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Original Article

Italian and North American dietary intake after ivacaftor treatment for Cystic Fibrosis Gating Mutations

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Abstract

Background: In patients with cystic fibrosis (CF), ivacaftor treatment results in significant weight gain and the impact on diet has not been explored.
Methods: A study in 22 subjects (6.1–61.6 years) compared diet, energy balance, weight gain, and body composition, before and after three months of treatment in Italians and North Americans with CFTR gating mutations.
Results: With no differences between groups in energy or macronutrient intake at baseline, fat intake increased in all subjects, and both fat and energy intake increased in Italians. Height, weight, BMI, lean and fat mass, and % body fat increased and resting energy expenditure decreased after treatment. Weight gain was associated with energy and fat intake.
Conclusions: Fat intake increased with treatment, possibly due to the recommendation to take ivacaftor with high fat meals. Increased energy and fat intake correlated with weight gain. Regional dietary patterns differed.

Keywords: Cystic fibrosis; Ivacaftor; Diet

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease due to mutations in the cystic fibrosis transmembrane regulator (CFTR) gene, which encodes for an anion channel present on epithelial cells throughout the body. The CF phenotype includes bronchiectasis, recurrent pulmonary infections, and exocrine pancreatic insufficiency (PI) in the majority of patients. There are 281 mutations currently known to cause CF, including class III or gating mutations, in which a normal number of CFTR channels are expressed, but function is decreased [1, 2]. Ivacaftor (Kalydeco®, Vertex Pharmaceuticals Inc.) is a CFTR potentiator that partially restores CFTR channel activity in gating mutations. Children and adults with the common gating mutation G551D demonstrate significant weight gain and improved pulmonary function with ivacaftor treatment [3, 4].

Weight gain with ivacaftor therapy is particularly promising, as optimization of growth and weight status is linked to improved outcomes in CF [5, 6]. The landmark study by Corey et al. was one of the first to demonstrate that improved nutritional status related to higher dietary caloric and fat intake

Abbreviations: AI, adequate intake; BMI, body mass index; CF, cystic fibrosis; CFA, coefficient of fat absorption; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CFTR, cystic fibrosis transmembrance conductance regulator; DXA, dual x-ray absorptiometry; EER, estimated energy requirement; EI, energy intake; FEV_1, forced expiratory volume at 1 s; FFM, fat free mass; FM, fat mass; PI, pancreatic insufficient; RDA, recommended dietary allowance; RQ, respiratory quotient; REE, resting energy expenditure; TEE, total energy expenditure; UAFA, upper arm fat area; UAMA, upper arm muscle area

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was predictive of better survival [6]. Nutrition management has since been a key component of care to improve quality of life and survival. Recent European CF guidelines recommend a dietary energy intake of 110–200% of the recommended intake for age to maintain age-appropriate growth and weight similar to healthy children [7]. The US guidelines are similar and recommend that fat comprise about 35–40% of energy intake [8].

We have previously demonstrated in the same cohort of participants that mechanisms of weight gain following ivacaftor use include improved energy balance, due to improved resting energy expenditure, dietary fat intake, fat absorption, and gut inflammation [9]. The impact of ivacaftor on dietary intake has not been explored in detail. The aim of this study was to assess macronutrient, dietary vitamin, and supplement intake in people with CFTR gating mutations before and after three months of ivacaftor treatment. The response to ivacaftor, including weight gain, energy balance, muscle function, and quality of life, was also compared between the Italian and North American cohorts.

2. Methods

2.1. Study design and participants

Subjects were participants in a study investigating mechanisms of weight gain with ivacaftor treatment in subjects with CFTR gating mutations [9]. Children ≥5 years of age and adults were recruited from the US, Canada, and Italy. Subjects were in their usual state of health without hospitalizations, emergency room visits, or acute illness visits for four weeks prior to the first visit. The decision to initiate ivacaftor was made by the primary CF-care clinician. Exclusion criteria included forced expiratory volume at 1 s < 40% predicted (FEV_1%), another illness affecting growth and nutritional status, pregnancy, or breastfeeding. Enrollment started in 2014 and visits were completed in December 2015. Visits were conducted at the Children's Hospital of Philadelphia (CHOP) and approved by the CHOP Institutional Review Board. Subjects stayed at a local hotel at the time of study visits and returned home in between baseline and follow-up visits. Written consent was obtained from subjects ≥18 years and parents/legal guardians of subjects 18 years with verbal assent from subjects 7.0 to <18.0 years. Assessors were not blinded to the sequence of study visits. One subject from North America was not included in the analysis due to an inability to follow study protocol.

2.2. Dietary intake

Three-day weighed food records were obtained at home after provision of detailed instructions and supplies. Average 3-day intake of calories, macro- and micro-nutrients was analyzed for North Americans (JS, CHOP research dietitian) using Nutrition Data System for Research software (Version 2012, National Coordinating Center, University of Minnesota. Minneapolis, MN), and MètaDieta software for Italians (CB, JS, Italian dietitian) (MètaDieta, ME.TE.DA. LLC, San Benedetto del Tronto, Italy). Energy intake was expressed as percentage of estimated energy requirement (% EER) at an active level of physical activity [10]. Supplemental intake of vitamins was recorded. Dietary and supplemental vitamin intake was expressed as percent recommended dietary allowance (% RDA) for vitamins A, D and E and percentage of adequate intake (% AI) for vitamin K [11].

2.3. Biochemical assessments

Home 72-h stool collections were performed after baseline and 3-month visits. Stool samples were frozen following collection and mailed to CHOP. Total fat content was assessed by the gravimetric method (Mayo Medical Laboratories, Rochester, MN). Fat intake was assessed from 3-day food records which coincided with stool collection. Coefficient of fat absorption (CFA) was calculated from daily grams of fat consumed and grams of fat excreted [12]. Fecal elastase 1 as a marker of pancreatic enzyme activity (Enzyme-Linked Immunosorbent Assay, ARUP Laboratory, Salt Lake City, UT) was classified as normal if 200 μg/g. Fecal calprotectin was measured as a marker of intestinal inflammation (QUANTA Lite® ELISA kit, Inova Diagnostics, San Diego, CA) [13]. Vitamin A status was assessed by serum retinol and vitamin E by alpha- and gamma-tocopherol (Craft Laboratories, Wilson, NC).

2.4. Body composition and energy expenditure

Using indirect calorimetry, resting energy expenditure (REE) was assessed using a computerized metabolic cart (Vmax ENCORE 29 N, Yorba Linda, CA). After a 12-h fast beforehand, subjects were transported by wheelchair with minimal physical activity before testing between 7:00 and 10:00 AM. Subjects rested quietly under a clear, plastic hood during testing [14, 15]. From the 1-hour test, data from the first 10 min and during periods of significant movement were eliminated, and the remaining data averaged for mean REE (kcal/day). Percent predicted REE (REE %) was calculated based on the Schofield equations adjusted for age, sex, weight, and height [16].

Total energy expenditure (TEE) over seven days was measured from urine samples at baseline and at 3 h, 4 h, and seven days post dose using the doubly labeled water stable isotope method. Subjects were dosed orally with 0.3 g H_2 [18] O/kg and 0.15 g ^2H_2O/kg body weight and mass spectrometry was used to quantify the abundance of deuterium (^2H) and oxygen-18 (^{18}O) in urine samples [17]. Isotope dilution spaces were determined based on elimination rates of ^{18}O and ^2H with a respiratory quotient (RQ) calculated based on an assumed RQ of 0.86. TEE was calculated using the modified Weir equation. TEE:REE ratio was assessed as a measure of energy for physical activity, weight gain and growth. The ratio of total energy intake (EI, kcal/day) to TEE (EI:TEE) was used to estimate accuracy of reported EI.

Weight (0.1 kg) was measured on an electronic scale (Seca, Munich, Germany) and stature (0.1 cm) with a stadiometer (Holtain, Crymych, UK) and BMI calculated. Age- and sex-specific Z scores for stature, weight, and BMI (5–19.9 year old subjects) were generated [18]. Mid upper arm circumference measured with a non-stretchable fiberglass tape (0.1) (McCoy, Maryland Heights, MO) and triceps skinfold thickness measures were used to calculate upper-arm muscle (UAMA) and fat areas (UAFA) [19]. Resultant areas were compared with reference data from the National Center for Health Statistics to generate the Z scores (UAMAZ and UAFAZ) [20]. Body composition, FFM, and FM and percent body fat (% Fat), were assessed by whole body dual energy x-ray absorptiometry (DXA) (Delphi A, Hologic, Inc., Bedford, MA).

Subjects were classified as adequately nourished based on ESPEN-ESPGHAN-ECFS guidelines [7]. Children ≤18 years of age were classified as adequately nourished if their BMI Z score was ≥0 and inadequately nourished if they had a BMI Z score < 0. Female subjects >18 years of age were classified as adequately nourished if they had a BMI ≥ 22 and male subjects >18 years of age were considered adequately nourished if they had a BMI ≥ 23.

2.5. Pulmonary and muscle assessments

Pulmonary function was assessed as forced expiratory volume at 1 s (FEV_1) using standard methods for spirometry and expressed as percent of reference values (FEV_1%) [21, 22].

Lower leg muscle strength was assessed using the Biodex Multi-Joint System 3 Pro (Biodex Medical Systems, Inc., Shirley, NY). Left quadriceps maximum isometric strength (lateral knee extension and flexion) was measured at the 60°/s angular velocity [23] using muscle efficiency calculated as muscle force/muscle cross-sectional area (foot-pounds). Leg strength was assessed using jump height (cm) and peak power (W) (Kistler Quattro-Jump Force Plate, Kistler Instrument Corp., Amherst, NY) [24]. Right and left hand grip strength (kg) were assessed by dynamometer (Takei Scientific Instruments Co., Ltd., Tokyo, Japan), using the maximum from three trials on each hand.

2.6. Quality of life questionnaire

Subjects completed the Cystic Fibrosis Questionnaire-Revised (CFQ-R) quality of life assessment at each visit in English or Italian. Surveys were for preadolescent children (6.0–13.9 years) and for adolescents and adults (≥14.0 years) [25]. CFQ-R Domain scores are based on a 100-point scale. Higher numbers indicate a better quality of life. Domains found in both surveys (Physical Functioning, Emotional Functioning, Eating Problems, Treatment Burden, Body Image, Social Functioning, Respiratory Symptoms, and Digestive Symptoms) were used, with a four-point difference in score considered important even if not statistically significant [25].

2.7. Adherence

Adherence to medications was assessed at the follow-up visit with questionnaires. Specifically, subjects were asked how many days over the past seven day period they had missed taking their medication, which included ivacaftor, pancreatic enzymes, and CF-specific vitamins. From this, the percentage of days per week of adherence to medication was calculated.

2.8. Statistics

Statistical analyses were performed using STATA version 14.1 (STATA, Inc., College Station, TX). Power and sample size calculations were performed for outcomes in a primary paper with the same study participants [9]. Descriptive statistics included frequency and percentages for categorical variables and means ± SD for continuous variables. Comparisons between groups (Italian, North American) were made using unpaired student's *t*-tests or Mann-Whitney *U* test for continuous variables depending on skewness and Pearson's chi-square or Fisher's exact tests for categorical data. Change in outcomes after three months for the whole sample and within groups was determined by paired student's *t*-tests or Wilcoxon sign rank test depending on skewness. Chi-squared tests were used for comparison of categorical variables before and after ivacaftor treatment. Associations between changes in outcomes at each time point between variables were assessed using Pearson or Spearman rank correlation coefficients depending upon skewness. Statistical significance was set at $p = .05$ for all tests.

3. Results

There were 15 Italian (27% male, 100% Caucasian, 18.2 ± 9.0 years) and seven North American subjects (57% male, 86% Caucasian, 17.0 ± 20.1 years) with various CFTR gating mutations (Table 1). Table 2 presents subject characteristics and outcomes at baseline and after three months of ivacaftor,

Table 1
Genotypes of subjects from Italy and North America with Cystic Fibrosis Gating Mutations.

Italy			North America		
Subject	Allele 1	Allele 2	Subject	Allele 1	Allele 2
1	G178R	F508del	1	G551D	F508del
2	G178R	G178R	2	G551D	F508del
3	G178R	G178R	3	G551D	G551D
4	G1244E	F508del	4	G551D	P67L
5	G1244E	F508del	5	S1215N	711+3A→G
6	G1244E	N1303K	6	S1255P	F508del
7	G1244E	N1303K	7	S549N	F508del
8	G1244E	T3381			
9	G1349D	1185delTC			
10	G1349D	4015delA			
11	S549R	F508del			
12	S549R	G542X			
13	S549R	S549N			
14	S549R	W1282X			
15	S549R	711+3A→G			

Table 2
Characteristics and dietary intake at baseline and follow-up of subjects with Cystic Fibrosis Gating Mutations and the respective Italian and North American Subgroups.

Characteristic	Baseline			Follow-up			3-Month change		
	All (n = 22)	Italian (n = 15)	North American (n = 7)	All (n = 22)	Italian (n = 15)	North American (n = 7)	All (n = 22)	Italian (n = 15)	North American (n = 7)
Sex, % males	36	27	57	36	27	57	–	–	–
Race, % Caucasian	95	100	86	95	100	86	–	–	–
Age, yr	17.8 ± 13.0	18.2 ± 9.0	17.0 ± 20.1	18.2 ± 13.0	18.6 ± 9.0	17.3 ± 20.1	–	–	–
Pancreatic insufficient, %	73	73	71	73	73	71	–	–	–
Height, cm	151 ± 18	158 ± 12	137 ± 19 ††	153 ± 17	159 ± 12	138 ± 18 ††	1.4 ± 1.4 ***	1.4 ± 1.5 **	1.5 ± 1.3 *
Weight, kg	45.2 ± 15.5	50.5 ± 11.4	33.8 ± 17.7 †	47.8 ± 15.5	53.4 ± 11.2	35.6 ± 17.1 ††	2.6 ± 2.2 ***	2.9 ± 2.5 ***	1.8 ± 1.1 **
BMI, kg/m	19.0 ± 3.5	20.0 ± 3.1	16.9 ± 3.5 ¥	19.8 ± 3.5	20.8 ± 3.2	17.6 ± 3.3 †	0.8 ± 0.8 ***	0.8 ± 0.9 **	0.7 ± 0.5 *
UAMA Z score	−0.0 ± 1.1	−0.1 ± 0.9	0.3 ± 1.5	0.1 ± 1.0	0.0 ± 0.8	0.3 ± 1.4	0.1 ± 0.4	0.2 ± 0.4	−0.1 ± 0.3
UAFA Z score	−0.4 ± 0.8	−0.2 ± 0.9	−0.8 ± 0.7	−0.1 ± 0.7	0.1 ± 0.7	−0.4 ± 0.6	0.3 ± 0.4 **	0.3 ± 0.4 *	0.4 ± 0.4 *
DXA, FFM, kg	31.2 ± 11.0	34.2 ± 9.2	24.6 ± 12.3 ¥	32.0 ± 10.5	35.3 ± 8.3	25.1 ± 12.0 †	0.9 ± 1.9 *	1.0 ± 2.2	0.6 ± 1.1
DXA, FM, kg	14.3 ± 6.1	16.5 ± 5.2	9.5 ± 5.4 ††	16.0 ± 6.4	18.4 ± 5.3	10.7 ± 5.3 ††	1.7 ± 1.5 ***	1.9 ± 1.8 **	1.2 ± 0.6 **
DXA, Fat, %	30.9 ± 6.2	32.5 ± 6.9	27.5 ± 1.4	32.7 ± 5.7	34.1 ± 6.3	29.8 ± 2.2	1.8 ± 2.4 **	1.6 ± 2.5 *	2.2 ± 2.1 *
FEV_1, % predicted	87 ± 21	83 ± 21	95 ± 20	97 ± 18	95 ± 19	101 ± 17	10.5 ± 10.7 ***	12.3 ± 10.4 ***	6.6 ± 11.1
Fecal elastase, ug/g stool	97 ± 132	100 ± 151	91 ± 86	137 ± 183	154 ± 212	98 ± 101	40 ± 107	55 ± 127	7 ± 27
Calprotectin, ug/g stool [1]	81 ± 118	87 ± 136	67 ± 76	48 ± 110	54 ± 133	37 ± 44	−32 ± 39 **	−34 ± 33 **	−30 ± 54
CFA, % [1]	91 ± 7	90 ± 7	93 ± 6	93 ± 5	92 ± 5	95 ± 5	1.5 ± 4.3	1.3 ± 5.0	2.1 ± 2.6
Stool fat, g [1]	7.1 ± 5.8	8.1 ± 6.6	4.9 ± 3.2	7.0 ± 5.4	8.4 ± 5.6	4.4 ± 4.1	0.0 ± 3.2	0.2 ± 3.9	−0.6 ± 1.5
Stool weight, g [1]	363 ± 270	412 ± 268	266 ± 266	363 ± 215	432 ± 204	226 ± 176 †	0 ± 173	20 ± 197	−40 ± 114
REE, Kcal/d [1]	1218 ± 236	1315 ± 223	1023 ± 107 ††	1162 ± 201	1222 ± 207	1043 ± 129 ¥	−56 ± 129	−94 ± 131 *	20 ± 92
REE, % predicted [1]	96 ± 11	98 ± 11	92 ± 11	89 ± 9	88 ± 9	91 ± 10	−6.8 ± 10.6 **	−9.7 ± 10.5 **	−1.1 ± 8.6
TEE, Kcal/d [2]	2309 ± 605	2482 ± 715	2036 ± 211	2440 ± 832	2615 ± 1013	2164 ± 324	131 ± 503	133 ± 622	128 ± 270
TEE:REE ratio [2]	1.93 ± 0.32	1.88 ± 0.37	2.00 ± 0.24	2.07 ± 0.41	2.07 ± 0.52	2.07 ± 0.13	0.15 ± 0.39	0.20 ± 0.46	0.07 ± 0.26
EI:TEE ratio [2]	0.95 ± 0.28	0.95 ± 0.35	0.94 ± 0.17	0.96 ± 0.30	1.02 ± 0.35	0.87 ± 0.18	0.01 ± 0.24	0.07 ± 0.23	−0.07 ± 0.25
Serum retinol, ug/dl	36.6 ± 10.6	37.0 ± 11.0	35.8 ± 10.4	37.4 ± 8.8	36.4 ± 8.3	39.7 ± 10.2	0.8 ± 6.9	−0.6 ± 6.6	3.9 ± 7.0
Serum α-tocopherol, ug/ml	10.2 ± 3.5	9.5 ± 3.3	11.5 ± 3.7	9.6 ± 2.6	8.9 ± 2.6	10.9 ± 2.0	0.6 ± 2.0	−0.6 ± 1.7	−0.6 ± 2.6
Serum γ-tocopherol, ug/ml	0.55 ± 0.44	0.35 ± 0.18	0.99 ± 0.53 †††	0.55 ± 0.41	0.38 ± 0.21	0.91 ± 0.51 ††	0.0 ± 0.2	0.0 ± 0.2	−0.1 ± 0.2
Dietary intake									
Kcal/d	2083 ± 530	2162 ± 576	1913 ± 401	2292 ± 574	2500 ± 546	1847 ± 342 ††	210 ± 514	338 ± 504 *	−66 ± 451
Kcal, %EER	93 ± 19	90 ± 21	97 ± 15	100 ± 21	103 ± 23	92 ± 16	7 ± 22	13 ± 21 *	−5 ± 22
Fat, g/d	84 ± 26	85 ± 30	81 ± 19	95 ± 25	101 ± 25	80 ± 19	11 ± 19 *	16 ± 18 **	−1 ± 17
Fat, % kcal	36 ± 4	35 ± 5	37 ± 4	37 ± 5	37 ± 5	38 ± 5	1.5 ± 3.6	1.5 ± 4.3	1.6 ± 1.8
Protein, g	77 ± 26	82 ± 25	66 ± 29	80 ± 25	90 ± 23	61 ± 18 ††	3.2 ± 19.5	7.2 ± 17.4	−5.4 ± 22
Protein, % kcal	15 ± 3	15 ± 3	14 ± 3	14 ± 3	15 ± 3	13 ± 3	−0.8 ± 2.2	0.8 ± 2.1	−0.7 ± 2.6
Carbohydrate, g	266 ± 69	281 ± 74	234 ± 44	294 ± 95	326 ± 95	226 ± 50 †	27 ± 84	44 ± 91	−8 ± 59
Carbohydrate, % kcal	49 ± 6	49 ± 6	49 ± 7	48 ± 6	48 ± 7	48 ± 6	−0.7 ± 4.2	−0.7 ± 5.0	−0.9 ± 22
Vitamin A, total eq/d	795 ± 491	789 ± 496	807 ± 518	746 ± 416	778 ± 411	679 ± 451	−49 ± 353	−12 ± 309	−128 ± 448
Vitamin A, IU/d	2650 ± 1636	2632 ± 1654	2691 ± 1727	2488 ± 1385	2593 ± 1369	2263 ± 1503	−163 ± 1175	−39 ± 1031	−428 ± 1494
Vitamin A, % RDA	144 ± 100	121 ± 79	192 ± 127	137 ± 96	119 ± 67	175 ± 138	−7 ± 76	−2 ± 45	−17 ± 125
Vitamin D, mcg/d	2.4 ± 2.2	1.6 ± 1.7	4.3 ± 2.0 ††	2.8 ± 3.2	1.4 ± 1.1	5.8 ± 4.3 ††	0.4 ± 2.8	−0.1 ± 1.9	1.4 ± 4.2
Vitamin D, IU/d	98 ± 87	63 ± 67	172 ± 81 ††	112 ± 128	57 ± 43	230 ± 172 ††	14 ± 112	−6 ± 75	58 ± 167
Vitamin D, % RDA	16 ± 15	11 ± 1	29 ± 14 ††	19 ± 21	10 ± 7	38 ± 29 ††	2 ± 19	−0.9 ± 12.4	10 ± 28
Vitamin E, mg/d	9.9 ± 5.6	8.5 ± 5.1	12.8 ± 5.9	10.7 ± 5.3	9.8 ± 5.9	12.6 ± 3.5	0.8 ± 6.6	1.3 ± 6.8	−0.2 ± 6.5
Vitamin E, % RDA	87 ± 56	67 ± 34	132 ± 71 ††	97 ± 61	79 ± 52	136 ± 64 †	10 ± 57	12 ± 55	3 ± 65
Vitamin K, mcg/d	–	–	87 ± 85	–	–	113 ± 144	–	–	26 ± 68
Vitamin K, % AI	–	–	122 ± 87	–	–	156 ± 149	–	–	33 ± 84

† Student's unpaired *t*-test for difference between Italian and NA groups, significant $P < .05$.
†† $p < .01$.
††† $P < .001$.
¥ $p = .05$.
* Paired *t*-test for change over time within group, significant $P < .05$.
** $P < .01$.
*** $P < .001$.
[1] n = 21 All, 14 Italian, 7 NA.
[2] n = 18 All, 11 Italian, 7 NA.

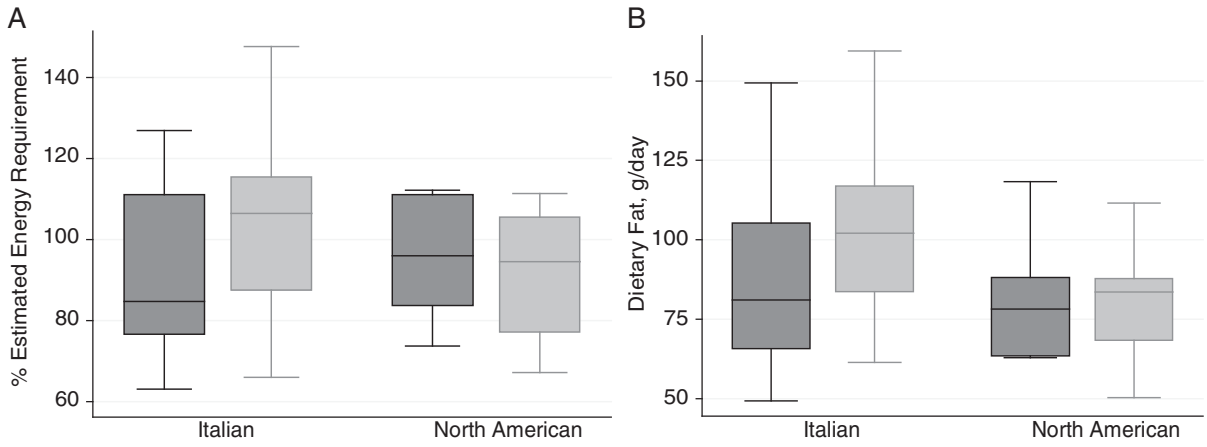

Fig. 1. Change in Dietary Intake of Energy and Fat in Italians compared to North Americans. Estimated energy requirement as percent predicted (1A) and total dietary fat intake in g/day (1B) before (black bars) and after (grey bars) 3-month ivacaftor treatment for Italian (n = 15) and North American (n = 7) cohorts. The bars present the interquartile interval (25th to 75th percentile) and the median (line within the bar), and the whiskers the upper and lower adjacent values for each variable. Energy intake as %EER and dietary fat intake after ivacaftor were significantly different from before treatment in the Italian cohort only.

and also presents comparisons between Italians and North Americans. At baseline, Italians had a significantly higher height, weight, and FM. Ten subjects (45%) were considered inadequately nourished based on CF guidelines [7]. There was no difference in % Fat and FFM tended to be higher in Italians. At baseline, there were greater deficits in fat stores based on UAFA Z scores than muscle stores (UAMA Z scores), and UAFA Z scores increased significantly with treatment. There was no difference in REE % or TEE (kcal/day) between groups at baseline and REE declined significantly with 3-month treatment. RQ calculated from the REE assessments averaged 0.86 (range 0.78–1.02, ± 0.06), which was identical to the assumed RQ of 0.86 used to calculate TEE.

At baseline, there was no significant difference between Italians and North Americans in energy or macronutrient intake (Table 2). The North Americans consumed significantly more vitamin D from both diet and supplements and more dietary vitamin E as % RDA, while the Italians took more supplemental vitamin K (Tables 2 and 5). Energy intake increased significantly in the Italians (Δ 338 ± 504 kcal/d, Δ13 ± 21%EER; $p < .05$) with no change for North Americans (Table 2 and Fig. 1). Dietary fat intake significantly increased (Δ 11 ± 19 g/d, $p < .05$) in all subjects after three months of ivacaftor, as well as in the Italian subgroup (Δ 16 ± 18 g/d, $p < .01$) (Table 2 and Fig. 1). Weight gain was positively correlated with change in energy intake ($r = 0.42$, $p = .05$) and change in fat intake ($r = 0.59$, $p = .004$) in all subjects, and the association with fat intake was stronger in the Italian subgroup ($r = 0.72$, $p = .002$). EI:TEE was 0.95 ± 0.28 at baseline in all subjects and did not change overall, but improved (Δ 0.07 ± 0.23) for Italians, while decreasing for North Americans (Δ −0.07 ± 0.25). At baseline, the North Americans had a significantly higher gamma-tocopherol serum concentration than the Italians. There was no significant change in serum vitamin A or E concentrations following ivacaftor use.

Height, weight, BMI, FM, FFM, % FAT, and FEV_1 significantly increased after three months of treatment and REE % significantly decreased in all subjects (Table 2). While height, weight, BMI, FM, and % FAT improved in both cohorts, the change in REE % and FEV_1 did not reach statistical significance in the North American subgroup. Fig. 2 demonstrates REE (kcal/day) vs. FFM in both cohorts, before and after ivacaftor treatment.

Table 3 presents growth status and muscle strength and function for subjects <20 years of age. At baseline, growth status tended to be poorer for North Americans. Weight Z scores significantly improved in both cohorts and BMI Z score in North American cohort. Italians had greater absolute grip strength, knee extension and flexion strength at baseline compared to North Americans as they tended to be

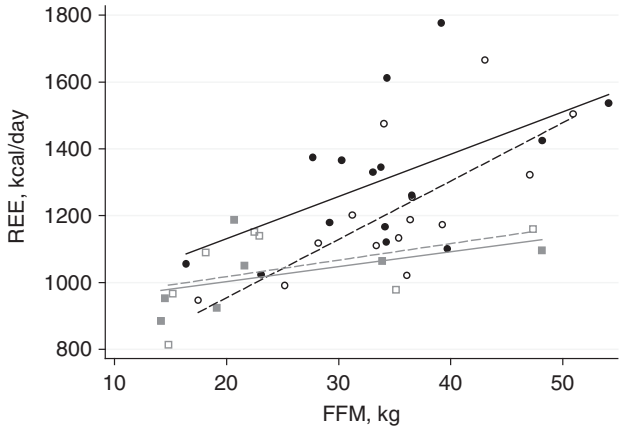

Fig. 2. Change in Resting Energy Expenditure in Italy Compared to North America. Change in Resting Energy Expenditure (REE) in Italians Compared to North Americans. The relationship between REE (kcal/day) and fat free mass (FFM) in kilograms assessed by whole body DXA, before and after ivacaftor treatment, separately by geographic location. Italian: (n = 15) are black solid circles and solid lines at baseline and black open circles and dashed lines at 3-month follow-up. North American (n = 7) are grey solid squares and solid lines at baseline and grey open squares and dashed lines at 3-month follow-up.

Table 3
Anthropometric data and strength measurements at baseline and follow-up in subjects <20 years of age with CF gating mutations and the respective Italian and North American subgroups.

Characteristic	Baseline			Follow-up			3-Month change		
	All (n = 17)	Italian (n = 11)	North American (n = 6)	All (n = 17)	Italian (n = 11)	North American (n = 6)	All (n = 17)	Italian (n = 11)	North American (n = 6)
Height Z score	0.1 ± 1.1	0.2 ± 1.2	−0.1 ± 1.1	0.1 ± 1.1	0.2 ± 1.2	−0.1 ± 1.1	0.0 ± 0.1	0.1 ± 0.1	0 ± 0.1
Weight Z score	−0.2 ± 0.9	−0.0 ± 1.0	−0.5 ± 0.8	0.0 ± 0.9	0.2 ± 1.0	−0.2 ± 0.6	0.2 ± 0.3 ***	0.2 ± 0.2 *	0.3 ± 0.2 **
BMI Z score	−0.3 ± 1.1	−0.1 ± 1.0	−0.8 ± 1.1	0.0 ± 0.8	0.1 ± 0.9	−0.2 ± 0.7	0.3 ± 0.4 **	0.2 ± 0.3	0.5 ± 0.4 *
Grip strength, kg (right) [1]	20.1 ± 8.2	23.4 ± 6.7	14.7 ± 8.0 †	21.4 ± 8.7	25.0 ± 7.0	15.3 ± 8.1 †	1.2 ± 1.8 *	1.6 ± 1.3 **	0.6 ± 2.5
Grip strength, kg (left) [1]	18.9 ± 7.1	21.8 ± 6.6	14.0 ± 5.2 ††	19.1 ± 7.7	22.2 ± 6.8	13.9 ± 6.6 †	0.2 ± 1.7	0.4 ± 1.8	−0.1 ± 1.6
Jump height, cm [2]	29.5 ± 8.2	30.1 ± 9.2	28.4 ± 6.6	30.9 ± 7.3	31.4 ± 8.0	30.1 ± 6.6	1.4 ± 2.6 §	1.3 ± 2.5	1.7 ± 3.1
Peak power, watts [1]	1392 ± 826	1651 ± 894	960 ± 501	1507 ± 771	1790 ± 776	1037 ± 523 ¥	115 ± 143 **	138 ± 179 *	76 ± 32 **
Knee extension, foot/lbs [1]	52.6 ± 31.1	63.1 ± 30.8	32.3 ± 22.2 †	53.6 ± 31.6	66.2 ± 31.2	32.8 ± 19.9 †	2.1 ± 7.9	3.0 ± 9.3	0.5 ± 5.3
Knee flexion, foot/lbs [1]	21.6 ± 12.1	26.5 ± 12.3	13.3 ± 5.5 †	28.3 ± 16.7	34.3 ± 16.9	18.1 ± 11.1 ¥	6.7 ± 7.9 **	7.8 ± 8.6 *	4.9 ± 7.0

† Student's unpaired *t*-test for difference between Italian and NA groups, significant $P < .05$.
†† $p < .01$.
¥ $p = .05$.
* Paired *t*-test for change over time within group, significant $P < .05$.
** $P < .01$.
*** $P < .001$.
§ $p = .05$.
[1] Baseline: $n = 16$ All (subjects <20 years), 10 Italian, 6 NA, follow-up.
[2] n = 15 All (subjects <20 years), Italian 10, 5 NA.

older. The whole cohort significantly increased muscle strength following ivacaftor for right grip strength, peak power, and knee flexion. Jump height tended to increase as well. The Italian subgroup had a significant increase in right grip strength and knee flexion. Both cohorts had significant improvement in peak power. Grip strength was reduced compared to healthy people of similar age and sex using reference data from the National Health and Nutrition Examination Survey [26]. In our subjects at baseline, 37.5% had grip strength below the 20th percentile and 75% below the 50th percentile for healthy subjects.

Notably, it was determined at follow-up that adherence to ivacaftor during a typical week was very high at 98% for the whole cohort. Adherence to pancreatic enzymes in those subjects with pancreatic insufficiency was 98% during a typical week, while adherence to CF-specific vitamins was 78% in all subjects.

There was no significant difference in CFQ-R quality of life domain scores between the two cohorts at baseline (Table 4). Italians had higher Eating Disturbances, Body Image, Social Functioning, Respiratory Symptoms, and Digestive Symptoms domain scores by ≥4 points and North Americans a higher Treatment Burden domain score. In all subjects, there was a significant improvement in the Respiratory Symptoms domain scores with ivacaftor and meaningful improvements in the Physical Functioning, Eating Disturbances, and Digestive Symptoms domains. The Italians improved in the Physical Functioning, Emotional Functioning, and Treatment Burden domains and the North Americans improved in the Eating Disturbances, Body Image, and Digestive Symptoms domains while decreasing in the Treatment Burden and Social Functioning domains.

4. Discussion

This study confirms previous findings that improved weight gain and pulmonary function result from ivacaftor treatment in subjects with CF and gating mutations [3, 4]. In this sample, we have previously shown that mechanisms of weight gain with ivacaftor treatment include decreased REE %, increased dietary fat intake, improved fat absorption, and reduced gut inflammation [27]. We confirm improved growth status, muscle strength, body composition, and gut inflammation in subjects on ivacaftor in both regions, while the Italians demonstrated greater improvement in energy balance and pulmonary function. Although Italians were taller and heavier at baseline, this difference was not sustained for height, weight, and BMI Z scores. There were no significant baseline differences in REE % predicted or in fecal calprotectin. This report focuses on detailed changes in dietary intake and regional differences in dietary fat and energy intake that accompanied ivacaftor treatment.

The participants had significantly increased fat intake (g/day) after three months and the Italian subgroup had a significant increase in fat and energy intake. The increase in energy intake in the Italians was accompanied by a greater magnitude decrease in REE% than in the North Americans (−9.7% vs. −1.1%) and by somewhat greater weight gain (2.9 vs. 1.6 kg) after ivacaftor. Patients are instructed to take ivacaftor twice daily with fat-containing foods to optimize absorption. This may partly account for the increased fat intake overall, but the relationship between high fat intake and time of medication intake could not be determined from our study. Increased energy intake in the Italians was accompanied by a trend towards improvement in the EI:TEE ratio from 0.95 to

Table 4
Quality of life at baseline and follow-up of subjects with CF gating mutations and the respective Italian and North American subgroups.

Characteristic	Baseline			Follow-up			3-Month change		
	All (n = 22)	Italian (n = 15)	North American (n = 7)	All (n = 22)	Italian (n = 15)	North American (n = 7)	All (n = 22)	Italian (n = 15)	North American (n = 7)
Physical Functioning	86 ± 15	87 ± 15	84 ± 16	90 ± 8	92 ± 8 [a]	84 ± 11	**4 ± 13**	**5 ± 15**	0 ± 10
Emotional Functioning	80 ± 14	81 ± 16	80 ± 12	83 ± 15	86 ± 14 [a]	76 ± 14	2 ± 10	**5 ± 10**	−3 ± 9
Eating Disturbances	83 ± 19	87 ± 17 [a]	75 ± 22	90 ± 13	90 ± 14	90 ± 10	**7 ± 21**	3 ± 17	**16 ± 27**
Treatment Burden	61 ± 23	58 ± 20	68 ± 30 [a]	62 ± 20	62 ± 18	62 ± 25	1 ± 24	**4 ± 23**	**−6 ± 27**
Body Image	83 ± 22	89 ± 15 [a]	71 ± 31	86 ± 19	88 ± 17 [a]	83 ± 23	3 ± 24	−1 ± 18	**11 ± 34**
Social Functioning	73 ± 21	76 ± 19 [a]	68 ± 26	73 ± 20	77 ± 18 [a]	64 ± 22	−1 ± 16	1 ± 17	**−5 ± 12**
Respiratory Symptoms	77 ± 15	80 ± 16 [a]	71 ± 12	90 ± 12	92 ± 9 [a]	85 ± 15	**12 ± 12** ***	**12 ± 11** **	**13 ± 14** *
Digestive Symptoms	81 ± 23	86 ± 19 [a]	71 ± 30	89 ± 18	87 ± 20	94 ± 13 [a]	**8 ± 24**	1 ± 21	**22 ± 25**

Bolded font indicates a notable change of ≥4-points following 3 months of ivacaftor use.
* Paired *t*-test for change over time within group, significant $P < .05$.
** $P < .01$.
*** $P < 0.001$.
[a] Indicates a ≥ 4-point difference in a given domain between the Italian and North American cohorts.

1.02 suggesting better reporting of dietary intake at follow-up, while the EI:TEE ratio tended to decline in the North Americans from 0.95 to 0.87 suggesting worsening reporting accuracy. Thus, differences in reporting may partially explain the difference in energy and fat intake by cohort. Finally, genotype differences between the two cohorts may affect the response to ivacaftor (Table 1).

There are a number of mechanisms by which ivacaftor may improve appetite. Our data supports improved fat absorption, as CFA improved after ivacaftor with increased fat intake and little change in fat excretion. Improved digestion and absorption may lead to fewer gastrointestinal symptoms and greater appetite. Reduced gut inflammation, as indicated by fecal calprotectin, may also improve GI symptoms and appetite. There is evidence for reduced chemosensitivity to taste and smell in CF [28, 29]. Dysfunctional CFTR on the sinonasal mucosa leads to chronic rhinosinusitis, which may lead to olfactory and gustatory sensory loss. Improvement in the taste and smell of food may occur with ivacaftor, leading to improved appetite and food intake [29]. Interestingly, the CFQ-R demonstrated that ivacaftor was associated with improved scores for the Eating Disturbances and Digestive Symptoms domains. Further studies are needed to confirm if ivacaftor truly improves taste and smell.

Table 5
Supplemental intake at baseline in patients with CF gating mutations and the respective italian and North American subgroups.

Vitamin supplement	All (n = 22)	Italian (n = 15)	North American (n = 7)
Vitamin A			
Retinol eq IU/d	2996 ± 1588	3127 ± 1536	2715 ± 1785
% RDA	514 ± 307	493 ± 262	559 ± 407
Vitamin D			
IU/d	2594 ± 2930	1613 ± 563	4694 ± 4664 *
% RDA	432 ± 488	269 ± 94	782 ± 777 *
Vitamin E			
IU/d	460 ± 603	430 ± 166	524 ± 1095
% RDA	3053 ± 5788	2239 ± 828	4798 ± 10,509
Vitamin K			
mcg/d	999 ± 594	1179 ± 383	613 ± 800 *
% AI	1430 ± 931	1602 ± 573	1061 ± 1426

* Student's unpaired *t*-test for difference between groups, significant $p < .05$.

Numerous studies have explored dietary intake in CF. Many children with CF do not meet the caloric intake goal of 110–200% of recommended intake nor the goal that fat intake comprises 35–40% of energy intake [7, 8, 30–32]. Calvo-Lerma et al. studied dietary intake in patients with CF across six European centers and found that patients with CF met the recommended energy intake in four centers and the recommended fat intake in three [32]. In this present study, neither cohort met the recommendations for daily energy intake either before or after ivacaftor, though both cohorts always met the recommended fat intake. In this context, it is notable that over half of subjects were adequately nourished at the start of the study.

In healthy Italian adults, energy intake in women and men 18–65 years of age has been shown to be 1834 and 2129 kcal/day, respectively [33]. Although the Italians in our study were younger, energy intake was equivalent or greater than healthy Italians, as expected based upon CF recommendations for higher energy intake. In a 2006 study by Colombo et al., dietary energy intake in 37 Italian children with CF was 2380 kcal/day, with 15% from protein, 33% from fat, and 55% from carbohydrates [34]. Both energy and fat intake were higher than healthy controls. Subjects in our present study had lower energy intake, but the macronutrient distribution was similar to that found by Colombo et al. [34].

Differences in dietary micronutrient intake between North Americans and Italians in the present study may be partially attributable to differences in national food fortification and enrichment practices. Significantly higher vitamin D intake in North Americans may be due to the consumption of vitamin D

Table 6
Fat soluble vitamin supplementation guidelines in cystic fibrosis in North America compared to Europe [7, 8, 36].

Supplement	North America				Europe			
	0–12 months	1–3 years	4–8 years	>8 years	0–12 months	1–3 years	4–8 years	>8 years
Vitamin A (IU)	1500	5000	5000–10,000	10,000	Start low and titrate to serum level	Start low and titrate to serum level	Start low and titrate to serum level	Start low and titrate to serum level
Vitamin E (IU)	40–50	80–150	100–200	200–400	50	100–400	100–400	100–400
Vitamin D (IU)	400-500 [a]	800-1000 [a]	800-1000 [a]	800–1000 [a] (800–2000 if > 10 years)	400–1000	800–2000	800–2000	800–2000 (4000 if >10 years)
Vitamin K (mg)	0.3–0.5	0.3–0.5	0.3–0.5	0.3–0.5	0.3–1.0	1–10	1–10	1–10

[a] Refer to Tangpricha et al. [36] for guidelines. Recommended to titrate vitamin D dose to serum 25-hydroxy vitamin D concentration.

fortified milk, cereal, and enriched grains in the US. Vitamin and mineral supplemental intake did not vary greatly between the two groups. There are no major nutrient dose differences between DKX® (Neupharma) used in Italy and CF-specific preparations commonly used in North America, AquADEKs® (Allergan) or MVW vitamins (MVW Nutritionals). Higher supplemental vitamin D intake in North Americans can be traced to the common prescription of an extra vitamin D supplement. The Italians consumed more supplemental vitamin K (mcg/day), but this was not significant when vitamin K was expressed as % AI, and the standard deviation was large. Interestingly, US consensus guidelines for CF recommend less vitamin D and greater vitamin K supplementation compared to recent European guidelines (Table 6) [7, 35].

In analysis of body composition, it is notable that both the Italian and North American subgroups had a significant increase in fat mass, percentage body fat, and UAFA Z score. While the cohort as a whole had a significant increase in fat free mass, this was not true of the individual subgroups potentially due to small sample size. UAMA was restored to normal in the whole cohort and the Italian subgroup, though these changes were not significant. Increased fat free mass or lean body mass has been associated with improved pulmonary function, but increased fat mass does not clearly correlate with improved pulmonary function [36, 37]. Further studies are needed to determine the effect of ivacaftor on body composition and to consider if longterm use of ivacaftor may warrant altered dietary recommendations regarding total energy intake.

Our data show that TEE overall trended upwards, while REE decreased significantly with ivacaftor use. These changes are reflected in the upward trend in the TEE:REE ratio. This ratio decreased because REE decreased and therefore, the basal metabolic energy needs were lower. This suggests that the cohort had more energy available for physical activity, as well as growth and normal metabolism. Our quality of life data on physical function matches this finding, as the whole cohort and the Italian subgroup demonstrated improvement in the Physical Functioning Domain of the CFQ-R. It is notable, that in general, REE was lower in this cohort compared with other studies due to the less severe gating mutations.

One limitation of this study is that the software programs used to calculate dietary nutrient composition differed for Italians and North Americans. Additionally, the RDA % and AI % for vitamin intake, which are recommendations for healthy people in North America, were calculated for both cohorts, understanding that the recommendations may not reflect the needs of a healthy Italian population. This was an observational study and we are also limited in our ability to attribute changes in outcome measures to ivacaftor alone. It is possible that outcome measures were affected by a change in adherence to elements of CF treatment or a change in physical activity attributable to study participation or also related to ivacaftor use. Finally, the sample size was limited and a larger study of subjects with gating mutations will strengthen understanding of dietary differences.

In summary, this study is the first to assess dietary intake changes, including macronutrient and micronutrient intake following therapy with ivacaftor. Dietary fat intake increases with ivacaftor treatment in people with CFTR gating mutations, which may be due to the practice to take ivacaftor with a high fat meal. Increased energy and fat intake correlated with weight gain. Longterm studies are needed to determine the effect of ivacaftor on weight gain, body composition, and risk of obesity and associated comorbidities over time. Our data support that clinicians should pay careful attention to the effect of ivacaftor on dietary intake, fat intake, and weight gain.

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Conflict of interest

The authors have declared no conflict of interest related to this work.

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