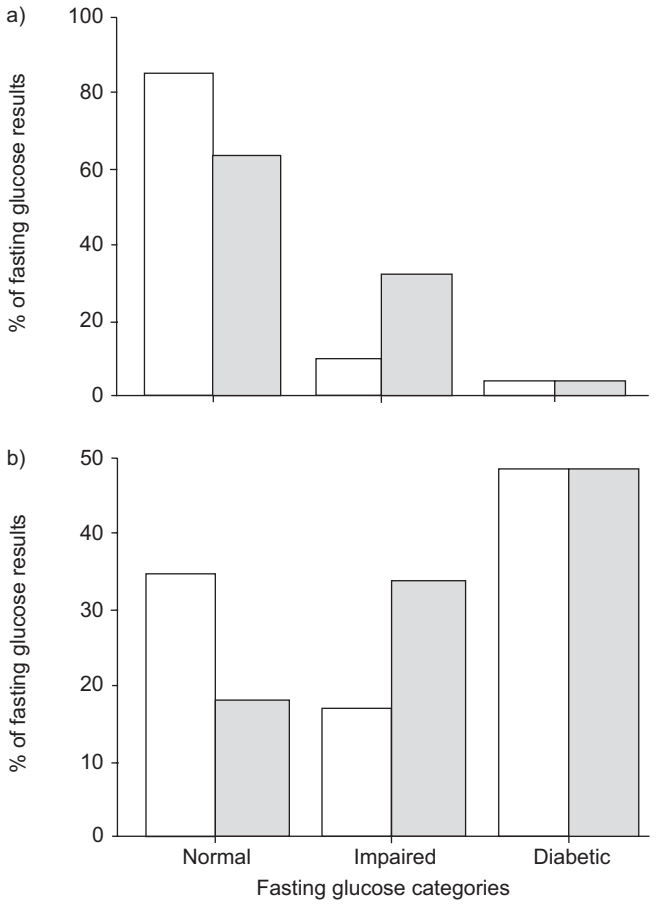

FIGURE 1. Changes in the percentage of fasting glucose categories using old (□) and new (■) American Diabetes Association criteria are shown for all oral glucose tolerance tests (OGTTs; a) and for those OGTTs that were diabetic (b) according to World Health Organization definitions.

initial step in order to diagnose CFRD. By definition, it needs at least two separate measures of glycaemic disturbance on separate days before the clinical diagnosis of CFRD can be made in this group of patients mainly displaying no acute symptoms of diabetes [10, 13]. In a non-CF population screened by OGTT for type-2 diabetes 1 yr after the initial diabetic OGTT, a second OGTT returned to nondiabetic in 47% of the subjects [14]. In a CF population with an annual OGTT screening programme, only 10 out of 15 patients who were diabetic in the annual OGTT were also diabetic in a repeated OGTT [15]. Recently, the current authors reported confirmation of a diabetic result in an annual OGTT as part of the present screening programme in 34 out of 73 (47%) patients [16]. In an attempt to overcome the burden of annual systematic OGTT to the patients and the impression that OGTT is time and resource consuming, FPG was evaluated in some earlier studies [4, 6]. At that time, the cut-off for elevated FPG was 7.8 $mmol \cdot L^{-1}$. Only four out of 25 patients with newly diagnosed CFRD had elevated FPG in a study of children and adults with systematic annual screening for CFRD using OGTT in a CF centre [4]. Using the same criteria in an adult cohort of CF patients, a sensitivity of only 25% for FPG to detect CFRD was reported [6]. Different to other types of diabetes mellitus [8], the course of glucose disturbance in CF is often insidious in its onset and is described by a continuum from NGT to severe glucose intolerance. This might contribute to the lower reliability of FPG in detecting diabetes mellitus in CF compared with other types of diabetes.

There is no general consensus about when to start the treatment of CFRD. In the USA, a consensus report recommended treatment with insulin only if fasting hyperglycaemia is present [13]. In Europe, treatment of CFRD that is independent of FPG is recommended by most centres [5, 12, 17]. Since data show that if patients who are diagnosed early with CFRD do profit from insulin therapy regarding their pulmonary function [5, 12], as well as their nutritional status [12, 17], one should screen for CFRD *via* OGTT and commence treatment after confirmation of the diabetes at the latest. In this report, the current authors focused on new criteria for IFG and the diagnosis of CFRD. Nevertheless, IGT needs also to be considered. It is known to be accompanied by a more rapid decline in pulmonary function compared with NGT in patients with CF [3]. In noninsulin-dependent diabetes, IGT is a risk factor for developing diabetes in the near future, but, for a single patient with CF, IGT is not a reliable predictor of diabetes [4].

In conclusion, if the diagnostic aim is to identify patients with cystic fibrosis-related diabetes mellitus early in order to start treatment immediately to improve clinical status, the American Diabetes Association approach of using impaired fasting glucose as an indication for performing selective oral glucose tolerance tests is unsuitable in the cystic fibrosis population, and it cannot replace an annual oral glucose tolerance test as a screening test for cystic fibrosis-related diabetes mellitus.

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