Original Communication

Low carbohydrate diet score and odds of neuromyelitis optica spectrum disorder: A case-control study

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Abstract: *Introduction*: Neuromyelitis optica spectrum disorder (NMOSD) is a demyelinating inflammatory disease of The Central nervous system. We aimed to investigate the association between low carbohydrate diet (LCD) and NMOSD odds. *Method*: Seventy NMOSD patients with definite diagnosis and 164 hospital-based controls were enrolled in this case-control study. Dietary data was obtained using a validated 168-item food frequency questionnaire. To determine the LCD score, participants were stratified into 11 groups according to carbohydrate, protein, fat, animal fat, animal protein, vegetable fat and vegetable protein intakes. Higher intake of protein and fat, and lower intake of carbohydrate received a higher score between 0-10. Macronutrients scores were summed together and LCD scores calculated. The association between LCD scores and likelihood of being assigned to NMOSD group was investigated using multiple regression models. *Results*: Total LCD scores increased from the median of 21.00 in the first decile to 53.00 in the tenth decile of LCD score. After adjustment for confounding factors including age, gender, BMI, energy intake, cigarette smoking and alcohol consumption, an inverse association was detected between LCD scores and odds of NMOSD. The odds of suffering from NMOSD declined significantly about 78% (OR: 0.22; 95% CI: 0.05–0.87) and 76% (OR: 0.24; 95% CI: 0.06–0.93) in the fifth and sixth deciles of LCD score compared to the first decile. *Conclusion*: From the obtained results it can be speculated that higher carbohydrate and lower protein and fat intakes may be associate with the increased odds of NMOSD. However, further studies are needed to confirm these results.

Keywords: Neuromyelitis optica spectrum disorder, diet, low carbohydrate, case-control

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an infrequent neuro-inflammatory autoimmune disorder of the central nervous system (CNS) that is characterized by demyelination in optic nerves and spinal cord [1–3]. This severe disabling disease leads to motor dysfunctions and visual deficit [2, 4]. The mean age of NMOSD incidence is reported as 36 years in Iran and it is more prevalent among females with a female to male ratio of 1.2:1 to 8:1 that has been reported in different studies [5, 6]. In 2019, the point prevalence of NMOSD in Tehran, the capital city of Iran has been estimated at 1.31 per 100,000 subjects [7].

It seems that the pathogenesis of NMOSD refers to the presence of immunoglobulin G autoantibodies (NMO-IgG) in NMOSD patient serum and it's binding to water channel aquaporin-4 (AQP4) on astrocytes as target antigen leads to inflammatory response and blood-brain barrier impairment that induce destruction in neurons and oligodendrocyte [2, 4, 8]. In addition, previous studies have shown the considerable role of pro-inflammatory cytokines in NMOSD pathogenesis. CNS and blood of NMOSD

patients have increased levels of cytokines such as interleukin (IL)-6, IL-2, IL-17, interferon-γ (INF-γ), Tumor necrosis factor α (TNFα), T helper (Th)-17, and Th2-related cytokines [9, 10].

A few studies have been published on the NMOSD risk factors, so far. According to the results of these studies, the possible modifiable risk factors for NMOSD are: low physical activity level and past history of trauma in both men and women, and intentional abortion and low body mass index (BMI) just in women [6, 11]. Dietary factors including low consumption of dairy, sea foods, egg, red meat, chicken, fats, fruits, and vegetables in ages 13-18, are also proposed as NMOSD risk factors [6]. Identification of other probable risk factors, especially the modifiable ones, might improve NMOSD management.

The effects of diet on the inflammatory status in the body have been widely investigated [12–18]. Several studies have outlined the inflammatory effects of high carbohydrate consumption [12, 13, 17, 19] and conversely, the anti-inflammatory property of low carbohydrate diet (LCD) by reducing the levels of pro-inflammatory cytokines like IL-1β, TNFα, and IL-6 [14–16].

A rising number of papers have suggested beneficial effects of LCD on the prevention or control of different diseases such as cardiometabolic disease, metabolic syndrome, Alzheimer's disease, Parkinson's disease, migraine, and autism spectrum disorder [20–24]. LCD is the main treatment followed in children who are suffering from drug resistant seizures [25–27].

According to neuro-inflammatory characteristic of NMOSD and the pieces of evidence on anti-inflammatory effects of LCD, this study was designed to investigate whether high LCD score is associated with a lower likelihood of being assigned to NMOSD group or not?

Method

Study participants

This case-control study was conducted at Sina hospital, a referral center for NMOSD patients in Tehran, the capital city of Iran during October 2017 to July 2018. Definite diagnosis of NMOSD were according to 2016 international consensus criteria [28] and confirmed by neurologists.

Based on the NMOSD uncommon nature, all NMOSD prevalence cases who referred to Sina hospital during the study period were enrolled in the case group. From 137 admitted NMOSD patients, 18 cases were unavailable during the study and 9 subjects were not interested in cooperating in the study. Considering the exclusion criteria, 40 patients were excluded from the study for aged less than 18 years old, having chronic diseases, being pregnant or lactating, or changing their diet after NMOSD diagnosis. Finally, 70 NMOSD cases were included in the study.

One hundred sixty-four hospital-based controls were also recruited in the study. Controls selected from patients who attended in the hospital for a reason unrelated to NMOSD, Multiple Sclerosis (MS) or any neurological disorders and were eligible for inclusion if they had no past history of head trauma, chronic diseases such as diabetes, cardiovascular disease or hyperlipidemia, gastrointestinal disorder, hormonal dysfunction, chronic kidney disease, and chronic liver disease. In addition, following any special diets such as pregnancy or lactation regimens, weight loss regimens, any kind of vegetarian diets, etc. were also considered as exclusion criteria (Figure 1).

Protocol approval and patients' consents

The method applied by the present study was approved at the Institutional Review Board of National Institute for Medical Research Development (IRB number: IR.NIMAD.REC.1397.431.).

The study aims and protocols were explained for all participants and informed consents were taken from all of them before data collection.

Demographic and anthropometric assessments

Data on age, sex, smoking and alcohol consumption were collected through in-person interview in case and control groups. Participants weights were measured using a Seca digital scale (Seca, Hamburg, Germany) while they were barefoot and only minimally clothed, and recorded with an accuracy of 100 grams. Their heights were measured using a tape measure barefoot, in standing and relaxed position. Finally, BMI was calculated as "weight in kg divided by the square of the height in meters".

Dietary assessments

Dietary data were obtained using a validated 168-item, semi-quantitative food frequency questionnaire (FFQ) [29, 30]. Participants were asked to report the average frequency of each nutrition item consumption per day, week, month, or year, as well as the average amount of each item intake per consumption time based on the specific portion size that was determined in FFQ for each item over the prior year of study attendance. The macronutrient contents of food items were calculated according to the USDA Food Composition Databases (https://www.nal.usda.gov/ndb).

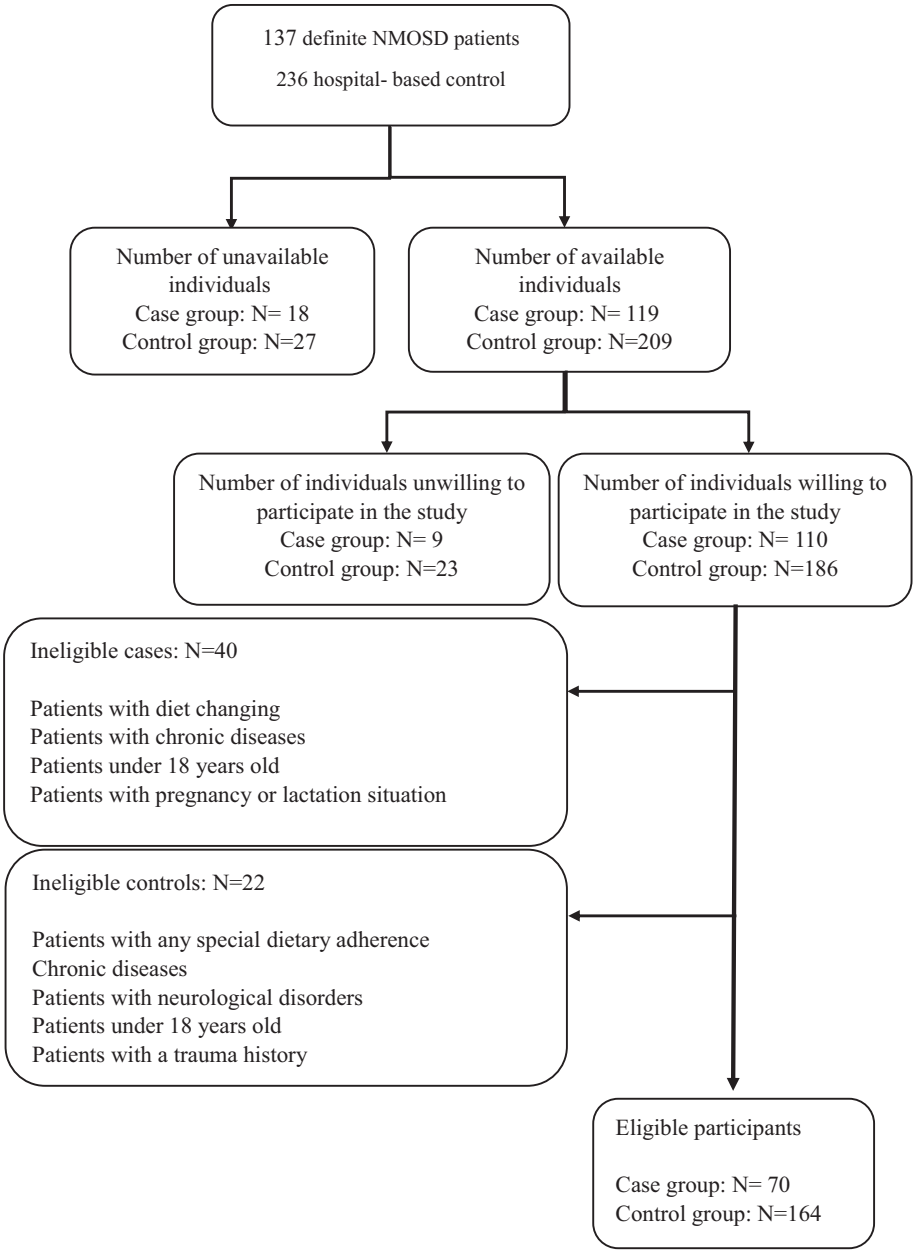

Figure 1. Flow chart for the selection of study participants.

Calculating low carbohydrate diet scores

LCD scores were determined using the method presented by Halton et al. in 2006 [31]. Study participants stratified into 11 equal groups according to each macronutrient intake including carbohydrate, total protein, total fat, animal fat, animal protein, vegetable fat, and vegetable protein intakes (Table 1). All seven items of the LCD score were used as a percentage of energy. Individuals with the highest intake of each nutrient (except carbohydrate) got 10 points in the 11th stratum, and participants in the next stratum got 9; thus, according to this scoring criterion, scores decreased across stratums to individuals in the first stratum with the lowest intake of each nutrient (except carbohydrate) who received 0. The criteria for scoring participants regarding carbohydrate intake was reversed, individuals in the lowest stratum received 10 points and participants' scores decreased across stratum to individuals in the 11th stratum who got 0. In the end, to calculate the LCD score, we summed these 7 nutrient points for each person and scored participants between 0-70. Therefore, those who had higher LCD scores had more dietary attendance to a low carbohydrate diet (having more fat and protein intakes and less carbohydrate intake) and participants with lower LCD scores had less

Table 1. The criteria for determining low carbohydrate diet scores

Scores	Total carbohydrate	Total protein	Animal protein	Vegetable protein	Total fat	Animal fat	Vegetable fat
			Percentage of energy				
0	56.79–74.97	7.03–11.33	1.79–3.90	4.24–6.42	16.30–31.18	3.54–6.35	11.73–17.74
1	54.92–56.57	11.43–12.90	3.91–4.70	6.42–6.85	31.26–32.84	6.42–7.80	17.91–20.32
2	53.86–54.87	12.96–13.80	4.75–5.31	6.87–7.16	32.84–34.36	7.82–8.71	20.49–21.92
3	52.51–53.61	13.83–14.38	5.32–5.94	7.16–7.55	34.38–35.40	8.75–9.67	21.93–22.86
4	51.53–52.50	14.39–14.90	5.95–6.54	7.56–7.83	35.40–36.29	9.71–11.01	22.87–24.21
5	50.30–51.51	14.95–15.47	6.58–7.00	7.83–8.22	36.39–37.38	11.04–11.73	24.24–25.58
6	49.40–50.18	15.47–16.08	7.00–7.44	8.22–8.65	37.40–38.24	11.75–12.46	25.58–26.87
7	48.11–49.39	16.10–16.68	7.46–8.34	8.65–9.18	38.34–39.56	12.52–13.74	26.95–28.86
8	45.65–48.07	16.83–17.71	8.36–9.26	9.19–9.58	39.60–41.94	13.75–15.27	29.08–30.72
9	42.89–45.64	17.75–18.49	9.33–10.25	9.60–10.86	41.95–44.92	15.34–17.05	30.77–35.22
10	30.86–42.82	18.57–23.01	10.25–14.11	10.88–15.02	45.18–63.79	17.07–29.90	35.49–58.86

attendance to a low carbohydrate diet (having less fat and protein intakes and more carbohydrate intake). The criteria for scoring participants in each item of LCD scores is shown in Table 1.

Statistical methods

The software used to analyze the data was Statistical Package for the Social Sciences (SPSS software), version 21 (Chicago: SPSS Inc. IBM Corp.). Participants were divided into 10 deciles based on their LCD scores. Baseline characteristics and dietary intakes of studied participants were reported as mean ± SD and compared through LCD score deciles applying linear regression analysis. In the case of categorical variables, the chi square test was used for making comparisons through these deciles. The association between LCD scores and odds of NMOSD was explored in 3 multiple regression models. Model 1 was adjusted for age (year, continuous) and gender (male, female, categorical). Model 2 was additionally adjusted for daily energy intake (kcal/d, continuous) and BMI (kg/m^2, continuous). Model 3 was further adjusted for cigarette smoking (yes, no, categorical) and alcohol consumption (yes, no, categorical). Odds ratios (OR) and 95% confidence intervals (CIs) were calculated accordingly. In order to estimate the linear trends across deciles of LCD scores, the median values of each decile considered as a continuous variable. P-value ≤ 0.05 was considered statistically significant.

Results

A total of 70 NMOSD cases and 164 controls were involved in this study by mean ages of 35.34 ± 9.87 and 42.94 ± 15.31 years in case and control groups, respectively. Eighty-five percent of participants in the case group and 62.2% in the control group were females.

Total LCD scores increased from the median of 21.00 in the first decile of LCD score to 53.00 in the tenth one. Median of total carbohydrate intake decreased from 56.08 to 43.29 percent of energy, from the first to the tenth deciles of LCD scores. Conversely, total protein and fat intakes raised across LCD scores deciles by the median of 13.19 to 17.37 and 32.35 to 41.47 percent of energy, respectively.

Participants' demographic and anthropometric data as well as dietary data according to deciles of LCD score are reported in Table 2. Total daily intakes of total fat, animal-based fat, plant-based fat, total protein, animal-based protein, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), cholesterol, legumes, poultry, red and processed-meat, total dairy, and low fat dairy had significant increasing trends across the LCD score deciles, while participants in higher deciles of LCD score had significantly lower daily intakes of total carbohydrate, total grain, refined grain, fiber, and fruits.

As it is presented in Table 3, there was an inverse association between higher LCD score and lower odds of suffering from NMOSD in all three models. By adjusting for age and gender in first regression model, higher LCD scores had 79% (OR: 0.21; 95% CI: 0.05–0.83) statistically significant decrease in NMOSD odds, in the fifth decile of LCD score vs the first decile (p-trend 0.11). After further adjustment for BMI and energy intake, fifth and sixth deciles of LCD scores showed significant lower OR for NMOSD as follows: (OR: 0.22; 95% CI: 0.05-0.86) for the fifth decile and (OR: 0.24; 95% CI: 0.06-0.93) for the sixth decile (p-trend 0.10). In the fully adjusted model which was additionally adjusted for cigarette smoking and alcohol consumption quite similar results to second model were obtained. All other deciles compared to the first reduced the NMOSD OR quite drastically, but only the 5 and 6 deciles were

Table 2. Baseline characteristics of participants according to the deciles of LCD scores

	Low carbohydrate diet scores										
	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	P-trend
Female (%)	70.8%	64.0%	59.3%	52.4%	73.9%	60.7%	83.3%	87.0%	64.0%	85.0%	0.14
Cigarette smoker (%)	16.7%	12.0%	7.4%	28.6%	8.7%	25.0%	5.6%	4.3%	20.0%	15.0%	0.24
Alcohol consumer (%)	16.7%	0.0%	14.8%	19.0%	13.0%	21.4%	11.1%	0.0%	16.0%	5.0%	0.21
Age (year)	36.75 ± 11.76	44.57 ± 14.75	43.78 ± 17.070	37.30 ± 9.42	40.48 ± 13.59	44.82 ± 14.76	37.17 ± 14.27	42.45 ± 17.17	37.26 ± 13.43	38.85 ± 13.01	0.51
BMI (kg/m^2)	24.60 ± 3.30	27.86 ± 5.26	29.66 ± 17.75	27.17 ± 4.70	26.48 ± 4.99	26.21 ± 4.19	26.05 ± 6.05	28.87 ± 4.59	26.79 ± 4.42	25.60 ± 6.39	0.76
Energy (Kcal)	2471.35 ± 882.63	2174.36 ± 730.30	2434.74 ± 696.04	2509.82 ± 818.92	2377.66 ± 568.42	2423.06 ± 682.14	2490.63 ± 999.51	2365.06 ± 754.44	2619.82 ± 1129.25	2319.09 ± 575.50	0.61
Carbohydrate (%energy)	57.43 ± 4.49	54.43 ± 1.76	53.91 ± 3.39	49.23 ± 7.45	50.94 ± 2.81	49.94 ± 3.51	48.64 ± 3.07	48.12 ± 3.03	45.97 ± 3.33	42.98 ± 3.86	0.00
Total protein (%energy)	13.00 ± 1.63	13.81 ± 1.71	15.13 ± 2.90	13.69 ± 3.44	15.03 ± 2.07	15.72 ± 2.69	15.63 ± 1.75	16.08 ± 1.82	16.55 ± 1.79	17.80 ± 2.28	0.00
Vegetable protein (%energy)	8.04 ± 1.38	8.43 ± 1.26	8.66 ± 2.05	7.31 ± 2.02	8.43 ± 1.74	8.30 ± 1.93	8.04 ± 1.74	7.98 ± 2.14	8.26 ± 1.40	8.96 ± 1.45	0.35
Animal protein (%energy)	4.96 ± 1.57	5.37 ± 1.56	6.47 ± 2.59	6.38 ± 2.24	6.60 ± 1.98	7.41 ± 2.24	7.59 ± 2.34	8.10 ± 1.97	8.28 ± 2.09	8.83 ± 2.27	0.00
Total fat (%energy)	32.63 ± 4.66	34.84 ± 3.34	34.58 ± 5.06	39.63 ± 10.16	37.26 ± 4.49	37.60 ± 5.00	38.72 ± 3.52	39.00 ± 4.38	40.43 ± 3.81	42.44 ± 4.57	0.00
Vegetable fat (%energy)	22.63 ± 5.33	25.98 ± 5.11	24.78 ± 6.26	29.45 ± 13.22	26.61 ± 6.03	23.46 ± 5.12	28.02 ± 6.10	25.18 ± 6.32	26.85 ± 6.14	28.15 ± 5.34	0.04
Animal fat (%energy)	10.00 ± 3.83	8.86 ± 3.13	9.79 ± 2.46	10.17 ± 4.06	10.66 ± 3.25	14.14 ± 4.84	10.70 ± 4.02	13.82 ± 4.98	13.58 ± 3.50	14.29 ± 3.80	0.00
Fiber (g)/1000 kcal	17.75 ± 4.12	17.79 ± 2.78	18.09 ± 4.83	15.62 ± 2.79	17.67 ± 3.91	15.40 ± 2.92	14.89 ± 3.78	15.55 ± 3.33	14.73 ± 2.90	15.85 ± 3.81	0.00
Total grain (g)	469.38 ± 179.63	387.59 ± 164.14	385.63 ± 139.51	403.83 ± 163.76	362.11 ± 143.11	367.53 ± 146.42	394.81 ± 143.25	337.86 ± 151.79	382.76 ± 206.27	280.54 ± 114.98	0.00
Whole grain (g)	80.29 ± 81.30	104.26 ± 83.83	110.51 ± 89.93	96.73 ± 97.64	103.96 ± 75.60	122.65 ± 89.83	68.74 ± 46.22	87.08 ± 58.89	89.04 ± 73.45	57.88 ± 47.24	0.11
Refined grain (g)	389.09 ± 167.85	283.33 ± 83.83	275.12 ± 143.00	307.09 ± 147.86	258.15 ± 120.54	244.88 ± 130.95	326.07 ± 142.01	250.79 ± 123.48	293.72 ± 164.56	222.67 ± 110.36	0.00
Total vegetables (g)	437.77 ± 203.51	391.44 ± 160.34	553.28 ± 518.58	396.35 ± 256.03	473.10 ± 214.95	432.10 ± 250.54	457.51 ± 342.68	431.77 ± 205.48	393.41 ± 188.24	481.52 ± 258.99	0.89
Simple sugars (g)	63.96 ± 70.97	56.75 ± 69.80	49.37 ± 70.18	56.63 ± 66.10	54.11 ± 50.15	42.73 ± 50.47	44.06 ± 36.20	69.41 ± 83.27	53.79 ± 71.25	39.93 ± 39.81	0.38
Fruits (g)	652.52 ± 475.67	362.49 ± 229.07	579.23 ± 413.08	462.09 ± 359.63	447.28 ± 266.67	405.27 ± 220.49	447.56 ± 321.48	445.12 ± 211.30	376.09 ± 224.98	400.40 ± 162.92	0.00
Nuts (g)	13.34 ± 17.39	8.82 ± 7.31	12.14 ± 12.61	10.59 ± 10.22	11.62 ± 11.18	10.62 ± 13.52	11.17 ± 13.83	12.69 ± 14.20	18.33 ± 27.10	17.09 ± 24.16	0.07
Poultry (g)	17.42 ± 15.07	24.99 ± 24.50	37.91 ± 29.79	32.16 ± 23.02	27.64 ± 17.64	31.13 ± 27.38	39.77 ± 36.85	40.34 ± 28.87	45.38 ± 31.95	53.10 ± 34.88	0.00
Fish (g)	10.88 ± 18.36	9.53 ± 15.37	12.87 ± 20.48	14.82 ± 24.76	17.22 ± 15.58	15.83 ± 28.61	11.51 ± 9.95	8.46 ± 6.79	19.98 ± 22.18	11.46 ± 10.12	0.39
Red and processed-meat (g)	43.03 ± 27.07	35.78 ± 22.23	31.56 ± 22.81	46.81 ± 27.15	42.08 ± 31.44	42.37 ± 24.78	52.63 ± 32.03	45.26 ± 25.82	52.97 ± 39.88	65.18 ± 45.70	0.00
Total dairy (g)	293.64 ± 142.81	258.24 ± 138.16	347.98 ± 189.78	342.43 ± 194.66	367.19 ± 209.10	470.13 ± 274.69	469.39 ± 466.16	528.77 ± 335.11	487.62 ± 238.28	467.87 ± 173.30	0.00
High-fat dairy (g)	138.25 ± 122.73	119.92 ± 127.84	129.76 ± 131.83	158.49 ± 168.76	171.25 ± 170.45	243.47 ± 187.54	253.64 ± 356.44	251.04 ± 324.89	200.13 ± 178.15	131.19 ± 124.60	0.09
Low-fat dairy (g)	155.39 ± 109.39	138.32 ± 95.27	218.23 ± 207.98	183.94 ± 174.75	195.94 ± 180.46	226.65 ± 284.82	215.75 ± 187.01	277.72 ± 246.29	287.49 ± 238.84	336.68 ± 216.81	0.00
Legumes (g)	32.30 ± 24.30	47.90 ± 32.43	55.57 ± 52.43	48.19 ± 39.79	54.92 ± 35.55	50.38 ± 41.66	60.16 ± 66.79	57.70 ± 51.98	60.15 ± 45.15	54.41 ± 31.95	0.05
PUFA (% total fat)	24.39 ± 4.43	28.27 ± 6.45	26.54 ± 5.38	28.81 ± 8.82	27.23 ± 5.51	23.44 ± 5.69	28.58 ± 7.40	25.10 ± 6.31	26.82 ± 6.73	25.45 ± 4.27	0.01
MUFA (% total fat)	31.71 ± 3.10	32.09 ± 5.40	31.21 ± 3.15	32.69 ± 2.93	31.90 ± 4.48	32.17 ± 4.43	31.40 ± 2.26	33.17 ± 3.72	31.71 ± 2.91	31.95 ± 3.86	0.00
SFA (% total fat)	28.44 ± 5.04	24.56 ± 4.87	26.20 ± 4.50	25.65 ± 6.80	25.66 ± 4.40	30.15 ± 4.88	27.10 ± 5.73	28.33 ± 5.94	27.71 ± 5.70	29.03 ± 4.14	0.00
Cholesterol (mg)	241.95 ± 133.60	206.31 ± 107.36	239.22 ± 110.25	278.30 ± 127.79	267.16 ± 191.39	287.84 ± 122.93	273.18 ± 135.10	297.87 ± 184.77	339.96 ± 185.13	315.65 ± 100.89	0.00

Plus-minus values are presented as mean ± standard deviation.

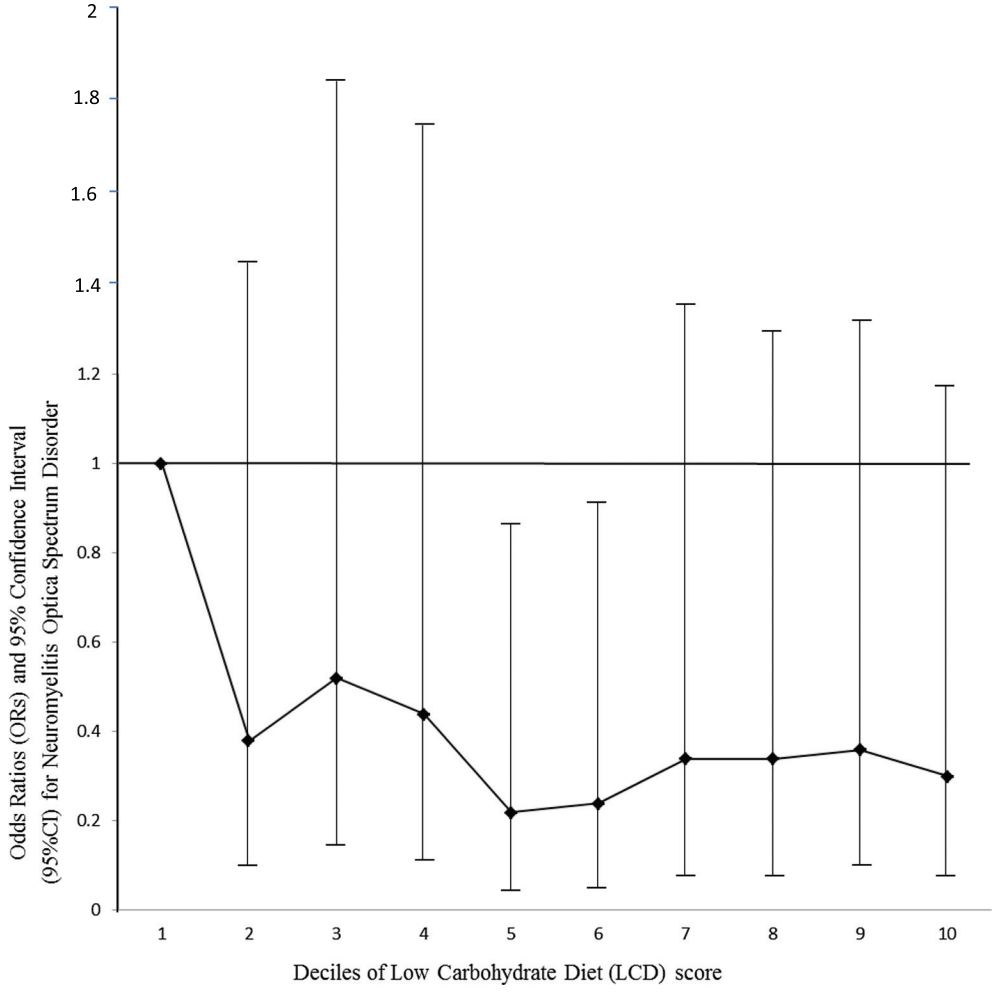

Figure 2. The adjusted odds ratio (OR) and 95% confidence interval (95% CI) for the odds of Neuromyelitis Optica Spectrum Disorder (NMOSD) based on the deciles of Low Carbohydrate Diet (LCD) score.

significant due to smaller confidence intervals. The obtained ORs and 95% CI of the third model are presented in Figure 2.

Discussion

The obtained results highlighted that reduced carbohydrate intake from 57% of total energy in the first decile to ~ 50% along with adequate consumption of protein ~ 15% and moderate fat intake to ~ 37% in fifth and sixth deciles of LCD scores could render NMOSD odds. About 25% of participants in the control group had a LCD score in the range of 5th and 6th deciles. All other deciles had decreased odds of NMOSD vs. the first decile, but were not significant due to the bigger confidence intervals. So, we cannot claim that the reverse association between LCD and NMOSD odds has a significant trend or the higher LCD score the greater protective it become.

It should be noted that more than half of the protein and about two third of the fat in these deciles came from plant sources. Data analysis underlined that lower intake of total carbohydrate in higher LCD score could be attributed to lower consumption of refined grain not lower whole grain.

According to the best of our knowledge, the present study is one of the first researches that assessed the association between dietary factors and NMOSD odds in NMOSD patients compared with controls. Until now, few studies have been published on environmental risks of NMOSD including nutritional factors. The results obtained from the present study appear to corroborate the observations of the Eskandarieh et al. study that NMOSD patients had a significant lower consumption of animal proteins including fish, chicken, meat, and dairy products compared to the control group. They also found that NMOSD patients had lower fat, fruit, and vegetable consumption [6].

For decades, it has been almost approved that a diet that is composed of approximately 45–65% of total daily energy intake of carbohydrate, 10–35% intake of protein

Table 3. ORs (95% CI) for NMOSD occurrence by deciles of LCD scores

	Low carbohydrate diet scores										
	Decile1	Decile2	Decile3	Decile4	Decile5	Decile6	Decile7	Decile8	Decile9	Decile10	P-trend
LCD score[¥]	21.00 (8.00–23.00)	25.00 (24.00–26.00)	28.00 (27.00–29.00)	31.00 (30.00–32.00)	34.00 (33.00–35.00)	37.00 (36.00–38.00)	39.50 (39.00–40.00)	41.00 (41.00–43.00)	47.00 (44.00–48.00)	53.00 (49.00–60.00)	
No. of cases	13	6	8	6	5	6	6	7	7	6	
No. of controls	11	19	19	15	18	22	12	16	18	14	
Model [1]	1.00	0.35 (0.09–1.30)	0.45 (0.13–1.57)	0.42 (0.11–1.58)	0.21 (0.05–0.83)	0.28 (0.07–1.02)	0.34 (0.08–1.31)	0.34 (0.09–1.26)	0.33 (0.09–1.20)	0.30 (0.08–1.14)	0.11
Model [2]	1.00	0.40 (0.10–1.53)	0.52 (0.15–1.84)	0.47 (0.12–1.82)	0.22 (0.05–0.86)	0.24 (0.06–0.93)	0.34 (0.08–1.35)	0.35 (0.09–1.35)	0.37 (0.10–1.33)	0.33 (0.08–1.27)	0.10
Model[3]	1.00	0.38 (0.10–1.45)	0.52 (0.14–1.84)	0.44 (0.11–1.74)	0.22 (0.05–0.87)	0.24 (0.06–0.93)	0.34 (0.08–1.37)	0.34 (0.08–1.31)	0.36 (0.10–1.34)	0.30 (0.07–1.18)	0.09

[¥]This variable is presented as median (minimum-maximum).
[1]Regression model adjusted for age and gender.
[2] Regression model adjusted for age and gender, BMI and energy intake.
[3]Regression model adjusted for age, gender, BMI, energy intake, cigarette smoking and alcohol consumption.

and 20–35% intake of fat can be considered as a healthy diet preventing the risk of several chronic disorders [32]. However, in recent years, some modifications have been made on these dietary guidelines. Especially, much attention has been paid on the association between reduced total carbohydrate content of diet (up to 45% of daily energy intake) and health outcomes such as weight reduction, and attenuating the risk and/or improving cardiovascular disorders, diabetes, nonalcoholic fatty liver disease, schizophrenia, epilepsy, cancer, and longevity [15, 33–37]. Alternatively, it is recommended that in a LCD, total protein as well as total fat intakes should be increased to moderate levels particularly from plant based sources [35–37]. It has been suggested that the effects of reduced carbohydrate on above mentioned conditions might be mediated through a variety of mechanisms. These mechanisms seem to include decreasing appetite, fatty acid synthesis and signaling of mammalian target of rapamycin (mTOR) pathway; increasing Peroxisome proliferator-activated receptor (PPAR)-α and nuclear factor erythroid 2–related factor 2 (NRF-2) signaling; and suppressing inflammatory markers which could occur subsequent to lower blood glucose levels and decreased signaling of insulin/insulin-like growth factor-1 (IGF-1) as a result of reducing the dietary carbohydrate intake [36–38].

From the nutritional point of view in chronic inflammatory disorders, some specific modifications in the diet known as "dietary approaches to reduce inflammation" have been implicated. In these approaches, a special emphasis has been made on whole dietary habit changes instead of individual food items. In this regard, the effect of dietary inflammatory index (DII) have received a lot of attention in recent years. There is no study on the association between DII and NMOSD but a little number of investigations have noted the positive association between DII and increased risk of MS as well as disability in MS patients [39, 40].

The anti-inflammatory effects of plant-based foods can be explained through suppressing expression of a proinflammatory markers including C-reactive protein (CRP), Nuclear Factor-kappa Beta (NFkB), and other related factors [32]. Consumption of a diet containing low glycemic index/load food items, restriction of sugars and refined carbohydrates, and increasing the intake of nuts and seeds (sources of plant-based fat) are recommended in these approaches [32]. Thus, the current results which revealed that a reduced carbohydrate intake concomitant with a higher consumption of plant fats and proteins associated with lower likelihood of suffering from NMOSD, further support the dietary recommendations to combat inflammation.

NF-κB and Activator protein 1 (AP-1) are two key pro-inflammatory transcription factors involved in the

induction of T-cells [41]. The up regulation of these two factors has been reported in multiple sclerosis [18] and NMOSD. High fat, high carbohydrate, and hyper caloric diets activate NF-kB and AP-1, and consequently cause the overexpression of pro-inflammatory factors such as TNF-alpha, IFN-γ, IL-1β, IL-2, 6, 18, hs-CRP, Receptor activator of nuclear factor kappa-B ligand (RANKL), Reactive oxygen species (ROS), Matrix metallopeptidase (MMP)-9, prostaglandins, lukotereiens, and adhesion molecules. As a result, extracellular matrix degeneration, inflammation, oxidative stress, and angiogenesis might be enhanced. Moreover, NF-kB is a protagonist of nuclear factor erythroid 2–related factor 2 (Nrf2), which is one of the main activators of cytoprotective genes. Conversely, NRF2 upregulation decreases NF-kB activation. Calorie restriction, omega-3 fatty acids, α-Linolenic acid (ALA), and butyrate (produced by gram positive gut bacteria as a result of metabolizing amino acids like tryptophan) activate NRF2 [41].

Moreover, in recent years, the gut-brain-axis (GBA) has received special attention. Gut dysbiosis affects many metabolic pathways and inflammatory processes. A high sugar/high fat diet triggers gut dysbiosis leading to elicit inflammation and consequent epithelium permeabilization, endotoxemia, and systemic low grade inflammation [41]. Chronic systemic inflammation begins and/or amplifies CNS inflammation [41].

Furthermore, when following low carbohydrate dietary recommendations, several dietary allergen sources containing gluten and processed food items might be eliminated or restricted from an individual's diet. Thus, an LCD could eventually lead to lower intakes of usual dietary allergens including artificial food additives, oral colors, and gluten [38]. On the other hand, it has been suggested that high intakes of these allergens might result in aggregating the risk of autoimmune conditions such as MS [38, 41, 42]. Meanwhile, the results of this study which demonstrated lower odds of NMOSD – as an autoimmune disorder – among participants with higher LCD scores would likely confirm this hypothesis.

Regarding the studies exploring the relationship between a diet and a demyelinating disease with inflammatory etiology, MS, it has been almost highlighted that a healthy dietary intervention might lead to improvements in MS related inflammation and physical symptoms including depression, fatigue, cognitive impairment, swallowing difficulties, impairments in mobility, and disability [43, 44]. Dietary factors that have been indicated to play a protective role in MS are as follows: unsaturated fatty acids, fibers, dietary items with anti-oxidant effects as well as treatment of deficiency or low serum levels of vitamins [41, 44]. It has also been demonstrated that increasing the intake of PUFAs and unrefined carbohydrate sources instead of refined carbohydrate could result in improving some of MS associated complications such as fatigue and weakness or reduce the risk of developing MS. Adequate consumption of proteins should also be considered in these patients [41, 44–46]. These findings are somewhat in accordance with the results obtained from the present research work. In addition, decreasing NMOSD odds following a diet with a higher proportion of fat and protein intakes, both from plant sources (as was found in this study), can be in line with the results of studies on patients with MS which indicated that higher intakes of plant based fat sources compared to animal sources might decrease the risk of this disabling disorder [41, 44–46]. In the same vein, the results of the Nurses' Health Study on 80920 and 94511 women from phase I and II, showed that low ALA intakes increase MS risk [47]. Another 7-months of trial on 34 Relapsing-remitting MS (RRMS) and 10 Primary-Progressive MS (PPMS) patients, demonstrated that the Mediterranean diet with/without dietary supplement (Inc.: fish oil, ALA, resveratrol, and multivitamin complex) ameliorates systemic inflammation (evaluated by Matrix metallopeptidase 9-MMP-9 serum level) [48]. The results share similarities with the results obtained from the present study. Like the Mediterranean diet, in the present study, 23-26 percent of energy in the 5^{th} and 6^{th} deciles came from plant sources which mainly consisted of Omega-3 and Omega-6 PUFAs.

In addition, amelioration of inflammation within a high-fat diet (HFD) subsequent to substituting saturated fats – which are mainly found in animal sources – with MUFAs or PUFAs – that are certainly found in plant sources – has also been reported. It has been suggested that this effect can be attributed to the reduction of NLRP3 signaling, modulation of adenosine monophosphate-activated protein kinase (AMPK) signaling, and improvement of insulin sensitivity [37, 49]. In addition, it has been put forward that generation of reactive oxygen species (ROS) might be attenuated following a ketogenic or LCD [38]. Although the anti-inflammatory effects of LCD have been proposed in several studies, studies on demyelinating diseases have barley focused on this type of diet.

Another remarkable finding of the current study was the importance of an adequate protein intake. At first view, it seems to be in contrast with previous findings. However, in the 5^{th} and 6^{th} deciles, 15–16% of total energy intakes came from proteins, that is in the range of dietary reference intakes for protein which is 10–35% of total energy for adults [32]. An adequate protein intake is critical for preserving gut function and microbial balance [50]. As an example, dietary tryptophan up-regulated Nrf2 gene expression in grass carp [50]. Moreover, it was shown that gram positive gut bacteria metabolized amino acids and produced short chain fatty

acids (acetate, butyrate, and propionate) which exerted Immunomodulatory properties in different studies. Furthermore, polyamines inhibited the inflammation by suppressing the secretion of TNF-α and IL-1 and IL-6 [50].

Strengths and limitations

We are from the first studies that assessed the dietary modifying factors of NMOSD and despite the uncommon characteristic of NMOSD we collected appropriate NMOSD cases. Our research had also some limitations. We did not assess the anthropometric measurement, dietary or inflammatory associated biomarkers in the serum samples of the studied subjects. This study has the recall bias limitation which is the nature of case-control studies. Nevertheless, we believe that our findings could be a starting point for the future studies exploring the etiology, risk, and protective factors of NMOSD.

Conclusion

The current results demonstrated that lowering LCD score can be a modifiable factor for decreasing NMOSD odds. This study could lend support to previous findings in the literature which showed protective effects of a diet with reduced content of carbohydrate and moderate levels of plant-based fats and proteins on inflammatory diseases. However, further well-designed clinical trials and longitudinal studies with a larger number of participants are required to confirm the effects of a diet on NMOSD.

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Conflict of interest
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