Identification and Treatment of Cystic Fibrosis–Related Diabetes

A survey of current medical practice in the U.S.

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OBJECTIVE — To describe physicians' attitudes and practices in screening for and treating abnormalities in glucose homeostasis in cystic fibrosis (CF) patients and to test the hypotheses that guidelines for screening for CF-related diabetes (CFRD) are not followed at most centers and that screening and treatment vary by the care provider's background.

RESEARCH DESIGN AND METHODS — This cross-sectional survey included three groups of physicians: *1*) 593 members of the Lawson Wilkins Pediatric Endocrine Society (LWPES), 2) 462 members of the pediatric assembly of the American Thoracic Society (ATS), and 3) 194 directors of cystic fibrosis centers (CFD). A mailed questionnaire was used for the survey.

RESULTS — The overall response rate was 67%. Of these, 224 LWPES, 143 ATS, and 135 CFD physicians reported actively seeing CF patients. About two-thirds of CF physicians (ATS and CFD) reported routine screening for impaired glucose tolerance (IGT) in asymptomatic CF patients; a random glucose is most often used (60%), followed by HbA_{1c} (50%), urine glucose (44%), fasting glucose (21%), and oral glucose tolerance test (2%). Only 40% of LWPES physicians reported intervening for stress-induced hyperglycemia, but 61% reported use of insulin for persistent IGT. Management of CFRD was similar for all groups; most physicians used insulin (91%). LWPES recommended more intensive glucose testing and nutritional guidelines than did ATS/CFD ($P < 0.0001$). LWPES reported less concern about risks of diabetes complications ($P < 0.0001$) and the importance of minimizing burdensome interventions ($P < 0.01$). All groups considered weight management a top priority.

CONCLUSIONS — Screening for IGT is not routinely done in CF patients and screening tests vary. Greater agreement exists on methods of treating patients with persistent IGT or CFRD, although goals and aggressiveness of treatment vary with the provider's background. A consensus conference is recommended.

Cystic fibrosis (CF) is the most common inherited life-threatening disease in the U.S., with a prevalence of ~1/2,000. It is characterized by progressive obstructive lung disease and by exocrine pancreatic insufficiency. The median survival of patients with CF has increased dramatically, from 14 years in 1969, to 21 years in 1978, to 28 years in 1990. Cystic fibrosis–related diabetes (CFRD) is a common complication of CF and a growing problem as survival of CF patients increases. Impaired glucose tolerance (IGT) occurs in 20–40% of adult patients with CF (1–3). IGT may be detrimental to the CF patient because of the catabolic effects of hypoinsulinemia and the loss of calories in the urine. CFRD occurs in 4–15% of patients with CF (1,4,5). It differs from both type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes in that it is characterized by insulinopenia, but ketoacidosis is extremely rare. It is unclear whether IGT or CFRD has a negative impact on life expectancy in patients with CF (5–8). Late complications of diabetes occur in patients with CFRD, but it is not known whether the risk is similar to that in type 1 diabetes (5,9–11).

Until 1990, there were no published guidelines for the identification of CFRD or for its treatment. In 1990, a consensus conference was convened by the Cystic Fibrosis Foundation (CFF) to develop such guidelines, which are summarized in Table 1 (12).

There is no literature on current practices to screen for or to manage IGT or CFRD. The purpose of this study was to describe present practices for identification and intervention in CFRD and to explore the differences in care and opinion among various care providers. The hypotheses were *1*) that published guidelines for screening for CFRD are not followed at most centers and 2) that the goals of therapy for CFRD vary, depending on the care provider's background.

RESEARCH DESIGN AND METHODS

— A five-page written questionnaire was mailed to three groups of physicians, chosen to include primary and referral physicians and some non–CF center physicians, and among whom a significant number care for patients with CFRD. The first group consisted of 593 pediatric endocrinologist members of the Lawson Wilkins Pediatric Endocrine Society (LWPES), listed in the 1994 directory. The second group was 462 physician members of the pediatric assembly of the American Thoracic Society (ATS), listed in the 1994 directory. The third group consisted of 194 directors of CF centers or satellite centers (CFD) whose names were provided by the CFF. Eighty-one physicians were both members of the pediatric assembly of the ATS and CF center directors; they were

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Abbreviations: ATS, American Thoracic Society; CF, cystic fibrosis; CFD, directors of cystic fibrosis centers; CFF, Cystic Fibrosis Foundation; CFRD, cystic fibrosis–related diabetes; IGT, impaired glucose tolerance; LWPES, Lawson Wilkins Pediatric Endocrine Society.

Table 1—*Summary of 1990 CFF Consensus Conference guidelines for CFRD*

Screening for glucose intolerance
Urinalysis 2–3 times per year
Fasting and 2-h postprandial blood glucose every 2–4 years during late childhood
Fasting and 2-h postprandial blood glucose every 2 years starting in mid-teenage years
HbA_{1c} not proven to be adequate except as a possible adjunct screening tool
Therapy
Short-term in patients who have multiple fasting blood glucose levels >140 mg/dl or 2-h postprandial blood glucose >180 mg/dl, usually during pulmonary infections, steroid therapy, or hyperalimentation
Continuous long term therapy if:
Diabetes is diagnosed based on standard criteria
2-h postprandial blood glucose is >180 mg/dl on multiple occasions in the absence of pulmonary exacerbation
Persistent IGT is associated with poor weight gain or increasing fatigue
Insulin is recommended for therapy. Oral hypoglycemics are insufficiently studied but may be useful for IGT.
Nutrition
Consistent timing of meals and snacks
Consistent quantity and quality of foods/nutrients
Easily available sucrose for treatment of hypoglycemia

Data in table is from Ref. 12.

included in the CFD group. Eligible physicians were identified as MDs with a U.S. address and were not listed as emeritus or associated with a pharmaceutical or medical product company.

Physicians who did not return a completed questionnaire in the stamped return envelope within 3 months received a second mailing. A telephone survey of a random sample of 65 nonresponders was made to assess reasons for no response.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, Chicago) and Epi Info (Centers for Disease Control and Prevention, Atlanta, GA) software. Contingency table methods were used for categorical descriptive variables. Outcome variables were divided into four groups: *1*) screening; 2) management of minor abnormalities of glucose tolerance; 3) management of CFRD; and 4) goals of management. Responses from each of the three groups were compared with the CFF guidelines. Comparative analysis of these variables was performed first by analyzing responses of ATS and CFD using contingency table methods. If responses between these groups did not significantly differ, the two groups were combined and compared with LWPES. Multiple logistic regression was used to describe the relative impact of variables that independently had a significant relationship ($P < 0.05$) to the primary outcome variables.

RESULTS — Survey responses were received from 71% of LWPES, 59% of ATS, and 73% of CFD physicians, yielding an overall response rate of 831/1,249 (67%). The response rate was significantly lower for ATS physicians than the other two groups ($P < 0.001$). Among the responders, about half of LWPES and ATS physicians and over 95% of CFD reported actively seeing CF patients in their practices. The 224 LWPES, 143 ATS, and 135 CFD respondents ($n = 502$) who reported actively seeing CF patients are included in these analyses.

To assess whether the physicians returning the surveys were a representative sample of these three groups, a telephone survey of a random sample of 122 physician nonresponders was performed. Extrapolating their responses to the entire group of nonresponders, we estimated that we received survey responses from 79% of LWPES, 70% of ATS, and 73% of CFD who actively care for CF patients.

The field of medical training of the LWPES and ATS groups was quite homogeneous, with 211 (94%) of LWPES reporting that their specialty was pediatric endocrinology and 130 (90%) of ATS reporting that they were pediatric pulmonologists. The specialties of CFD physicians were much more heterogeneous, with just over half reporting that they were pediatric pulmonologists and the remainder distributed among general pediatrics (14%), adult pulmonology (13%), internal medicine (6%), gastroenterology (4%), and others (7%). A majority of physicians in all three groups reported having an academic practice (88%) and a CFF affiliation.

Seventy-nine percent (220 of 278) of ATS/CFD physicians saw more than 30 CF patients per year and 65% saw more than 50. Responding CFD physicians had larger CF practices than ATS physicians, with 72% of CFD versus 59% of ATS seeing more than 50 CF patients per year ($P = 0.03$). LWPES physicians had fewer contacts with CF patients but saw numbers of patients with CFRD comparable to those seen by ATS/CFD physicians. Eighty-nine percent of LWPES physicians saw fewer than 10 CFRD patients per year; 82% of ATS/CFD saw fewer than 10. Only two LWPES physicians reported seeing more than 50.

Screening

Because IGT and CFRD screening is done primarily by CFD and ATS physicians, LWPES physicians were not included in this set of analyses (Table 2). Significantly more CFD than ATS physicians reported routine screening (76 vs. 64%, $P < 0.01$). Over 60% of these physicians initiated screening in CF patients under the age of 10 years. A number of different screening tests were reported. Random blood glucose was the most commonly used screening test; it was used by 66% of CFD and 55% of ATS physicians ($P = 0.04$). HbA_{1c} was also commonly used, and it was used yearly or more often by more CFD than ATS physicians (60 vs. 43%, $P = 0.004$). Urine glucose and fasting blood glucose, which are recommended in the 1990 CFF consensus guidelines, were used by <50% of the physicians who obtained screening tests, and use did not differ between ATS and CFD. The oral glucose tolerance test was very infrequently used as a screening tool, with only six physicians from the two groups reporting its use annually or more often in CF patients.

To assess the relative importance of affiliation with a CF center and the importance of practice size, academic practice, and field of medical training in predicting screening practice, we used contingency table methods with stratification and logistic regression analysis. We found that the size of the physician's CF practice was the best predictor of screening. Among CF center–affiliated physicians from the ATS or CFD group, the percentage who routinely

Table 2—*Reported screening for IGT or CFRD among members of ATS and CFD*

	ATS	CFD	*P* value
Routine screening	87 (64)	103 (76)	0.006
Age screening started (years)			
<10	57 (66)	63 (62)	
11–15	23 (26)	22 (21)	NS
16–20	6 (7)	14 (13)	
>20	1 (1)	4 (4)	
Screening test used yearly or more often			
Fasting blood glucose	27 (19)	31 (23)	NS
Random blood glucose	78 (55)	90 (66)	0.04
HbA_{1c}	61 (43)	81 (60)	0.004
Urine glucose	63 (44)	58 (43)	NS
Oral glucose tolerance test	4 (3)	2 (2)	NS

Data are *n* (% of physicians who responded to the question).

screened CF patients directly correlated with the size of their practice (Fig. 1). Non-CF center–affiliated physicians screened as often as CF center–affiliated physicians when adjustment was made for practice size. Logistic regression confirmed the primary importance of size of CF practice in predicting screening, and it accounted for the apparent relationship between CF center status and screening. Models that included practice size as an independent variable resulted in all other variables becoming nonsignificant (data not shown).

Management of minor abnormalities in glucose tolerance

Stress-induced hyperglycemia was defined as a fasting glucose >140 mg/dl during illness, with resolution when the patient is well. IGT was defined as a fasting glucose <140 mg/dl, with a random glucose >200 mg/dl, which is persistent even when the patient is well. This definition includes both impaired and diabetic glucose tolerance as defined by World Health Organization criteria using response to a standard oral glucose tolerance test (13). Because glucose tolerance tests are rarely performed, we wanted to include all patients with significant abnormalities in glucose metabolism, short of frank diabetes. More than half of the CF physicians reported that they had seen fewer than five patients with stress-induced hyperglycemia (57% of ATS, 61% of CFD) or CFRD (68% of ATS, 61% of CFD) in the past year. LWPES physicians similarly saw few patients with CF-related glucose homeostasis abnormalities, 86% saw fewer than five patients with stress-induced hyperglycemia, and 79% saw fewer than five patients with CFRD in the past year.

Because there were no significant differences between ATS and CFD in responses to any of the questions about stress-induced hyperglycemia or IGT, their responses were combined (Table 3). LWPES physicians were more likely to report intervention and more likely to use short-term insulin in patients with stress-induced hyperglycemia than were ATS/CFD physicians. Most physicians from all groups (88%) reported that they intervened when hyperglycemia is persistent, but LWPES physicians were more likely to use insulin to treat such patients.

Treatment of CFRD

CFRD was defined as persistent fasting hyperglycemia (glucose >140 mg/dl) (Table 4). Physicians were requested to respond to this section of the questionnaire only if they managed patients with CFDM (LWPES, *n* = 194; ATS, *n* = 39; CFD, *n* = 57; total, *n* = 290). There were no significant differences between the ATS and CFD physicians, so their responses were combined. The great majority of physicians reported primarily treating such patients with insulin (94% of LWPES, 86% of ATS/CFD). A small percentage of physicians reported using oral hypoglycemic agents alone (7% of LWPES, 12% of ATS/CFD) or oral agents with insulin (5% of LWPES, 10% of ATS/CFD). The intensity of therapy was assessed by questions about the number of injections per day and number of blood glucose tests per day, as well as the target range for blood glucose. Although there were no significant differences in the requested number of injections per day and in the target blood glucose range, LWPES physicians requested that patients perform more frequent blood glucose tests ($P < 0.0001$). Nutritional guidelines given to patients with CFRD by LWPES physicians were almost equally distributed: unchanged from other patients with CF (22%), no concentrated sweets (21%), carbohydrate counting (24%), exchange (26%), and other (7%). ATS/CFD physicians reported less use of carbohydrate counting (7%) and an exchange diet (14%) and more frequent recommendation of no concentrated sweets (51%); 19% recommended no changes from other CF patients. The recommendations of ATS/CFD were significantly different and less intensive than the recommendations of LWPES ($P < 0.0001$).

Management goals

Physicians were requested to rank the importance of six goals for management of the patient with CFRD on a Likert scale of

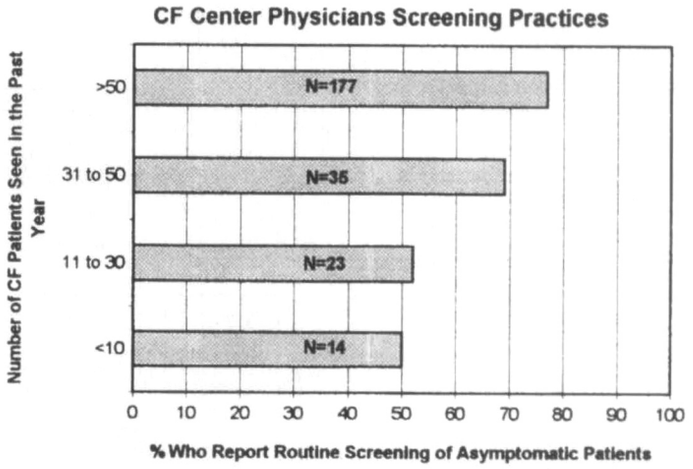

Figure 1—*CF center physicians' screening practices for IGT in CF patients.*

Table 3—*Reported treatment of patients with stress-induced hyperglycemia or persistent hyperglycemia*

	LWPES	ATS/CFD	*P* value
Patients with stress-induced hyperglycemia seen in past year	*n* = 211	*n* = 269	
0	56 (26)	36 (14)	
1–5	127 (60)	129 (50)	
6–10	24 (11)	65 (25)	<0.001
11–20	3 (1)	28 (11)	
>20	1	11 (4)	
Treatment of stress-induced hyperglycemia	*n* = 205	*n* = 275	
No intervention	122 (60)†	198 (72)	
Oral hypoglycemic agents	14 (7)	22 (8)	<0.001
Insulin	57 (28)§	33 (12)	
Diet	12 (6)	22 (8)	
Treatment of persistent hyperglycemia	*n* = 218	*n* = 277	
No intervention	27 (12)	32 (12)	
Oral hypoglycemic agents	45 (21)*	82 (29)	0.03
Insulin	133 (61%)‡	136 (49)	
Diet	13 (6)	27 (10)	

Data are *n* (%). The *P* values reflect the significance of an overall test of differences between LWPES and ATS/CFD physicians for each group of related responses. When the *P* value for a related group of responses was significant, each individual response was analyzed (*$P < 0.05$ vs. ATS/CFD; †$P < 0.01$ vs. ATS/CFD; ‡$P < 0.001$ vs. ATS/CFD; §$P < 0.0001$ vs. ATS/CFD).

1–5, with 1 being not important; 3, somewhat important, and 5, very important (Fig. 2). Weight maintenance or growth in the younger patient was very important for a majority of physicians in all groups. Reducing the number of infections, keeping the patient out of the hospital, and avoiding symptoms of hyperglycemia or hypoglycemia were less important than weight maintenance but were still ranked 4 or 5 by >80% of physicians. Reducing the risk of long-term complications of diabetes was less highly ranked than the above goals and was reported to be more important by ATS/CFD physicians than LWPES physicians ($P < 0.0001$). Minimizing burdensome interventions for patients was also ranked as significantly more important by ATS/CFD physicians than LWPES physicians ($P < 0.0001$).

CONCLUSIONS — The present study addressed the questions of whether physicians caring for CF patients follow published guidelines for screening and therapy and whether there are differences in the approaches to CF patients related to the care providers' background. We report that despite the presence of abnormalities of glucose homeostasis in a significant and increasing minority of CF patients, individual physicians care for small numbers of such patients. Treatment of CF patients with IGT and CFRD was generally consistent with CFF recommendations in all groups. Most physicians reported treating patients with CFRD with insulin, which is recommended by the CFF and appears rational because such patients are insulinopenic. A majority responded that they usually intervened with insulin therapy in patients with persistent IGT, especially when it is associated with poor weight gain or increasing fatigue. Most physicians reported that they did not intervene with short-term therapy in patients who had transient hyperglycemia associated with illness or use of steroids or hyperalimentation. The CFF Consensus Conference recommended that such short-term intervention "be considered." We conclude that most physicians report practices for treatment of abnormal glucose tolerance and CFRD that are in line with the CFF consensus guidelines.

Screening for glucose intolerance was the area in which physician responses differed most dramatically from CFF recommendations. Despite 1990 guidelines recommending routine screening, only about two-thirds of physicians reported screening for abnormalities in glucose homeostasis in asymptomatic patients. Screening was most frequently accomplished with random blood glucose measurements or HbA_{1c}. Very few physicians used an oral glucose tolerance test as a screening tool. A minority of physicians reported checking urine glucose yearly or more frequently in their patients, whereas it is recommended two to three times per year.

There are several possible sources of bias in this study. Response bias is present when the survey respondents differ from the nonrespondents in their answers to the

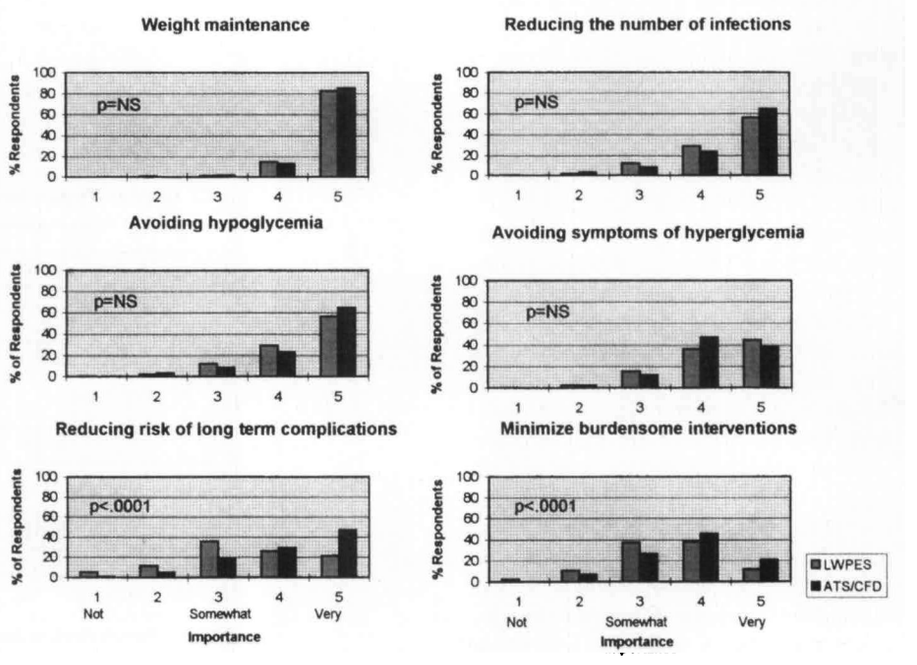

Figure 2—*Physicians' goals in the management of CFRD.*

survey questions. From a telephone survey of a random sample of nonresponders, we found that a majority of the physicians who did not respond do not see CF patients. It may be that responders are more interested in the topic of CF and its related glucose abnormalities than nonresponders and may be more aggressive in their screening practices and/or treatment of these problems. When practice patterns are based on self-report, there may be differences between what is done and what is reported to be done. One might speculate that respondents report more aggressive screening and/or treatment practices than are actually in place. In fact, there were a number of comments on the questionnaires that practices for CFRD would be reexamined, that connections with endocrinologists would be made, or that respondents did not feel that their practices were ideal. Because one of the goals of this survey was to provide a starting point for improvements in the care of these patients, such comments were welcomed, but they do support the possibility that reporting bias exists.

It was felt that asking if physicians were aware of the 1990 CFF recommendations might exacerbate reporting bias. Therefore, it was not possible to determine if physicians did not follow the guidelines because they were not aware of them or did not agree with them or because of some other reason.

It is unclear whether adherence to the 1990 CFF Consensus Conference guidelines reduces morbidity or mortality in CF. Screening is most valuable when there is an appropriate intervention in the event of an abnormal screening result. An intervention for CF patients with abnormal glucose tolerance has not been described. There is a pressing need for research directed at determining the best method of detecting CF patients with abnormal glucose homeostasis who might benefit from intervention and the impact of intervention in CF patients with intermittent or persistent IGT.

CF patients are cared for by a team, which often involves specialists in nutrition/gastroenterology and pulmonology. These patients have traditionally been seen primarily by pediatricians, but as their life expectancy increases, more are eventually seen by internists. Examining differences in perspectives and priorities of internists versus pediatricians who care for CF patients becomes increasingly important as this shift in care occurs. CF patients with IGT or diabetes also frequently receive care from pediatric endocrinologists. Specialists have differing perspectives and priorities. We have shown that pediatric endocrinologists tend to manage IGT and diabetes in CF patients more aggressively than ATS or CFD physicians. Compared with LWPES physicians, ATS/CFD physicians reported greater concern about minimizing burdensome interventions, as well as greater concern about reducing the risk of long-term complications of diabetes. Unfortunately, at the present time, reducing the risk of long-term complications and reducing the burden of diabetes management are mutually incompatible. One might speculate that pulmonologists are less aware of the literature correlating intensive diabetes management with improved control and long-term outcome. Pediatric endocrinologists may be less attuned than pulmonologists to the already cumbersome and demanding requirement for optimal management of CF patients. Pediatric endocrinologists may be less concerned about the long-term complications of diabetes because they are less aware of the remarkable increases in life expectancy that have occurred over the past 10 years in CF patients or of the risk of diabetic complications in CF patients.

Our results indicate that there is substantial variability in physician practices in screening for abnormalities in glucose homeostasis but more consensus on the treatment of IGT, intermittent or persistent CFRD and frank CFRD, although the intensity and the therapeutic goals vary, depending on the provider's background.

Table 4—*Management of CFRD*

	LWPES	ATS/CFD	*P* value
Patients seen in the past year			
0	19 (9)	32 (12)	
1–5	151 (70)	143 (53)	<0.001
6–10	32 (15)	51 (19)	
11–20	12 (6)	27 (11)	
>20	1 (<1)	18 (7)	
Number who manage diabetes	194 (90)	96 (35)	<0.00001
Therapy most often used			
Insulin	171 (93)	75 (85)	
Oral hypoglycemics	5 (3)	6 (7)	NS
Insulin and oral hypoglycemics	7 (5)	7 (8)	
Number of injections per day			
1	12 (6)	6 (6)	
2	156 (81)	85 (89)	NS
3	24 (12)	3 (3)	
≥4	1 (0.5)	2 (2)	
Number of blood glucose tests per day			
1	1 (0.5)	6 (6)	
2	57 (29)	50 (52)	<0.0001
3	60 (31)	25 (26)	
≥4	75 (39)	15 (16)	
Target blood glucose			
Less than that for patients with IDDM	18 (10)	5 (5)	
Equal to that for patients with IDDM	134 (71)	66 (70)	NS
Greater than that for patients with IDDM	38 (20)	24 (25)	
Sees nutritionist	186 (96)	91 (93)	NS
Nutritional guidelines			
Like other CF	42 (22)	18 (19)	
No concentrated sweets	40 (21)‡	48 (51)	<0.0001
Carbohydrate counting	46 (24)†	7 (7)	
Exchange	49 (26)*	13 (14)	
Other	13 (7)	7 (7)	

Data are *n* (% of physicians who responded to the question). The *P* values reflect the significance of an overall test of differences between LWPES and ATS/CFD physicians for each group of related responses. When the *P* value for a related group of responses was significant, each individual response was analyzed (*$P < 0.05$ vs. ATS/CFD; †$P < 0.001$ vs. ATS/CFD; ‡$P < 0.0001$ vs. ATS/CFD).

To provide more uniform and quality care for CF patients with abnormalities in glucose homeostasis, continued dissemination of information about these topics and increased communication among the team of providers are needed.

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