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Full length article:

Carbohydrate intake and insulin requirement in children, adolescents and young adults with cystic fibrosis-related diabetes: a multicenter comparison to type 1 diabetes.

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Non-standard abbreviations

BMI-SDS	Body mass index standard deviation score
BS	Body surface
EsKiMo	Eating Study as a KiGGS Module
HbA1c	Hemoglobin A1c
KiGGS	German Health Interview and Examination Survey for Children and Adolescents
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
CF	Cystic fibrosis
CFRD	Cystic fibrosis-related diabetes
INDET	Indeterminate glucose tolerance
NPH	Neutral Protamin Hagedorn

Conference presentation

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Abstract (250 words)

Background & aims: In cystic fibrosis-related diabetes (CFRD), energy needs differ from type 1 (T1D) or type 2 diabetes, and endogenous insulin secretion is not totally absent. We analyzed whether daily carbohydrate intake, its diurnal distribution and insulin requirement per 11 grams of carbohydrate differ between CFRD and T1D.

Methods: Anonymized data of 223 CFRD and 36,780 T1D patients aged 10-<30 years from the multicenter diabetes registry DPV were studied. Carbohydrate intake and insulin requirement were analyzed using multivariable regression modelling with adjustment for age and sex. Moreover, carbohydrate intake was compared to the respective recommendations (CFRD: energy intake 130% of general population with 45% carbohydrates; T1D: carbohydrate intake 50% of total energy).

Results: After demographic adjustment, carbohydrate intake (238±4 vs. 191±1 g/d, p<0.001) and meal-related insulin (0.52±0.02 vs. 0.47±0.004 IU/kg*d, p=0.001) were higher in CFRD, whereas basal insulin (0.27±0.01 vs. 0.38±0.004 IU/kg*d, p<0.001) and total insulin requirement per 11 grams of carbohydrate (1.15±0.06 vs. 1.70±0.01 IU/d, p<0.001) were lower compared to T1D. CFRD patients achieved 62% [Q_1;Q_3: 47;77] of recommended carbohydrate intake and T1D patients 60% [51;71] of age- and gender-specific recommended intake (p<0.001). CFRD and T1D patients had a carbohydrate intake below healthy peers (79% [58;100] and 62% [52;74], p<0.001). The circadian rhythm of insulin sensitivity persisted in CFRD and the diurnal distribution of carbohydrates was comparable between groups.

Conclusions: In pediatric and young adult patients, carbohydrate intake and insulin requirement differ clearly between CFRD and T1D. However, both CFRD and T1D patients seem to restrict carbohydrates.

75 **Keywords (max. 6):** cystic fibrosis, diabetes mellitus, dietary carbohydrates, insulin dose,
76 child, adolescent

1. Introduction

Previous studies indicated that cystic fibrosis-related diabetes (CFRD) is a separate clinical entity with different pathophysiology [1,2]. In CFRD, total pancreatic islet mass is reduced by 50% [3]. Hence, the loss of pancreatic ß-cell mass is incomplete and endogenous insulin secretion will not be totally absent in CFRD [3], even though a very low endogenous insulin secretion was recently reported also in type 1 diabetes (T1D) [4]. Furthermore, due to the underlying illness, nutritional needs in CFRD differ from other types of diabetes. Patients with T1D or type 2 diabetes (T2D) are often advised to eat a low-fat, low-salt, and in case of overweight or obesity an energy-reduced diet. By contrast, in CFRD, energy needs are increased due to infections, increased work of breathing and other factors related to cystic fibrosis (CF). In parallel, energy uptake is decreased due to malabsorption, loss of appetite and gastrointestinal problems. Depending on individual nutritional status, CF patients are therefore advised to consume a very high-calorie diet with 120-150% of daily recommended energy intake for age and sex [5-7]. The German CF guidelines recommend a high-fat, high-fiber diet providing up to 130% of daily energy intake based on the reference values from the German, Austrian and Swiss Nutrition Societies [8]. However, international guidelines do not agree with this dietary intervention and do not recommend a high-fiber diet in order to not compromise energy intake in CFRD [5,6]. Contrary to T1D or T2D, no restriction on type of carbohydrates (e.g. low glycemic index or high-fiber content) exists in CFRD [5,6]. Artificial sweeteners should be avoided as they provide no calories [5]. According to international guidelines, nutritional CF recommendations are not changed by an additional diagnosis of diabetes [5]. In CFRD, insulin therapy has to be adjusted to carbohydrate intake and not vice versa [7]. Due to conflicts between nutritional recommendations for CF and for diabetes, dietary counseling for CFRD is challenging. Overall, studies on nutrition in CFRD are scarce and no randomized controlled trials on dietary interventions exist. Thus, detailed nutritional

guidelines are lacking and current dietary recommendations for CFRD have low levels of evidence.

Based on the pathophysiological and nutritional differences, we hypothesized that total carbohydrate intake, its diurnal distribution and insulin requirement per 11 grams of carbohydrate differ between CFRD and T1D. Furthermore, we compared carbohydrate intake in CFRD and in T1D patients with the respective recommendations and with healthy peers.

2. Materials and methods

2.1. Ethics statement

The DPV initiative has been approved by the local ethical committee of the University of Ulm, Germany and anonymized data collection by the local review boards of each participating center.

2.2. Diabetes patient registry DPV

Anonymized data from the multicenter, standardized, prospective German/Austrian diabetes registry, DPV, were analyzed (www.d-p-v.eu). Since 1995, specialized diabetes care centers enter demographics and clinical data of diabetes patients regularly in an electronic health record system. Every 6 months, locally documented data are transmitted anonymously to Ulm University for central analyses and quality assurance [1,2,9]. Implausible entries are reported back to centers. All valid data are aggregated into a cumulative database. At the end of 2013, the registry comprised plausible data on 323,745 diabetes patients from 404 specialized diabetes clinics in Germany and Austria.

For the present study, patients aged 10-<30 years with either CFRD or T1D and with age at diabetes onset >6 months were included. In patients aged ≤6 months at diabetes onset, non-T1D was assumed. In patients <10 years of age, CFRD is rare. Further inclusion criteria are

given in Fig. 1. A diagnosis of CFRD or T1D was made by clinicians based on current guidelines [5,10]. The final study population comprised 37,003 insulin-treated patients from 374 diabetes care centers. 36,780 patients were diagnosed with T1D and 223 patients had CFRD. For each patient included, the most recent year of care was evaluated. Multiple datasets per year were aggregated.

2.3. Demographic and clinical characteristics

Contemporary national reference data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) was applied to compute body mass index standard deviation score (BMI-SDS) [11]. For subjects aged >18 years, coefficients were extrapolated. Patient's body surface (BS) was estimated using the formula from Du Bois and Du Bois [12].

Based on local reference ranges, hemoglobin A1c (HbA1c) was mathematically standardized to the Diabetes Control and Complication Trial (4.05-6.05%) using the multiple of the mean method.

For this analysis on meal-related insulin requirement, meal-related insulin was specified as rapid-acting insulin analogue or regular insulin. Type of basal insulin was classified as long-acting insulin analogue, intermediate-acting insulin (NPH/zinc insulin) and no basal insulin. The number of insulin injections was defined as number of injection time-points per day.

Severe hypoglycemia, hypoglycemia with coma, microalbuminuria and retinopathy were defined as described in reference [13].

2.4. Carbohydrate intake

In the two countries of the present analysis, diabetes patients and their parents learn how to count carbohydrates in diabetes education programs. 10-12 grams of carbohydrate equal one

carbohydrate unit in Germany and Austria. For this study, 1 carbohydrate unit was calculated as 11g carbohydrates. Reported carbohydrate intake per day and per meal were analyzed. Daily frequency of carbohydrate-containing meals was studied.

Total daily carbohydrate intake was compared to the respective age- and gender-specific recommendations. In T1D, a carbohydrate intake of 50% of total daily energy intake based on reference values of the German, Austrian and Swiss Nutrition Societies is recommended, as described previously [14,15]. In CFRD, an energy intake between 120-150% of daily recommended intake for age and sex is advised and carbohydrates should be 45-50% of total energy [5-7]. For this analysis, 130% of daily energy intake based on general recommendations [14] was used and carbohydrates should be 45% of total energy.

To compare carbohydrate intake with healthy peers, national reference data from the Eating Study as a KiGGS Module (EsKiMo) was used for subjects aged 10-<18 years and from the Second German National Nutrition survey for subjects aged 18-<30 years [16,17].

2.5. Statistical analysis

All statistics were carried out with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics are given as median with quartiles for continuous variables and as percentage for dichotomous variables. For group comparisons of continuous parameters Kruskal-Wallis test was used. χ^2-test was applied for dichotomous parameters.

To compare carbohydrate intake, meal frequency, insulin requirement and the use of insulin types between CFRD and T1D, hierarchic multivariable regression modelling was applied in order to adjust for potential confounding effects (age, gender). Treatment center was entered as random factor in each model (Cholesky covariance structure). For continuous parameters linear regression was used and for dichotomous parameters logistic regression. In linear regression, parameters were estimated using residual maximum likelihood technique and in

logistic regression maximum likelihood. Between-within method was applied to calculate denominator degrees of freedom. The confounder 'age' was categorized as 10.0-<16.2 years, 16.2-<18.3 years, 18.3-<22.0 years and 22.0-<30.0 years. Median age with lower and upper quartile of CFRD patients was used as cut-offs in order to achieve comparable numbers of CFRD patients per age group. Sensitivity analyses were performed: all models were additionally adjusted for BMI-SDS, except the models for insulin dose per kg body weight or per square meter BS. Based on observed marginal frequencies of gender ratio and age category, adjusted estimates (mean±SE, proportions) were calculated. A two-sided p-value <0.05 was considered significant.

3. Results

Baseline characteristics of CFRD and T1D are presented in Table 1 for all patients and for both genders separately. In CFRD, a female preponderance was observed compared to T1D ($p<0.001$). Independent of gender, CFRD patients were older, had a shorter duration of diabetes and a lower BMI, BMI-SDS and HbA1c (all $p<0.001$). The proportion of patients with migration background did not differ significantly between groups.

CFRD patients included in the study were on average three years younger than CFRD patients excluded due to missing information on total carbohydrate or body weight (Fig. 1, n=62) ($p=0.002$). By contrast, diabetes duration, BMI-SDS, HbA1c, occurrence of microalbuminuria or retinopathy and frequency of severe hypoglycemia or hypoglycemia with coma did not differ significantly. T1D patients included in the study were younger, had a shorter duration of diabetes and a lower HbA1c compared to T1D patients excluded due to missing data (Fig. 1, n=2,441) (all $p<0.05$). As suspected the occurrence of microalbuminuria or retinopathy was less common in the younger included T1D patients ($p<0.001$), whereas

BMI-SDS and the frequency of severe hypoglycemia or hypoglycemia with coma were comparable to the older excluded patients.

3.1 Carbohydrate intake

In CFRD, total daily carbohydrate intake was higher (238.2±3.6 vs. 191.1±1.0 g/d, $p<0.001$) and compared to T1D, patients consumed more carbohydrates at each time-point during the day (Fig. 2) (after adjustment for age and sex). Furthermore, the percentage of carbohydrates delivered by snacks was significantly higher in CFRD than T1D (23.6 vs. 21.2% of total carbohydrates, $p=0.005$). By contrast, the daily number of carbohydrate-containing meals (3.63±0.15 vs. 3.60±0.06 meals/day, $p=0.820$) and the distribution of carbohydrates throughout the day (Fig. 2) were comparable between groups. All findings persisted after additional adjustment for BMI-SDS, except the significant differences for carbohydrate intake at first snack and for percentage of carbohydrates delivered by snacks.

Even though recommendations for energy and carbohydrate intake differ between CFRD and T1D, neither CFRD nor T1D patients achieved the respective recommended age- and gender-specific amount of carbohydrates (median [quartiles] CFRD vs. T1D: 61.7% [47.3;77.1] vs. 60.1% [50.5;71.3] of recommended values for CFRD/T1D). However, in CFRD, achievement of the respective recommendation was better than in T1D ($p<0.001$). With increasing age, a progressive fall of carbohydrate intake below recommendations was present in T1D, whereas in CFRD no trend with age could be observed. The respective value for T1D in the age groups 10.0-<16.2 years, 16.2-<18.3 years, 18.3-<22.0 years and 22.0-<30.0 years was 64.1% [54.9;74.6], 55.9% [46.9;64.9], 55.3% [46.6;66.1] and 52.6% [45.1;60.1], and for CFRD 61.0% [48.9;75.3], 55.1% [43.2;74.0], 66.8% [48.8;77.1] and 63.7% [49.1;77.1].

In CFRD, carbohydrate intake was closer to healthy peers than in T1D ($p<0.001$). CFRD patients had an average carbohydrate intake of 79.2% [57.5;100.4] of healthy peers and T1D patients of 61.5% [51.9;73.9].

3.2 Insulin requirement

In CFRD, insulin requirement per 11 grams of carbohydrate in total (1.15±0.06 vs. 1.70±0.01 IU/d, $p<0.001$) and at each time-point during the day (Fig. 3) was lower compared to T1D (after adjustment for age and sex). Furthermore, the reported total or basal insulin doses per kg body weight or per square meter BS, the basal number of insulin injections and the use of long-acting insulin analogues were also lower in CFRD (Table 2). Some patients with CFRD did not use basal insulin, whereas in T1D all patients had basal insulin therapy (Table 2). Meal-related insulin dose per kg body weight was significantly higher in CFRD, while no difference could be observed per square meter BS (Table 2). Insulin dose per square meter BS was additionally calculated because underweight is often present in CFRD and we assume that square meter BS might be a better reference basis for insulin dose than kilogram body weight. Number of total or meal-related insulin injections and the use of rapid-acting insulin analogues or regular insulin or intermediate-acting insulin were comparable between groups (Table 2). The circadian rhythm of insulin sensitivity persisted in CFRD (Fig. 3): reported insulin requirement per 11 grams of carbohydrate was highest in the morning, lowest at noon and in the evening somewhat higher than at noon. All findings remained significant after additional adjustment for BMI-SDS. Insulin doses per kg body weight or per square meter BS were not additionally adjusted for BMI-SDS.

4. Discussion

Our analysis indicated that despite the additional diagnosis of diabetes, carbohydrate intake in CFRD is higher than in T1D in order to meet energy requirement. In CFRD, all meals and snacks contained a higher amount of carbohydrates compared to T1D. In the latest Australian clinical practice guidelines for CFRD, a high-calorie, carbohydrate-rich diet is advised [18]. Total carbohydrate intake should not be restricted [19]. Many CF patients with diabetes consume several sugar-rich snacks and beverages additionally to regular meals in order to increase energy intake [20]. Restricting refined sugars in CFRD may result in a reduction of total caloric intake. The UK Cystic Fibrosis Trust recommends consumption of simple carbohydrates together with other foods or directly after meals [7].

Due to varying appetite and gastrointestinal problems in CF, we hypothesized that patients with CFRD have smaller meals than patients with T1D, but a higher meal frequency to reach energy needs. However, daily number of carbohydrate-containing meals was comparable between groups. Compared to the routine dietary therapy suggested by Wilson et al. [19], our CFRD patients did not reach the daily frequency of 6 meals (3 main meals, 3 snacks). One reason might be the additional consumption of fat-rich snacks that could not be considered in our analysis. Moreover, patients with CFRD may skip meals due to less appetite or gastrointestinal problems [20]. As in other types of diabetes [21], there is no general recommendation on the optimal frequency of carbohydrate-containing meals in CFRD. In case of suboptimal metabolic control, distribution of carbohydrates throughout the day might be beneficial [18].

The trend towards a higher percentage of carbohydrates delivered by snacks in CFRD leads to the hypothesis that more carbohydrates are shifted from main meals to snacks than in T1D, as otherwise it might be difficult for CFRD patients to achieve the high-calorie intake.

Compared to the respective recommendations and to healthy peers, CFRD and T1D patients revealed a lower carbohydrate intake. For T1D, this supports previous reports [15,22,23]. In 136 pancreatic-insufficient Scandinavian CF patients, carbohydrate intake was marginally below the Nordic Nutrition Recommendations [24]. However, patients with CFRD revealed a higher energy intake from fat and a lower energy intake from carbohydrates than non-diabetic CF patients [24]. As suggested by our findings, carbohydrates seem to be restricted in patients with diabetes. In CFRD, this might be due to avoidance of additional insulin doses and insulin injections. However, an adequate amount of carbohydrates, especially during puberty, is essential to achieve energy needs, and with this optimal growth and weight gain. In the diet of CFRD patients, carbohydrates should be liberalized and patients should be trained sufficiently in carbohydrate counting. The progressive fall of carbohydrate intake below recommendations in our pediatric and young adult T1D patients confirms previous findings [15]. In CFRD patients aged 16.2 to <18.3 years, the low carbohydrate intake may indicate underestimation of carbohydrate requirement during puberty.

In addition, our study demonstrated a lower total insulin requirement in CFRD compared to T1D. A feasible explanation is the incomplete destruction of pancreatic ß-cell mass in CFRD [3]. Contrary to most previous studies in T1D, endogenous insulin secretion is therefore not totally absent in CFRD. A recent study on 155 insulin-treated CFRD patients indicated low doses of insulin and concluded that exogenous insulin requirement is moderate in CFRD due to the presence of endogenous insulin secretion [25]. A circadian variation in insulin requirement was already reported for T1D [26] and persisted in CFRD.

The most logical explanation for the higher meal-related insulin dose per kg body weight in CFRD compared to T1D is the larger amount of carbohydrate intake in CFRD. Moreover, a complex interaction of other factors may influence insulin requirement. In CFRD, insulin

deficiency is the hallmark. However, varying degrees of insulin resistance during acute and chronic illness are also present in CFRD and are more pronounced and more common compared to T1D. In addition, a typical observation during an oral glucose tolerance test in CFRD is the elevation of one hour blood glucose values, whereas fasting and two hour blood glucose values are normal [27,28]. This phenomenon is known as indeterminate glucose tolerance (INDET). A further aspect in patients with an early stage of CFRD is the frequent elevation of postprandial glucose values, whereas fasting and pre-meal blood glucose values are normal. As in early stages of T2D, injections of short-acting insulin analogues prior to main meals (supplementary insulin therapy) might be a possible treatment option for these patients. The residual endogenous insulin secretion in CFRD is likely responsible for the low basal insulin dose.

In CFRD, the lower number of basal and the comparable number of meal-related insulin injections compared to T1D further confirm the assumption that patients with CFRD require predominantly meal-related insulin supplementation and - due to the residual endogenous insulin secretion - less basal insulin.

A possible explanation for the more frequent use of long-acting insulin analogues in T1D compared to CFRD is that CFRD patients secrete more endogenous insulin and are often not treated with any basal insulin in early stage of CFRD. In our study, 27.2% of CFRD patients were on no basal insulin, whereas in T1D all patients received basal insulin therapy. As patients with nocturnal tube feeding were excluded, this could not bias the use of long-acting insulin analogues in patients with CFRD.

Major strengths of our study are the multicenter nature and the large number of patients included. To our best knowledge, this is the first study analyzing carbohydrate intake and insulin requirement per 11 grams of carbohydrate in such a large number of CFRD patients

(n=223). One limitation is the evaluation of carbohydrate intake on the basis of carbohydrate units reported by patients or their parents. Thereby, carbohydrates delivered e.g. by fiber could not be considered. Moreover, only carbohydrate-containing meals could be used to analyze meal frequency. Patients with tube feeding were excluded from the analysis. As tube feeding is often present in older CF patients this might bias total energy intake as well as carbohydrate intake. The exclusion of some eligible patients due to missing data on carbohydrate intake or body weight (Fig. 1) is another limitation of the study. Even though most demographics and diabetes-related complications did not differ between included and excluded CFRD patients, a selection bias cannot be totally ruled out especially in T1D where more differences were observed between included and excluded patients. The inclusion of more compliant patients with less severe disease may bias estimates of carbohydrate intake and insulin requirement.

In conclusion, our analysis of a large cohort of pediatric and young adult patients (n=37,003) revealed clear differences between CFRD and T1D regarding carbohydrate intake and insulin requirement per 11 grams of carbohydrate. Moreover, patients with diabetes seem to restrict carbohydrate intake. Due to the differences observed in our study and due to distinct nutritional needs, dietary counseling and anti-hyperglycemic therapy for CFRD should never be the same as for T1D or T2D.

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Statement of authorship

NS drafted and edited the manuscript, created figures and contributed to data analysis. AT, KK, MB, CK, TM, JS, ES, CS and JW collected data and reviewed/edited the manuscript. RWH is the coordinator of the DPV initiative, contributed to data analysis and reviewed/edited the manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

None of the authors had a conflict of interest related to this manuscript.

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Table 1 Baseline characteristics. Values are median with quartiles or percentage. Except for the proportion with migration background, p-values were <0.05 for comparisons between CFRD and T1D in the whole study population and in gender-specific analysis. Kruskal-Wallis test for continuous variables, χ^2-test for dichotomous variables.

	CFRD			T1D		
	All	Females	Males	All	Females	Males
N	223	144	79	36,780	16,836	19,944
Female sex (%)	64.6	100.0	0.0	45.8	100.0	0.0
Migration background (%)	10.8	11.1	10.1	13.6	14.1	13.1
Age (years)	18.3 [16.2; 22.0]	18.3 [15.9; 22.7]	18.3 [16.5; 21.5]	15.8 [13.2; 17.6]	15.6 [12.9; 17.6]	16.0 [13.5; 17.7]
Duration of diabetes (years)	3.7 [1.5; 6.5]	4.1 [1.5; 7.4]	3.2 [1.4; 5.7]	5.0 [2.2; 8.7]	5.2 [2.3; 8.7]	4.9 [2.1; 8.6]
BMI (kg/m²)	19.6 [17.9; 21.2] (n=219)	19.6 [18.2; 21.1] (n=142)	19.4 [17.6; 21.8] (n=77)	21.7 [19.4; 24.3] (n=36,546)	22.1 [19.6; 24.8] (n=16,719)	21.4 [19.2; 23.9] (n=19,827)
BMI-SDS	-0.75 [-1.56; -0.09]	-0.77 [-1.42; -0.17]	-0.75 [-1.82; 0.00]	+0.29 [-0.31; +0.88]	+0.41 [-0.20; +0.99]	+0.19 [-0.39; +0.76]
HbA1c (%)	7.0 [6.2; 8.5] (n=206)	7.0 [6.2; 8.2] (n=132)	7.1 [6.2; 8.7] (n=74)	7.9 [7.0; 9.1] (n=36,298)	7.9 [7.1; 9.1] (n=16,607)	7.9 [7.0; 9.0] (n=19,691)

Table 2 Insulin requirement in CFRD and T1D. Values are adjusted means±SE / adjusted proportions based on hierarchic multivariable regression models. Adjustments for age and gender, treatment center as random intercept.

Adjusted estimates	CFRD	T1D	p-value
N	223	36,780	
Type of basal insulin (%)			
Long-acting insulin analogue	34.4	52.5	<0.001
Intermediate-acting insulin (NPH/zinc insulin)	38.4	47.5	0.194
No basal insulin	27.2	-	-
Type of meal-related insulin (%)			
Rapid-acting insulin analogue	55.6	56.5	0.801
Regular insulin	44.4	43.5	0.801
Reported insulin dose (IU/kg*d)			
Total	0.749±0.022	0.835±0.006	<0.001
Basal	0.274±0.013	0.381±0.004	<0.001
Meal-related	0.522±0.015 (n=219)	0.472±0.004 (n=36,586)	0.001
Reported insulin dose (IU/m²*d)			
Total	24.1±0.8 (n=219)	30.1±0.2 (n=36,548)	<0.001
Basal	8.6±0.5 (n=219)	13.8±0.1 (n=36,548)	<0.001
Meal-related	16.9±0.6 (n=212)	17.0±0.1 (n=36,316)	0.878
Insulin injection time-points per day (n)			
Total	3.17±0.14	3.35±0.07	0.169
Basal	0.57±0.07	0.71±0.02	0.029
Meal-related	3.03±0.16	3.08±0.07	0.732

497 **Fig. 1.** Selection of study population.

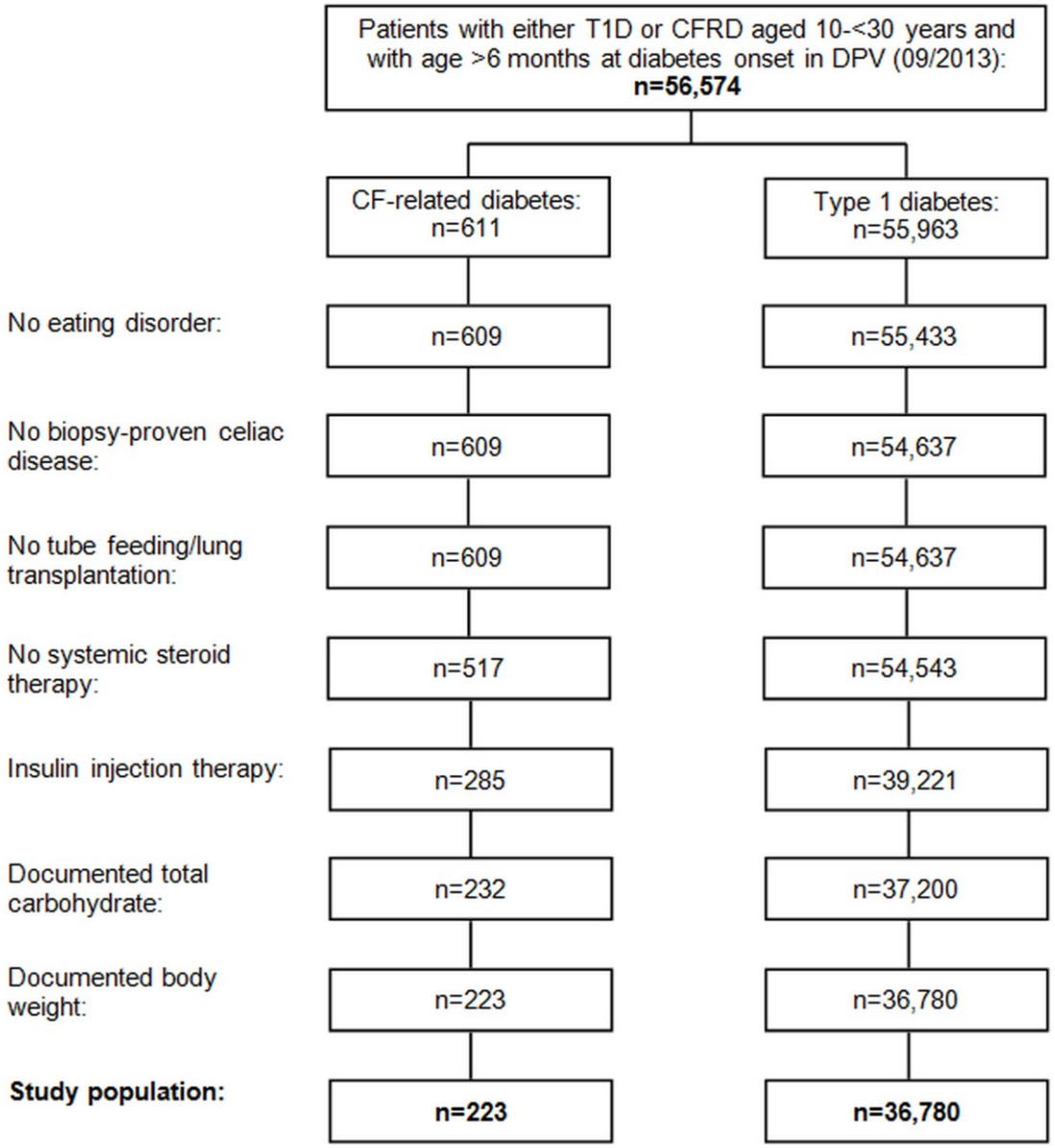

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Fig. 2. Daily distribution of carbohydrate intake in CFRD (hashed bar) and T1D (black bar). Values are adjusted means±SE based on hierarchic multivariable regression models. Adjustments for age and gender, treatment center as random intercept. T1D: n=36,780, CFRD: n=223.

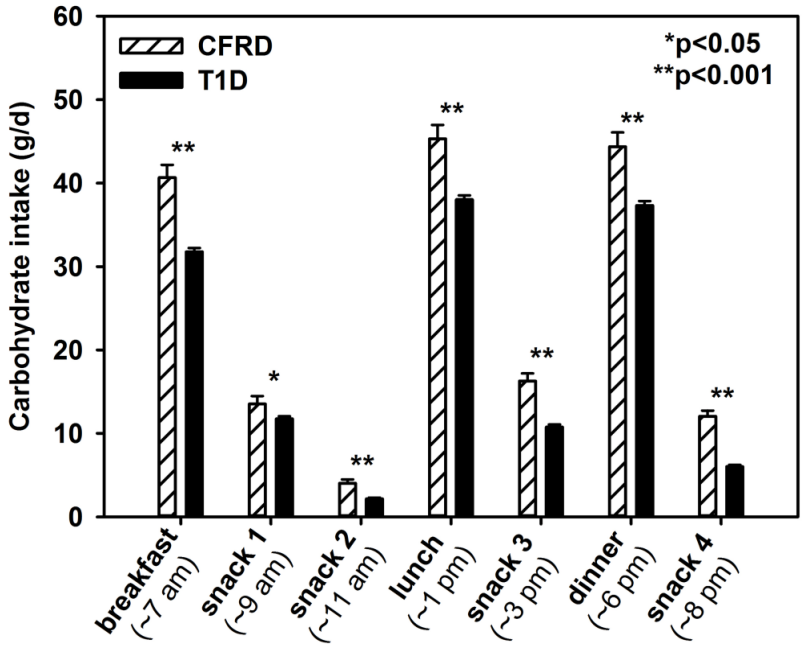

Fig. 3. Insulin requirement per 11 grams of carbohydrate throughout the day in CFRD (dashed line) and T1D (solid line). Values are adjusted means±SE based on hierarchic multivariable regression models. Adjustments for age and gender, treatment center as random intercept. T1D: n=36,669, CFRD: n=220.