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ORIGINAL ARTICLE

Comparing effects of low glycemic index/high-fat, high-calorie diet and high-fat, high-calorie diet on cytokine levels of patients with cystic fibrosis: A randomized controlled clinical trial

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ABSTRACT. The importance of the host inflammatory response, as a central pathological feature of cystic fibrosis, is well recognized. Additionally, hyperglycemia can induce an immune response and consecutively may exacerbate symptoms of this disease. Hence, adherence to a low glycemic index diet, through normalizing blood glucose levels, may reduce inflammation in patients with this disease. This study aimed to compare effects of a low glycemic index/high-fat, high-calorie diet and routine high-fat, high-calorie diet on inflammatory biomarkers in patients with cystic fibrosis. In this randomized clinical trial, 44 children and adolescents with cystic fibrosis were randomly assigned to receive for three months either a high-fat, high-calorie diet (n = 22) or a low glycemic index/high-fat, high-calorie diet (n = 22) with similar calorie and macronutrients composition to the control diet. Patients in first arm were allowed to use all sources of carbohydrates with different glycemic indices, whereas those in another arm consumed carbohydrates from low glycemic index sources. Serum levels of the pro-inflammatory cytokines IL-6, IL-17A, and IFNγ, and the anti-inflammatory cytokine IL-10 were measured at baseline and after the end of the trial. There were significant differences between groups for IL-6 (P = 0.02) and IL-17 (P = 0.01), in favor of the low glycemic diet, but no between-group differences were detected in IL-10 and IFN-γ. Although serum levels of IL-17 were reduced in both the groups as compared with the baseline values, this reduction was only significant in the group assigned to the low glycemic diet (P= 0.007), In addition, IL-6 serum levels decreased and those of IL-10 increased significantly as compared with the baseline values in the low glycemic diet (P= 0.01). It seems that adherence to a low glycemic index/high-fat, high-calorie diet for three months can improve some inflammatory biomarkers in children and adolescents with cystic fibrosis compared with the high-fat, high-calorie diet.

Key words: blood glucose, cystic fibrosis, diet, glycemic control, glycemic index, inflammation

INTRODUCTION

Cystic fibrosis (CF) is an autosomal-recessive inherited disorder and the result of a defect in the CF transmembrane conductance regulator (CFTR) on chromosome 7 [1]. The *CFTR* gene is translated into a chloride channel and its absence or failure causes incomplete chlorine transport and excess intracellular sodium and water resorption, which in turn results in abnormal and sticky mucus secretions in various organs such as the lungs and the pancreas, persistent pulmonary infections, airway obstruction, exocrine insufficiency [2, 3]. Currently, the disease occurs in a raising trend worldwide and its incidence is reported to be approximately 1 in 3000 births [4, 5].

The host inflammatory response in CF has long been recognized as a central pathological feature and an important therapeutic target [3, 6]. Patients with CF have excessive neutrophil response, and higher levels of inflammatory cytokines, contributing to lung tissue

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damage and ultimately lung dysfunction [3]. Given that inflammation is associated with increased risk of mortality, strategies aimed at reducing inflammation could be beneficial in the prevention of CF-related complications [7].

Studies have shown that postprandial hyperglycemia is present in patients struggling with CF, regardless of showing common complication of CF-related diabetes [7]. Management of hyperglycemia is particularly important since hyperglycemia exacerbates the clinical symptoms in CF by inducting an immune response [7, 8]. Pervious experimental studies have shown an increased lymphocytic response in hyperglycemia. It appears that hyperglycemia observed in patients with CF leads to impaired function of lymphocytes such as T helper-17 and regulatory T cells (Treg), which in turn leads to elevated levels of IL-17A, creating a vicious cycle and an abnormal immune response [7]. Hence, dietary interventions that enhance glucose homeostasis seem to be potentially effective in modulating immune responses in these patients.

Low glycemic index (GI) diet, containing foods with carbohydrates that are more slowly digested and absorbed than a high GI diet, could normalize glycemia and down regulate inflammation [9]. Low GI foods have shown to be potentially effective in improving glycemic control in other forms of diabetes [10-12], whereas high GI foods have been associated with increased oxidative stress and inflammation [13, 14]. However, evidence for the use of low GI diets in patients with CF is lacking.

As the primary goal of nutrition therapy in CF is to achieve optimal weight gain and growth, a high-fat, high-calorie diet (HFHC) has been recommended for these patients [15]. However, such diet does not take into consideration the significant effects of GI diet on inflammatory biomarkers. Hence, we designed this study to compare effects of a low-GI, high-fat, high-calorie diet (LG) and routine HFHC diet on inflammatory biomarkers in patients with cystic fibrosis.

MATERIALS AND METHODS

Study design

This is a randomized, double-blinded, parallel-group, clinical trial, which was approved by the local Ethics Committee of Tehran University of Medical Sciences (No: IR.TUMS.VCR.REC.1396.3171). The study was registered in the Iranian Registry of Clinical Trial (http://www.irct.ir, No. IRCT2017102325267N5). All the patients were given a brief explanation about study objectives, and also all were informed regarding the diets. Moreover, all the patients signed a written informed consent prior to their enrolment.

Abbreviations

CF	Cystic fibrosis
GI	Low glycemic index
LG	Low-GI, high-fat, high-calorie diet
HFHC	High-fat, high-calorie diet
CFTR	CF trans membrane conductance regulator
CFRD	Cystic fibrosis-related diabetes mellitus
Treg	Regulatory T cells
IPAQ	International physical activity questionnaire
ANCOVA	Analysis of covariance

Participants

The study was conducted on 44 children and adolescents with CF who were referred to the Cystic Fibrosis Clinic of the Children's Medical Center, affiliated with Tehran University of Medical Sciences, from December 2018 to June 2019. All children and adolescents aged 6-18 years old who were diagnosed with CF by a sweat test or genetic test had eligibility criteria. Also, levels of oral glucose tolerance test (OGTT) were checked from participants' medical records and those who had normal OGTT and no CFRD were considered in the study. The patients were excluded if they:

1) had other chronic diseases such as diabetes and thyroid disease, liver diseases (i.e., hepatitis and cirrhosis);
2) were hospitalized at the beginning of the study or one month earlier;
3) had a history of surgery one month prior to the intervention or were supposed to undergo surgery (except for dental surgery) in the next three months;
4) had allergy or intolerance to certain foods;
5) used steroids;
6) were not willing to follow the prescribed diets; and
7) were unable to adhere to the diets.

Sample size

The sample size was determined by a previous trial [16] and formula suggested for randomized clinical trials, with type I error of 5%, type II error of 20%, and 4 pg mol/ml of IL17-A difference between groups. The number of adequate samples was calculated as 21 patients. However, due to possible drop out during the study period, we recruited 30 patients in each group to get a more confident result.

Randomization and blinding

Patients were randomly allocated to either a HFHC group (n = 30) or a GI group (n = 30) by an assistant, using permuted block randomization method. Stratified randomization was employed to match participants based on age and sex distribution.

Given the nature of the intervention (diet), investigators were not blinded to the intervention. However, all the outcomes were measured by an independent assessor who was blinded to the group allocation. Also, patients and data analysts were blinded to group allocation.

Intervention

During the three-month intervention, the patients in the HFHC diet arm received a high-fat, high-calorie diet plan, containing 40% fat, 20% protein, and 40% carbohydrate. The participants of this group were allowed to consume all sources of carbohydrates with different glycemic indices. According to the pediatrics

clinics formula [17, 18], total energy was estimated for each participant.
The patients in the LG diet arm received in the same time period a high-fat, high-calorie diet plan, with macronutrients composition similar to that of the HFHC diet group; however, these patients were instructed to obtain their intake of carbohydrates from low GI food sources. All the patients received a leaflet, presenting the number of portions per meal, food exchange list, food recommendations. The patients in the low GI diet group were also given a list of allowed and forbidden high GI foods (high GI was considered GI≥50). All the patients were trained to follow the instructions of the diet plans.

Data collection

Patients or their parents completed a general information form, including items about patients' baseline characteristics (age, sex, height, weight, physical activity, age at the diagnosis of CF, and current medications and supplements). Body weight was measured using a weighing scale (Seca, Hamburg, Germany) while wearing light clothing and without shoes. By using the Seca stadiometer to the nearest 0.1 cm, height was measured in the standing position. Two 3-day dietary recalls were collected throughout the trial to assess dietary intakes. To estimate dietary intakes of energy, macro- and some micronutrients, Nutritionist software version 4 (First Data Bank, San Bruno, CA, USA) was used. Also, a dietitian was assigned to check participants via telephone weekly to assess their adherence during the study period. The criterion for compliance in the low GI group was GI< 50, calculated from the food diaries. To extract GI values the Iranian GI table was considered reference [19]. Also, the international table of GI [20] was used for GI values which are not reported on the Iranian-specific table. The GI for foods not included in the Iranian or the international table was estimated using the GI for the most similar food. To calculate the mean GI for diet, the reported formula was used [21].
During the study period, the patients were monitored weekly by the investigator, and any occurrence of adverse events was recorded.
After a 12-hour overnight fast, venous blood samples (10 ml) were taken by trained nurses in seated position to measure biomarkers. Then, blood samples were centrifuged at 3000 rpm for 10 min at 4 °C to obtain the serum and were stored at −80 °C until biochemical analyses. Serum of IL-6, IL-10, IL-17A, and IFNγ were determined by the ELISA kits of Shanghai Crystal Day commercial kits (Intra-assay CV < 8% and Inter-assay CV < 10%) and sandwich ELISA using an automatic device (Elisys Uno Human®). All the biochemical measurements were assessed at baseline and at the end of the intervention period in both the groups [22].

Statistical analyses

Statistical analyses were performed by SPSS version 23.0 (SPSS, Chicago, IL, U.S.A). The level of significance was set at a probability of ≤ 0.5 for all analyses. The Kolmogorov-Smirnov test was applied to explore the normality distribution of variables. Data followed a normal distribution; hence, parametric tests were used to analyze the data. The paired t-test was performed for within-group changes comparisons (baseline vs. post-intervention values) of quantitative variables. The analysis of covariance (ANCOVA), adjusted for age, energy intake, and baseline values, was used for evaluation of between-group differences. Also, the Chi-Square test was used to compare the groups in terms of qualitative variables.

RESULTS

In this trial, a total of 60 patients with CF were randomized to either a LG diet or a HCHF diet. During the follow-up period, 8 patients in the LG group and 8 in the HCHF group were dropped out, and finally a total of 44 patients were analyzed (LG diet: n = 22; HCHF diet: n = 22) (*figure 1*).
There were no significant differences between two groups in terms of baseline characteristics (*table 1*). Also, there were no significant differences in energy and macronutrients intake between the two groups throughout the trial (*table 2*).
In the LG group, IL-17 decreased significantly compared with baseline values (P= 0.007), but this reduction was not statistically significant in the HCHF group (P= 0.56). Significant differences in the level of IL-17 were detected between two groups at the end of the study period after adjustment for age, energy intake, and baseline values. (P= 0.01). In the LG group, IL-6 decreased and IL-10 increased significantly compared with baseline values (P= 0.01). However, there was significant between group difference only for change of IL-6 after adjustment for age, energy intake, and baseline values (P= 0.02), in favor of the LG diet group. Regarding INF-γ, no significant between-group and within-group differences were found. Also fasting blood glucose (P= 0.003) significantly decreased after the intervention in the low glycemic index group, whereas in another group a significant increase in fasting blood glucose (P= 0.038) was found and between-group differences were marginally significant (P= 0.05) (*table 3*).

DISCUSSION

To our knowledge, no study has yet evaluated the effects of a low GI diet, with similar calorie and macronutrient composition to the routine HFHC diet on inflammatory biomarkers in patients with CF. Although the potential role of low GI diets as an intervention for CF has been recognized [23], evidence that paid attention to low GI diets in CF is lacking.
It is recommended that energy intake for CF patients should be between 120 and 150% of the recommended diet for healthy people based on age and sex. A high energy intake is recommended in patients with CF because they are at increased risk of malnutrition due to impaired digestion and absorption, imbalances between energy intake and energy expenditure, and inflammation-induced increases in resting metabolic rate [8, 24, 25]. However, the energy-dense routine CF

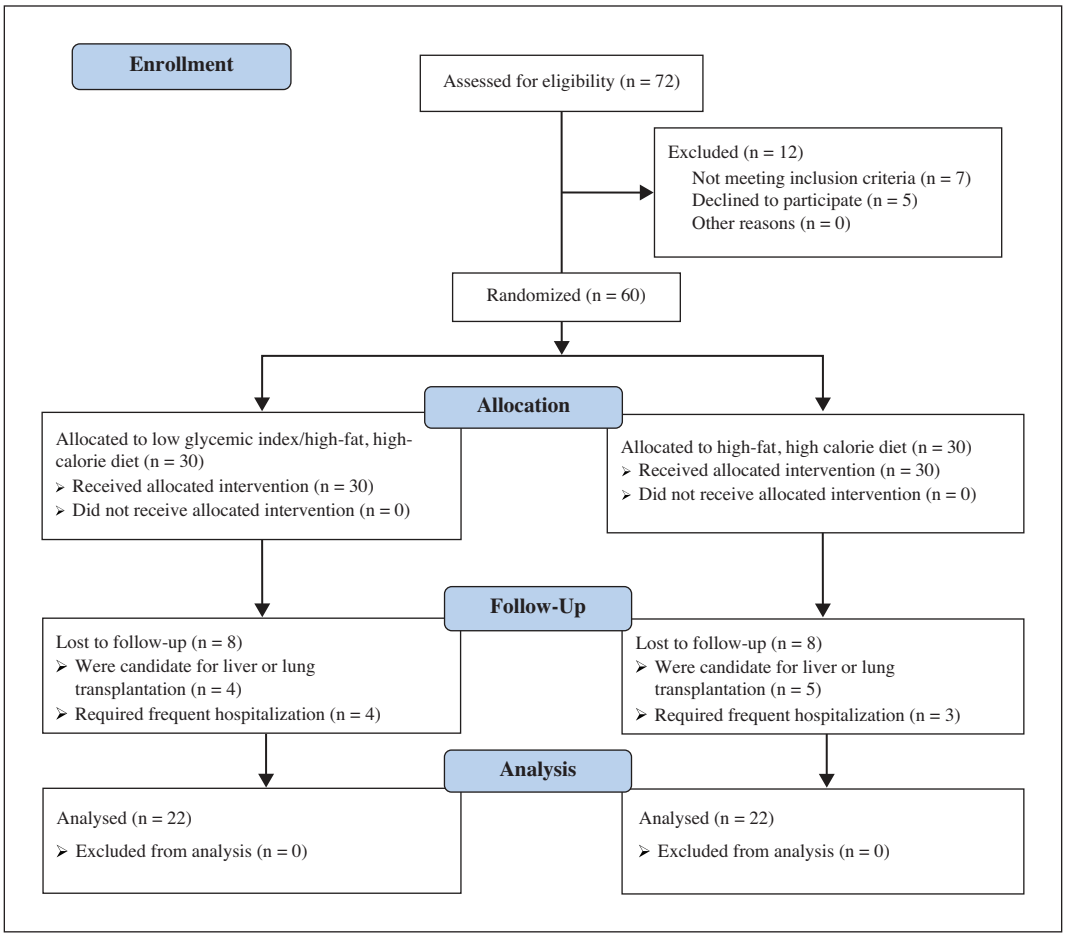

Figure 1
CONSORT 2010 flow diagram.

diet is often high in sugar; hence, it may contribute to poor glycemic control in patients suffering from this disease [26]. Glycemic control is known to promote clinical status and pulmonary function and to reduce mortality [27, 28].

Currently studies have shown the importance of elevated lymphocyte responses; specifically enhanced Th-17 and Th2 activity in CF [29, 30]. Moreover, the activity of the anti-inflammatory regulatory T cells (Tregs) is impaired in CF [31]. There also have been interests in Th-17 T-cells in CF because of their potentiality to promote neutrophil recruitment into the lungs [32, 33]. Studies have found elevated levels of IL-17 and Th-17 in patients with CF compared with healthy controls [34-36]. Other studies have demonstrated that adaptive immunity is also modulated in

Table 1
Baseline characteristics of patients in the intervention and control groups.

Variables		HFHC group (n= 22)	LG group (n= 22)	P-value
Age (year)		7.86 ± 3.53	10.15 ± 4.34	0.06†
Weight (Kg)		22.40 ± 11.27	28.10 ± 12.20	0.11†
Height (cm)		119.29 ± 21.70	129.69 ± 19.25	0.10†
Age at diagnosis of CF		2.75 ± 1.17	2.79 ± 1.22	0.90†
Gender (male)		21.6	25.5	0.54¼
Physical activity (active) (%)		27.3	31.8	0.43¼
Current medications and supplements	Pancreatin use (%)	45.5	40.9	0.25¼
	Dornase alfa use (%)	45.5	45.5	
	Hypertonic saline (%)	9.1	13.6	

The results are described as mean ± standard deviation(SD) or number (%). HFHC: high-fat, high-calorie diet; LG: low-glycemic index/high-fat, high-calorie diet.
† Obtained by independent sample t-test.
¼ Obtained by Chi-Square test.

Table 2
Dietary intakes of patients with cystic fibrosis who received either a high fat, high-calorie diet or a low glycemic index/high fat, high-calorie diet throughout the trial.

Variables	HFHC group (n= 22)	LG group (n= 22)	P-value†
Energy (kcal/d)	1791.63 ±108.42	1844.09 ±129.68	0.15
Protein (g/d)	53.64 ± 8.71	57.58 ± 8.81	0.14
Fat (g/d)	78.47 ±11.94	74.0 ±10.44	0.19
Carbohydrate (g/d)	224.85 ±28.07	243.74 ±33.99	0. 15
PUFA (g/d)	22.25 ±5.21	21.15 ±4.10	0.44
Iron (mg/d)	10.25 ±1.92	11.61 ±2.61	0. 5
Magnesium (mg/d)	220.91 ±33.74	232.98 ±37.88	0.27
Vitamin C (mg/d)	78.05 ±40.26	87.92 ±44.72	0.44
Dietary fiber (g/d)	14.20 ±2.48	15.42 ±4.50	0.27
Calcium (mg/d)	565.39 ±164.76	526.52 ±125.16	0.38

The results are described as mean ± standard deviation(SD). HFHC: high-fat, high-calorie diet; LG: low-glycemic index/high-fat, high-calorie diet; PUFA: polyunsaturated fatty acids.
† Obtained by independent sample t-test.

patients with CF [37]. Brodlie et al. reported increased production of IL-6 by stimulating epithelial cells with IL-17 [38]. Another study in mice has also reported that Th-17 cells and IL-17 are implicated in the pulmonary immune response by stimulating the secretion of CXCL8 and IL-6 from epithelial cells [39]. The present study revealed that LG diet significantly decreased serum levels of IL-6 and IL-17, whereas it increased serum levels of IL-10. Our findings are in agreement with the results of the previous studies showing that both IL-17 and IL-6 can decrease with low GI. One experimental study reported that lymphocytes responded in an overstate fashion to hyperglycemia [40]. In addition, in a review article it was mentioned hyperglycemia and glucose fluctuations in patients with CF might negatively affect lymphocyte subsets such as Th-17 and promote its production of IL-17 [7].

Based on our findings a low GI diet for three months decreased serum IL-17 levels and it increased serum levels of IL-10. IL-17 has been shown to up-regulate epithelial mucin-producing genes, which is present in the pathophysiology of CF [36, 41]. Also, previous observations have shown CF airways are deficient in IL-10 that terminates the acute inflammatory response, down regulates production of pro-inflammatory cytokines and chemokines, inhibits pro-inflammatory transcription factors, and induces neutrophil apoptosis [42, 43].

Earlier studies also reported the association between dietary GI and inflammation [13]. Some studies reported an inverse association between dietary GI and GL (glycemic load) and serum concentrations of inflammatory biomarkers [13], whereas others found no significant associations [44]. Nevertheless, there is a dearth of evidence in this area in CF patients.

The main strength of our study is that it was the first randomized clinical trial exploring the effects of a LG diet on inflammatory biomarkers in patients with CF. However, our study had some limitations. When

Table 3
Inflammatory biomarkers at study baseline and 3 months after intervention in patients with cystic fibrosis who received either a high fat, high-calorie diet or a low glycemic index/high fat, high-calorie diet

	HFHC group (n= 22)				LG group (n= 22)				P-value†
	Baseline	End	Change	P-value¼	Baseline	End	Change	P-value¼	
IL-10(ng/ml)	241.34±110.80	242.5±111.34	1.16 ± 7.54	0.47	213.27±95.90	216.35±96.14	3.08 ± 5.54	0.01	0.3
INFγ(ng/ml)	149.91±98.83	156.47±111.11	6.55 ±18.05	0.10	165.46±116.86	169.70±121.08	4.24±10.39	0.06	0.3
1L-17A(ng/L)	423.60±98.05	427.44±314.21	-5.15±40.91	0.56	418.45±247.22	377.80±205.04	-40.64±63.41	0.007	0.01
IL-6(ng/L)	173.58±98.05	174.39±97.51	0.80 ± 9.84	0.7	177.81±67.31	168.21±57.14	-9.60 ±17.11	0.01	0.02
Glucose (mg/dl)	89.23±6.21	94.55±13.48	5.31 ±11.23	0.038	103.82±15.90	92.86±11.64	-10.95 ± 15.19	0.003	0.05

The results are described as mean ± standard deviation(SD). IFNγ: interferon-gamma; IL: interleukin ; HFHC: high-fat, high-calorie diet; LG: low-glycemic index/high-fat, high-calorie diet.
† Obtained by by ANCOVA (between -group differences after adjusting for age,energy intake and baseline values).
¼ Obtained by paired sample t-test.

evaluating inflammatory biomarkers, only four inflammatory cytokines were assessed, and other inflammatory cytokines were not considered. Also, there was no biochemical indicator used to assess adherence to the diet. Future studies should consider examining inflammation in induced sputum and exhaled breath of patients suffering from CF. Finally, future studies are recommended to investigate serum metabolomics, proteomics, and lipidomics in addition to measuring cytokines.

Adherence to a LG diet for three months seems to be effective in improving some inflammatory biomarkers in children and adolescents with CF. Further studies are needed to confirm these results, considering aforesaid limitations.

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REFERENCES

1. Riordan JR, Rommens JM, Kerem B-S, *et al*. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989; 245(4922):1066-73.
2. Berdiev BK, Qadri YJ, Benos DJ. Assessment of the CFTR and ENaC association. *Mol Biosyst* 2009; 5(2):123-7.
3. Nichols DP, Chmiel JF. Inflammation and its genesis in cystic fibrosis. *Pediatr Pulmonol* 2015; 50(Suppl 40):S39-56.
4. Parker-McGill K, Nugent M, Bersie R, *et al*. Changing incidence of cystic fibrosis in Wisconsin, USA. *Pediatr Pulmonol* 2015; 50 (11):1065-72.
5. Hangul M, Pekcan S, Kose M, *et al*. The incidence of cystic fibrosis in the central region of Anatolia in Turkey between 2015 and 2016. *Balkan Med J* 2019; 36(3):179-83.
6. Chmiel JF, Berger M, Konstan MW. The role of inflammation in the pathophysiology of CF lung disease. *Clin Rev Allerg Immunol* 2002; 23(1):5-27.
7. Ziai S, Coriati A, Gauthier MS, Rabasa-Lhoret R, Richter MV. Could T cells be involved in lung deterioration and hyperglycemia in cystic fibrosis? *Diabetes research and clinical practice* 2014; 105(1):22-9.
8. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc* 2008; 108(5):832-9.
9. Jenkins DJ, Kendall CW, McKeown-Eyssen G, *et al*. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. *JAMA* 2008; 300(23):2742-53.
10. Jarvi AE, Karlstrom BE, Granfeldt YE, Bjorck IE, Asp NG, Vessby BO. Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients. *Diabetes Care* 1999; 22(1):10-8.
11. Gilbertson HR, Brand-Miller JC, Thorburn AW, Evans S, Chondros P, Werther GA. The effect of flexible low glycemic index dietary advice *versus* measured carbohydrate exchange diets on glycemic control in children with type 1 diabetes. *Diabetes Care* 2001; 24(7):1137-43.
12. Esfahani A, Wong JM, Mirrahimi A, Srichaikul K, Jenkins DJ, Kendall CW. The glycemic index: physiological significance. *J Am College Nutr* 2009; 28 : 439s-s445.
13. Buyken AE, Goletzke J, Joslowski G, *et al*. Association between carbohydrate quality and inflammatory markers: systematic review of observational and interventional studies. *Am J Clin Nutr* 2014; 99(4):813-33.
14. Rouhani MH, Kelishadi R, Hashemipour M, *et al*. The impact of a low glycemic index diet on inflammatory markers and serum adiponectin concentration in adolescent overweight and obese girls: a randomized clinical trial. *Horm Metab Res* 2016; 48 (4):251-6.
15. Lai HC, Kosorok MR, Laxova A, Davis LA, FitzSimmon SC, Farrell PM. Nutritional status of patients with cystic fibrosis with meconium ileus: a comparison with patients without meconium ileus and diagnosed early through neonatal screening. *Pediatrics* 2000; 105(1 Pt 1):53-61.
16. Karabulut S, Afsar CU, Karabulut M, *et al*. Evaluation of serum interleukin-17 (IL-17) levels as a diagnostic marker in pancreatic adenocarcinoma. *Int J Gastrointest Cancer* 2016; 47 (1):47-54.
17. Lusman S, Sullivan J. Nutrition and growth in cystic fibrosis. *Pediatr Clin North Am* 2016; 63(4):661-78.
18. Ramsey BW, Farrell PM, Pencharz P. Nutritional assessment and management in cystic fibrosis: a consensus report. The Consensus Committee. *Am J Clin Nutr* 1992; 55(1): 108-16.
19. Azadbakht L, Mohammadifard N, Akhavanzanjani M, Taheri M, Golshahi J, Haghighatdoost F. The association between dietary glycemic index, glycemic load and diet quality indices in Iranian adults: results from Isfahan Healthy Heart Program. *Int J Food Sci Nutr* 2016; 67(2):161-9.
20. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* 2002; 76(1):5-56.
21. de Rougemont A, Normand S, Nazare JA, *et al*. Beneficial effects of a 5-week low-glycaemic index regimen on weight control and cardiovascular risk factors in overweight non-diabetic subjects. *Br J Nutr* 2007; 98(6):1288-98.
22. Daneshi-Maskooni M, Keshavarz SA, Qorbani M, *et al*. Green cardamom supplementation improves serum irisin, glucose indices, and lipid profiles in overweight or obese non-alcoholic fatty liver disease patients: a double-blind randomized placebo-controlled clinical trial. *BMC* 2019; 19(1):59.
23. Balzer BW, Graham CL, Craig ME, *et al*. Low glycaemic index dietary interventions in youth with cystic fibrosis: a systematic review and discussion of the clinical implications. *Nutrients* 2012; 4(4):286-96.
24. Frost F, Dyce P, Ochota A, *et al*. Cystic fibrosis-related diabetes: optimizing care with a multidisciplinary approach. *Diabetes Metab Syndr Obes* 2019; 12 : 545-52.
25. Pencharz PB, Durie PR. Pathogenesis of malnutrition in cystic fibrosis and its treatment. *Clin Nutr* 2000; 19(6):387-94.
26. Birch L, Lithander FE, Hewer SL, Harriman K, Hamilton-Shield J, Perry R. Dietary interventions for managing glucose abnormalities in cystic fibrosis: a systematic review protocol. *Syst Rev* 2018; 7(1):98.
27. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence and mortality. *Diabetes Care* 2009; 32(9):1626-31.

28. Rana M, Munns CF, Selvadurai H, Donaghue KC, Craig ME. Cystic fibrosis-related diabetes in children–gaps in the evidence? *Nat Rev Endocr* 2010; 6(7):371-8.

29. Regamey N, Tsartsali L, Hilliard TN, *et al*. Distinct patterns of inflammation in the airway lumen and bronchial mucosa of children with cystic fibrosis. *Thorax* 2012; 67(2):164-70.

30. Hartl D, Griese M, Kappler M, *et al*. Pulmonary T(H)2 response in Pseudomonas aeruginosa-infected patients with cystic fibrosis. *J Allergy Clin Immunol* 2006; 117(1):204-11.

31. Hector A, Schafer H, Poschel S, *et al*. Regulatory T-cell impairment in cystic fibrosis patients with chronic pseudomonas infection. *Am J Respir Crit Care Med* 2015; 191(8):914-23.

32. Guran T, Ersu R, Karadag B, *et al*. Association between inflammatory markers in induced sputum and clinical characteristics in children with non-cystic fibrosis bronchiectasis. *Pediatr Pulmonol* 2007; 42(4):362-9.

33. Konstan MW, Doring G, Heltshe SL, *et al*. A randomized double blind, placebo controlled phase 2 trial of BIIL 284 BS (an LTB4 receptor antagonist) for the treatment of lung disease in children and adults with cystic fibrosis. *J Cyst Fibros* 2014; 13 (2):148-55.

34. McAllister F, Henry A, Kreindler J L, *et al*. Role of IL-17A, IL-17F, and the IL-17 receptor in regulating growth-related oncogene-alpha and granulocyte colony-stimulating factor in bronchial epithelium: implications for airway inflammation in cystic fibrosis. *J Immunol* 2005; 175(1):404-12.

35. Tan HL, Regamey N, Brown S, Bush A, Lloyd CM, Davies JC. The Th17 pathway in cystic fibrosis lung disease. *Am J Respir Crit Care Med* 2011; 184(2):252-8.

36. Decraene A, Willems-Widyastuti A, Kasran A, De Boeck K, Bullens DM, Dupont LJ. Elevated expression of both mRNA and protein levels of IL-17A in sputum of stable Cystic Fibrosis patients. *Respir Res* 2010; 11 : 177.

37. Moss RB. Lymphocytes in cystic fibrosis lung disease: a tale of two immunities. *Clin Exp Immunol* 2004; 135(3):358-60.

38. Brodlie M, McKean MC, Johnson GE, *et al*. Raised interleukin-17 is immunolocalised to neutrophils in cystic fibrosis lung disease. *Eur Respir J* 2011; 37(6):1378-85.

39. Nembrini C, Marsland BJ, Kopf M. IL-17-producing T cells in lung immunity and inflammation. *J Allergy Clin Immunol* 2009; 123(5):986-94.

40. Maciver NJ, Jacobs SR, Wieman HL, Wofford JA, Coloff JL, Rathmell JC. Glucose metabolism in lymphocytes is a regulated process with significant effects on immune cell function and survival. *J Leukoc Biol* 2008; 84(4):949-57.

41. Lubberts E, van den Bersselaar L, Oppers-Walgreen B, *et al*. IL-17 promotes bone erosion in murine collagen-induced arthritis through loss of the receptor activator of NF-kappa B ligand/ osteoprotegerin balance. *J Immunol* 2003; 170(5):2655-62.

42. Moss RB, Bocian RC, Hsu YP, *et al*. Reduced IL-10 secretion by CD4+ T lymphocytes expressing mutant cystic fibrosis transmembrane conductance regulator (CFTR). *Clin Exp Immunol* 1996; 106(2):374-88.

43. Cantin AM, Hartl D, Konstan MW, Chmiel JF. Inflammation in cystic fibrosis lung disease: Pathogenesis and therapy. *J Cyst Fibros* 2015; 14(4):419-30.

44. Mager DR, Iniguez IR, Gilmour S, Yap J. The effect of a low fructose and low glycemic index/load (FRAGILE) dietary intervention on indices of liver function, cardiometabolic risk factors, and body composition in children and adolescents with nonalcoholic fatty liver disease (NAFLD). *JPEN J Parenter Enteral Nutr* 2015; 39(1):73-84.