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COMMENTS AND RESPONSES

Response to Allen et al. and Holl et al.

I read with interest the recent article by Allen et al. and the letter by Holl et al. regarding the diagnosis of cystic fibrosis–related diabetes (CFRD) (1,2). CFRD has become increasingly common as cystic fibrosis (CF) patients survive longer. CFRD has distinctive clinical and pathological features compared with type 1 and type 2 diabetes (3), and this condition should be considered as a separate clinical entity. Allen et al. found that random blood glucose (RBG) was the most common method used in the diagnosis of CFRD in the centers studied. It is important to note that RBG has not been found to be sufficiently sensitive or specific in the diagnosis of CFRD. My colleagues and I had previously reported that even in CF patients with normal glucose tolerance, as defined by an oral glucose tolerance test (OGTT), the RBG can exceed 180 mg/dl, provided that a large enough glucose load is taken before blood sampling (4). This finding may be related to a more rapid gut absorption of glucose in patients with CF. Lanng et al. had also reported that whereas OGTT is the "gold standard" diagnostic method in the diagnosis of CFRD, fasting blood glucose and glycosylated hemoglobin are not sufficiently sensitive in the diagnosis of CFRD (5).

Between August 1996 and May 1997, 91 clinically stable adult CF patients (aged ≥16 years) who were not known to be diabetic and who were attending the adult CF clinic at the Royal Brompton Hospital in London (a national CF center) underwent OGTTs according to the standard protocol (6). All patients had RBG measured within 1 month before their OGTTs. The mean age of the studied patients was 27 years (range, 16–60), and the ratio of male to female subjects was 58:33. Of the 91 patients studied, 12 were found to have OGTT-defined diabetes; of these 12 patients, 3 had abnormal fasting blood glucose (>110 mg/dl) and 4 had abnormal RBG (>180 mg/dl). Thus, the sensitivities of the above-mentioned two methods in the diagnosis of CFRD (using OGTT as the "gold standard") were found to be only 25% (95% CI, 1–50) and 33% (7–60), respectively. These data confirm the point made by Holl et al. that OGTTs should be used in preference to other methods in the diagnosis of CFRD. Because there is evidence that the development of CFRD may be associated with a deterioration in patients' clinical status that may be reversed by prompt treatment (7), CF patients should be screened for diabetes regularly using OGTTs.

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Response to Yung

Should the oral glucose tolerance test be performed as a routine screening test for diabetes in cystic fibrosis patients?

Dr. Yung makes several valid and important points regarding screening for cystic fibrosis–related diabetes (CFRD). The purpose of our study surveying physicians' attitudes and practices for patients with CFRD was not to imply that these attitudes or practices are correct or well informed, but simply to report that this is what the U.S. physicians surveyed are doing. Dr. Yung's observation that random blood glucose (RBG) correlates poorly with glucose tolerance testing in adult British cystic fibrosis (CF) patients is important because there is no literature on the sensitivity or specificity of RBG or urine glucose measurements. Poor correlations between fasting blood glucose or HbA_{1c} and the oral glucose tolerance test (OGTT) have been described by several investigators (1–5), but not by all (6,7). Lanng et al. (3) found in a prospective study that only 16% of CF patients had abnormal elevations of HbA_{1c} on the day of a diabetic glucose response to the OGTT.

If CFRD is defined as diabetic glucose response to OGTT, then by definition the OGTT is 100% sensitive and specific for the diagnosis of CFRD. Defining diabetes in the general population has proved to be a challenge, and recently an Expert Committee on the Diagnosis and Classification has revised blood glucose criteria and de-emphasized the OGTT (8). It is not known whether these criteria are appropriate for the CF population. A factor that is important in determining a meaningful definition of diabetes in any population is whether identification of the disease allows for an intervention that improves outcome. Although some investigators describe a deterioration in clinical status that occurs

before the development of overt diabetes (9) (presumably during a period of decreasing glucose tolerance), others have not found such an association between clinical status and deteriorating glucose tolerance (1,10). One can speculate on the number of ways in which insulinopenia, before causing overt symptoms of hyperglycemia, might be detrimental to CF patients (increased protein catabolism, intermittent glucosuria, altered immune function). Yet, to date, there is no reported evidence that treatment of asymptomatic CF patients with normal fasting glucose levels and a diabetic response to OGTT improves clinical status or delays the onset of overt diabetes.

In February 1998, a Cystic Fibrosis Foundation consensus conference recommended screening with random glucose levels, with follow-up of abnormal random glucose levels (≥126 mg/dl) by fasting glucose level. A confirmed elevated fasting glucose level (≥126 mg/dl) is diagnostic for CFRD. The OGTT is reserved for patients participating in research or for those in high-risk circumstances (unexplained polyuria or polydipsia, failure to gain or maintain weight, delayed puberty, or unexplained chronic decline in pulmonary function).

Our study revealed that screening for glucose abnormalities in CF patients is erratic and is performed using a variety of methods, but that only a handful of CF practices in the U.S. are performing OGTTs. It is hoped that this discussion, in conjunction with the new consensus conference guidelines, will raise the level of consciousness about disorders of carbohydrate metabolism in CF patients and standardize our approach to these problems. Before recommending that all adult CF patients have annual OGTTs, we must have solid evidence that a worthwhile intervention is available to those who have abnormal results.

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Glycemic Control in Type 1 Diabetes

A cross-sectional study in 1,200 Belgian patients

We read with interest the recent article by Rosilio et al. (1) reporting an HbA_{1c} value of 8.97 ± 1.98% (mean ± SD) in a French population of 2,579 patients with type 1 diabetes aged 1–19 years. Approximately 33% of their cohort had HbA_{1c} <8%, whereas 14.5% had values >11%. Rosilio et al. conclude that these overall results are unsatisfactory, since they will expose a majority of these young patients to developing microangiopathic complications.

We analyzed, in a cross-sectional survey, the clinical characteristics of a cohort of 1,200 insulin-treated Belgian patients attending our University Diabetes Center, consisting mostly (>80%) of subjects with type 1 diabetes (2,3). As in the study of Rosilio et al., the Belgian Health Service offers near total coverage of diabetes care. Patients were followed on an outpatient basis (1–4 visits/year). None had participated in interventional trials aimed at improved glucose control. Their mean age was 43 ± 19 years, with 9% of the subjects being <18 years old. Respectively 51, 22, and 23% of patients were treated with two (2ii), three (3ii), or four (4ii) daily insulin injections; continuous subcutaneous insulin infusion (CSII) was used in 4%.

In this mostly adult population, we observed a level of glycemic control, as assessed by HbA_{1c}, similar to that reported by Rosilio et al. in their pediatric cohort. Thus, HbA_{1c} was 8.63 ± 1.55% (8.54 ± 1.46% in male subjects and 8.72 ± 1.62% in female subjects). It is remarkable that this overall value of HbA_{1c} was identical to that recorded in France in the subgroup of patients followed by Rosilio et al. in university-affiliated hospitals. We found that 36 (2ii), 31 (3ii), 38 (2ii), and 21% (CSII group) had an HbA_{1c} <8%, a proportion comparable to that reported by these authors (33%). As far as home blood glucose monitoring was concerned, the mean strip consumption in our Belgian cohort was 2.2 per subject per day (vs. 2.8 in the French study). We observed no correlation between daily insulin injection number or strip consumption and HbA_{1c} levels.

In conclusion, in a mainly adult Belgian population with type 1 diabetes and free access to diabetes care, overall glycemic control, assessed by HbA_{1c} was comparable to that measured in a mostly pediatric French population.

Global HbA_{1c} levels in both studies were above the threshold suggested by the Diabetes Control and Complications Trial (DCCT) results and those of other studies (4,5), since only a third of patients in the Belgian and French cohorts could attain HbA_{1c} values <8% (i.e., below the realistic threshold beyond which there is a rapid increase in the likelihood of developing microangiopathy). Thus, both surveys