



Original article

Adherence to low carbohydrate diet in relation to glioma: A case-control study



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SUMMARY

Background: Observational studies that investigated the association between adherence to low carbohydrate diet and odds of glioma are sparse. This is particularly relevant in developing countries where dietary carbohydrate intake is very high.

Objective: This study was, therefore, conducted to investigate the association between adherence to low carbohydrate dietary pattern and odds of glioma among Iranian adults.

Methods: In this hospital-based case-control study, 128 newly diagnosed glioma cases were recruited and 256 age- and sex-matched subjects were enrolled as controls. Dietary intakes were examined by the use of a 126-item validated FFQ. Low carbohydrate diet (LCD) score was computed for each participant based on deciles of percentages of energy from carbohydrates, proteins, and fats. Individuals in the lowest decile of carbohydrate consumption received 10 points. Participants in second decile received 9 points and so on down to participants in the highest decile received 1 points. For fat and protein intakes, the points assigned to deciles were reversed; such that those in the highest decile received 10 points and those in the lowest decile received 1 point. We then summed all points of the three macronutrients to achieve the overall diet score, which ranged from 3 (highest carbohydrate intake and lowest fat and protein intakes) to 30 (lowest carbohydrate intake and highest fat and protein intakes). The higher the score, the greater adherence to the LCD dietary pattern.

Results: After adjustment for age and sex, we found that individuals in top tertile of LCD score were 60% less likely to have glioma compared with those in the bottom tertile (OR: 0.40; 95% CI: 0.23, 0.67). Additional controlling for other potential confounders made the association slightly attenuated (OR: 0.49; 95%CI: 0.26, 0.93). Further adjustment for dietary nutrient intakes strengthened the association (OR: 0.32; 95%CI: 0.12, 0.81). After additional controlling for BMI, we found that adherence to LCD was protectively associated with reduced odds of glioma (OR: 0.32; 95%CI: 0.12, 0.81).

Discussion: We found an inverse association between adherence to LCD and odds of glioma among Iranian population. Prospective cohort studies are needed to confirm these findings.

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1. Introduction

Gliomas are primary brain malignancies, the most frequent and aggressive type of brain tumors with poor prognosis. Median overall survival time for these patients is 12–15 months. Its 5-year survival rate is less than 5% [1]. According to the report of National

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Cancer Registry (NCR) in Iran, the astrocytoma and glioblastoma together are 60.4% of the primary malignant registered brain tumors [2]. The overall incidence of glioma is 2.74 per 100,000 person-years [3].

Given the high mortality rates of brain tumors, findings appropriate preventive strategies is of great importance [4,5]. Several environmental factors, including dietary factors, have been related to the incidence of glioma. One of the most interesting dietary factors that has received great attention in several cancers, including glioma, is carbohydrate restriction (CR). Glioma cells critically depend on glucose as main source of energy to survive and invade due to dys-regulation of mitochondrial metabolism. Therefore, dietary carbohydrate intake can result in the proliferation of glioblastoma multiform (GBM) cells and might play a role in the initiation of neoplasia in these cells [4,6]. Low carbohydrate dietary patterns have been linked with reduced risk of metabolic syndrome, diabetes, coronary heart disease and some cancers [7–11]. However, we are aware of no epidemiologic studies investigating consumption of low carbohydrate diets in relation to glioma. However, short-term clinical trials have reported beneficial effects of low carbohydrate diets, in the framework of high fat ketogenic diet, on improving the quality of life in these patients. Such diets have also been shown to increase survival time of these patients. We all know that findings from clinical trials cannot be extrapolated to general population because of the use of a high-dose intervention in short terms. Observational studies are required to examine the possible association of usual carbohydrate intake in routine lifestyle with the risk of glioma. This is particularly relevant in developing countries where dietary carbohydrate intake compose the greatest percentage of energy. This study was, therefore, conducted to investigate the association between adherence to low carbohydrate dietary pattern and glioma among Iranian adults.

2. Participants and methods

2.1. Participants

This hospital-based case-control study was conducted on newly diagnosed patients (not passed more than one month since the diagnosis) and healthy controls in Tehran, capital city of Iran, between 2009 and 2011. To select both cases and controls convenience-sampling method was used. The sampling was carried out in the hospitals affiliated to Shahid Beheshti University of Medical Sciences. The main aim of the project was to examine the link between dietary patterns and risk of glioma; therefore, the sample size was computed based on the consumption of fruit and vegetables. According to earlier investigations in the country, almost 60% of Iranian adults consume fruit and vegetables lower than the recommended levels [12]. Considering previous publications, we assumed that low fruit and vegetable consumption can increase the risk of glioma two times than adequate intake [13]. With the 80% study power and type I error of 0.05, we reached the sample size of 115 cases and 230 controls. However, we enrolled 128 cases and 256 controls. Both cases and controls were aged 20–75 years old. Cases were glioma patients, whom disease status was pathologically confirmed throughout the last month they attended Neurosurgery department. We selected healthy controls from orthopedic and surgical departments of the same hospitals or outpatients attended to the hospitals. Participants in case and control groups were individually matched by age (± 5) and sex. The whole participation rate among cases was 100% but the one for controls was 89%. Individuals who met the following criteria were excluded from this study: having history of cancer (except glioma) and those that were on chemotherapy and radiotherapy.

Participants were asked to fill an informed consent form. The Medical Ethics Committee of the Tehran University of Medical Sciences, Tehran, Iran ethically approved the study.

2.2. Dietary assessment

A validated block-format 123-item semi-quantitative FFQ was used to evaluate the dietary intakes of subjects during a year before the diagnosis of glioma in cases and during a year before the interview in controls. This questionnaire was consisted of 123 food items with standard portion sizes commonly consumed by Iranian people. FFQ was completed by the cooperation of individuals who were involved in the preparation and cooking of foods. Trained interviewers completed the questionnaires through face to face interviews. The interviewers were the same for cases and controls. The frequencies of participants' food intakes were converted to grams per day by using household measures. The modified US Department of Agriculture food consumption database was used to compute the daily intakes of energy and nutrients for each person.

Findings from the validation study of the current FFQ on 131 apparently healthy subjects aged 35–65 y revealed good correlations between dietary intakes assessed by FFQ and those obtained from 12 dietary recalls (a 24-h recalls/month) [14]. We assessed the reliability of FFQ by comparing nutrient intakes obtained from the FFQ on four occasions 3-month apart. The intra-class correlation coefficients for the reproducibility of the FFQ were 0.75 for carbohydrates, 0.76 for proteins and 0.72 for fat intakes. The correlation coefficients for the validity of FFQ, compared to the average of twelve 24-hour dietary recalls, for dietary carbohydrate, protein and fat were 0.75, 0.76 and 0.65, respectively [14]. These data indicated that the FFQ provides valid measurements of long-term nutrient intakes [14].

2.3. Calculation of the low carbohydrate diet (LCD) score

We computed LCD score for each participant based on deciles of percentages of energy from carbohydrates, proteins, and fats. Individuals in the lowest decile of carbohydrate consumption received 10 points. Participants in second decile received 9 points and so on down to participants in the highest decile received 1 points. For fat and protein intakes, the points assigned to deciles were reversed; such that those in the highest decile received 10 points and those in the lowest decile received 1 point. We then summed all points of the three macronutrients to achieve the overall diet score, which ranged from 3 (highest carbohydrate intake and lowest fat and protein intakes) to 30 (lowest carbohydrate intake and highest fat and protein intakes). Therefore, the higher the score, the greater adherence to the LCD dietary pattern.

2.4. Assessment of glioma

Glioma was diagnosed based on pathological test according to International Classification of Diseases for Oncology third edition and morphology codes of 9380–9481 (ICD-O-3 morphology codes 9380–9481) [15]. Only patients who elapsed one month of glioma confirmation were included in the study.

2.5. Assessment of other variables

We used a pretested questionnaire to gather information on several variables of general characteristics including age, gender, the status of their marriage, the place they live, education, their job status, smoking status, the use of dietary supplements (including iron, calcium and multivitamins), existence of family history of cancers and glioma, any background on of allergy and trauma,

previous history of hypertension, exposing to chemicals (Formaldehyde, plastics, benzene, mercury, arsenic and lead), food preparation methods, medication use, personal hair dye use, duration of cell phone use (years) and history of exposure to the radiographic X-ray. To examine physical activity, we used International Physical Activity Questionnaire (IPAQ). The questionnaire was filled through the face to face interviews. Findings of IPAQ were stated as Metabolic Equivalents per week (METs/week). Anthropometric measures including weight and height were examined by standard methods. We calculated Body Mass Index (BMI) by considering weight and height. In the current study we defined farmers as those who have a high risk job for glioma [16]. In addition, participants who were living in places close to electromagnetic fields and broadcast antennas were defined as those residing in a high risk regions [17]. Subjects that were using fried foods at least two times in a week were defined as frequent fried food users. The same definition was applied for barbecue use, microwave use as well as consumption of canned foods.

2.6. Statistical analysis

We categorized participants based on total LCD score into tertiles. General characteristics and dietary intakes of study participants across tertiles of the LCD scores were examined using one-way ANOVA for continuous variables and chi-square for categorical variables. The association of LCD scores with glioma was assessed by using conditional logistic regression in different models. First we controlled for age (continues) and gender (male/female). Then, additional controlling was performed for physical activity (continues), family history of cancers (yes/no), family history of glioma, marital status (yes/no), education (university graduated/non-university graduated), high-risk job (farmer/non-farmer), high-risk living area (yes/no), duration of cell phone use (continues),

supplement use (yes/no), history of exposure to the radiographic X-ray (yes/no), history of head trauma (yes/no), history of allergy (yes/no), history of hypertension (yes/no), smoking (smoker/non-smoker), exposing to chemicals (yes/no), medication use (yes/no), personal hair dye use (yes/no), frequent fried food intake (yes/no), frequent use of barbecue (yes/no), canned foods and microwave (yes/no). Dietary intakes of vitamin A, vitamin C, vitamin D, vitamin E, vitamin B12, vitamin B6, zinc, copper, potassium, calcium, selenium, total fiber, salt, cholesterol and methionine consumption were taken into account in the third model. Finally, we adjusted the analysis for BMI. All confounders were chosen based on previous publications. The statistical analyses were carried out by using SPSS version 18. P values were considered significant at <0.05.

3. Results

Main characteristics of the study participants in both case and control groups as well as across tertiles of the LCD score are presented in Table 1. Cases with glioma were more likely to have high-risk occupations, live in high-risk residential areas, and be frequently exposed to radiographic X-ray and chemicals. History of head trauma and family history of glioma were more prevalent among them than controls. In addition, they were more likely to be frequent fried food consumers than controls. In contrast, cell phone use, microwave use, personal hair dye use and smoking were less prevalent among them than controls. Mean age, BMI and physical activity were not significantly different between the two groups. No other significant difference was also seen in the distribution of participants in terms of other categorical variables.

When examined across tertiles of the LCD score, individuals in the highest tertile were less likely to have exposure to chemicals, high-risk occupations and be physically active, smoker, medication user compared with those who were in the lowest tertile. By

Table 1
General characteristics of study participants.

	Groups			Tertiles of LCD score			P ^a
	Cases (n 128)	Controls (n 256)		1 (n 137)	2 (n 114)	3 (n 133)	
Age (year)	43.4 ± 14.6	42.7 ± 13.3	0.65	43.6 ± 13.4	44 ± 14.5	42 ± 13.3	0.36
BMI (kg/m ²)	26.2 ± 4.2	26.1 ± 3.8	0.75	26 ± 4	26.2 ± 4	26.2 ± 4	0.80
Physical activity (MET-h/week)	34.7 ± 6.3	33.8 ± 5.5	0.12	35 ± 6.2	33.1 ± 5.5	34 ± 5.5	0.03
Duration of cell phone use (years)	2.85 ± 2.89	3.70 ± 2.56	0.003	3.11 ± 2.8	3.28 ± 2.38	3.87 ± 2.82	0.054
Females (%)	41	42	0.99	35	42.1	48.1	0.09
Married (%)	79	80	0.66	81	84.2	74.4	0.30
University graduated (%)	12	17	0.22	6.6	15.8	23.3	0.001
High risk job ^b (%)	10	3	0.003	10.9	2.6	1.5	0.001
High-risk living area ^c (%)	30	21	0.05	26.3	27.2	20.3	0.37
History of exposure to radiographic X-ray (%)	16	7.4	0.01	13.1	6.1	10.5	0.18
History of head trauma (%)	44	29	0.004	37.2	38.6	26.3	0.07
History of allergy (%)	25	29	0.40	26.3	28.9	28.6	0.87
History of hypertension (%)	2	5	0.28	2.2	5.3	5.3	0.35
Smoker (%)	16	25	0.02	28.5	21.1	15.8	0.04
Frequent fried food intake ^d (%)	91	78	0.001	82.5	84.2	80.5	0.74
Frequent use of barbecue ^e (%)	16	21	0.21	15.3	15.8	9	0.2
Frequent microwave use ^e (%)	8	19	0.002	7.3	15.8	23.3	0.001
Frequent canned foods intake ^e (%)	6	7	0.52	3.6	3.5	10.5	0.02
Medication use (%)	8	5	0.36	10.2	6.1	1.5	0.01
Personal hair dye use (%)	22	41	<0.001	29.9	36	38.3	0.32
Exposure to chemicals (%)	20	11	0.01	19	13.2	8.3	0.04
Family history of glioma (%)	19	5	<0.001	12.4	13.2	5.3	0.07
Family history of cancer (%)	33	34	0.90	29.2	32.5	39.1	0.21
Supplement use (%)	8	16	0.36	6.6	9.6	22.6	<0.001

All values are Means ± SD unless indicates; MET, metabolic equivalents.

^a P values were obtained from independent Student's t test, one-way ANOVA or χ^2 test, where appropriate.

^b Farmers were considered as having a high-risk job.

^c Individuals who lived in places near electromagnetic fields and cell phone and broadcast antennas in the last 10 years were defined as living in high-risk areas.

^d Individuals who consumed fried food at least twice per week were considered as frequent fried food users.

^e Individuals who used barbecue, microwave and canned foods at least twice per week were considered as frequent users.

contrast, they were more likely to be university graduated, supplement user, frequent microwave and canned foods consumers than those in the lowest tertile. There were no significant differences in other variables across tertiles of LCD score.

Table 2 presents the dietary intakes of study participants separately by cases and controls as well as across tertiles of LCD score. Compared with controls, cases had higher intakes of carbohydrates, cholesterol, vitamin B₁₂, sodium, selenium, red and processed meat, fish, refined grains, whole grains and partially hydrogenated vegetable oils and lower intakes of total fats, saturated fats, polyunsaturated fats, vitamin D, vitamin E, vitamin B₆, potassium, calcium, fruits, vegetables, legumes and nuts, dairy products and salt. Adherence to LCD was associated with greater intakes of fats, saturated fats, polysaturated fats, cholesterol, vitamin A, vitamin D, vitamin E, vitamin B₆, vitamin B₁₂, methionine, potassium, calcium, zinc, copper, white meat, red and processed meat, fish, egg, dairy, sugar sweetened beverages and non-hydrogenated vegetable oils and lower intakes of carbohydrates, refined and whole grains, and partially hydrogenated vegetable oils.

Multivariable-adjusted ORs for glioma across tertiles of the LCD score are shown in Table 3. After adjustment for age and sex, we found that individuals in top tertile of LCD score were 60% less likely to have glioma compared with those in the bottom tertile (OR: 0.40; 95% CI: 0.23, 0.67). Additional controlling for other potential confounders made the association slightly attenuated (OR: 0.49; 95%CI: 0.26, 0.93). Further adjustment for dietary nutrient

intakes strengthened the association (OR: 0.32; 95%CI: 0.12, 0.81). After additional controlling for BMI, we found that adherence to LCD was protectively associated with reduced odds of glioma (OR: 0.32; 95%CI: 0.12, 0.81).

4. Discussion

We found an inverse association between adherence to the low carbohydrate diet (LCD) and odds of having glioma among Iranian population. This association persisted in multivariate models accounting for several confounders. To the best of our knowledge, this is the first observational study examining the association between adherence to the LCD and odds of glioma.

Low carbohydrate diets were primarily suggested for management of metabolic syndrome, diabetes and cardiovascular disease [7,9,18,19]. Numerous observational studies and clinical trials indicated that adherence to the LCD, characterized by high intakes of proteins and fats and low intakes of carbohydrates, was associated with a lower risk of metabolic abnormalities [7,9,18–21]. In the current study, we found that adherence to the LCD was associated with a lower odds of glioma. However, beneficial effects of LCD in cancer patients were not well studied. There were several clinical trials on the efficacy of ketogenic diet, which is very similar to LCD, for the management of glioma [4]. Findings from these clinical trials have suggested that consumption of LCD may positively affect survival and quality of life in these patients [4]. Some studies have

Table 2
Dietary intakes of study participants.

	Groups			Tertiles of LCD score			
	Cases (n 128)	Controls (n 256)	P ^a	1 (n 137)	2 (n 114)	3 (n 133)	P ^a
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	Mean ± SD	
Total energy (kcal/d)	2580 ± 560	2561 ± 722	0.72	2681 ± 670	2514 ± 561	2494 ± 745	0.06
Nutrients							
Carbohydrates (g/d)	425 ± 101	412 ± 128	0.02	467 ± 135	406 ± 87	373 ± 109	<0.001
Proteins (g/d)	98 ± 22	97 ± 30	0.76	95 ± 20	95 ± 21	102 ± 36	<0.001
Fats (g/d)	62 ± 19	66 ± 22	0.003	55 ± 14	65 ± 17	75 ± 24	<0.001
Saturated fats (g/d)	19 ± 7	21 ± 9	0.02	17 ± 5	20 ± 7	24 ± 10	<0.001
Polyunsaturated fats (g/d)	13 ± 4	14 ± 4	0.001	12 ± 3	14 ± 4	15 ± 4	<0.001
Cholesterol (mg/d)	251 ± 141	235 ± 121	0.21	208 ± 84	225 ± 78	287 ± 178	<0.001
Total fiber (g/d)	23 ± 11	23 ± 14	0.83	23 ± 12	22 ± 9	24 ± 17	0.29
Vitamin A (μg/d)	1353 ± 604	1397 ± 650	0.45	1264 ± 562	1418 ± 509	1470 ± 774	<0.001
Vitamin D (mg/d)	1.3 ± 1	1.7 ± 1.1	0.002	1.2 ± 1	1.6 ± 1.1	2 ± 1.2	<0.001
Vitamin E (mg/d)	5 ± 2	6 ± 3	0.015	4.5 ± 2.7	5.5 ± 2.5	6.4 ± 3	<0.001
Vitamin C (mg/d)	126 ± 98	143 ± 113	0.09	138 ± 147	135 ± 42	138 ± 68	0.73
Vitamin B ₆ (mg/d)	1.9 ± 0.54	2 ± 0.76	0.047	1.8 ± 0.6	1.9 ± 0.4	2.1 ± 0.9	<0.001
Folate (mg/d)	349 ± 90	382 ± 302	0.230	361 ± 117	357 ± 78	392 ± 406	0.27
Vitamin B ₁₂ (g/d)	10 ± 16	6 ± 4	0.001	6.6 ± 5.8	6.2 ± 4.9	8.6 ± 15.8	0.02
Methionine (g/d)	1603 ± 431	1555 ± 569	0.24	1537 ± 356	1522 ± 349	164 ± 751	<0.001
Potassium (mg/d)	4074 ± 783	4364 ± 1423	0.006	4213 ± 1241	4212 ± 879	4368 ± 1518	0.004
Calcium (mg/d)	1020 ± 263	1139 ± 358	<0.001	1068 ± 282	1083 ± 289	1144 ± 408	<0.001
Zinc (mg/d)	12.4 ± 3	12.1 ± 4	0.26	12.1 ± 2.9	11.9 ± 2.7	12.3 ± 4.7	0.002
Copper (mg/d)	2.3 ± 0.7	2.4 ± 0.8	0.32	2.3 ± 0.6	2.3 ± 0.5	2.4 ± 0.9	<0.001
Selenium (mg/d)	0.07 ± 0.04	0.06 ± 0.04	0.02	0.07 ± 0.04	0.06 ± 0.03	0.07 ± 0.05	0.27
Food groups							
Fruits (g/d)	325 ± 100	361 ± 124	0.001	351 ± 113	344 ± 120	351 ± 121	0.71
Vegetables (g/d)	258 ± 83	274 ± 86	0.04	251 ± 70	281 ± 88	276 ± 94	<0.001
White meat (g/d)	30 ± 13	33 ± 22	0.16	26 ± 12	33 ± 12	37 ± 29	<0.001
Red and processed meat (g/d)	41 ± 28	36 ± 20	0.01	33 ± 17	37 ± 15	43 ± 31	<0.001
Fish (g/d)	9.3 ± 12	9.1 ± 9	0.01	7 ± 8	8 ± 7	13 ± 13	<0.001
Egg (g/d)	26 ± 17	27 ± 20	0.55	23 ± 16	26 ± 14	30 ± 23	<0.001
Legumes and nuts (g/d)	40 ± 23	46 ± 20	0.008	39 ± 18	48 ± 21	47 ± 23	<0.001
Dairy (g/d)	309 ± 117	355 ± 131	<0.001	314 ± 131	341 ± 120	365 ± 128	<0.001
Refined grains (g/d)	501 ± 175	421 ± 182	<0.001	531 ± 171	425 ± 160	380 ± 182	<0.001
Whole grains (g/d)	177 ± 134	150 ± 108	0.04	179 ± 132	164 ± 108	134 ± 107	0.05
Salt (g/d)	5.8 ± 2	6.3 ± 2	0.01	6.1 ± 2.1	6.3 ± 2.2	6 ± 2	0.41
Sugar sweetened beverages (g/d)	79 ± 67	83 ± 74	0.54	67 ± 56	83 ± 68	97 ± 86	<0.001
Partially hydrogenated vegetable oils (g/d)	15 ± 15	9 ± 12	<0.001	18 ± 15	8 ± 11	5 ± 9	<0.001
Non-hydrogenated vegetable oils (g/d)	6 ± 5	7 ± 4	0.26	4 ± 4	7 ± 4	8 ± 4	<0.001

^a Obtained by ANOVA.

Table 3
Multivariable-adjusted ratios for glioma across different categories of the low-carbohydrate diet (LCD) score.

	Tertiles of LCD score					P trend
	1 (n 137)		2 (n 114)		3 (n 133)	
	OR	OR	95% CI	OR	95% CI	
LCD score range	<13	13–20		>20		
Crude	1.00	0.49	0.29–0.83	0.40	0.24–0.67	<0.001
Model I	1.00	0.49	0.29–0.83	0.40	0.23–0.67	<0.001
Model II	1.00	0.48	0.25–0.89	0.49	0.26–0.93	0.02
Model III	1.00	0.45	0.21–0.98	0.32	0.12–0.81	0.01
Model IV	1.00	0.46	0.21–0.98	0.32	0.12–0.81	0.01

Model I: Adjusted for age and gender.

Model II: Further controlled for physical activity (continues), family history of cancer (yes/no), family history of glioma (yes/no), marital status (married/single/divorced), education (university graduated/non-university education), high-risk job (farmer/non-farmer), high-risk living area (yes/no), duration of cell phone use (continuous), supplement use (yes/no), history of exposure to the radiographic X-ray (yes/no), history of head trauma (yes/no), history of allergy (yes/no), history of hypertension (yes/no), smoking status (smoker/non-smoker), exposure to chemicals (yes/no), medication use (yes/no), personal hair dye use, frequent fried food intake (yes/no), frequent use of barbecue, canned foods and microwave (yes/no).

Model III: Additionally adjusted for dietary intakes of vitamin A, vitamin C, vitamin D, vitamin E, vitamin B₁₂, vitamin B₆, zinc, copper, potassium, calcium, selenium, total fiber, salt, cholesterol and methionine.

Model IV: All variables in Model III + BMI.

demonstrated that low serum glucose levels, induced by LCD, during the treatment of malignant glioma may improve the response to radio- and chemotherapy [22]. To the best of our knowledge, there was no observational study linking LCD and risk of glioma. In a longitudinal study, consumption of low carbohydrate along with high protein and fat intakes was not associated with total cancer risk; however, the investigators in that study reported a positive association between consumption of LCD and risk of respiratory tract cancer in men, not in women [23]. The story for colorectal cancer was different in that study; such that women with the greatest adherence to the LCD had lower risk of colorectal cancer than those with the lowest adherence, while men with the highest consumption of LCD had greater odds for colorectal cancer than those with the lowest consumption [23]. Given the limited and controversial data in this regard, it seems that additional studies are needed to reach a conclusive finding about the association of LCD with different cancers.

The protective association of LCD with glioma in the current study might be explained by several mechanisms. According to “Warburg effect”, energy metabolism in human cancer cells is remarkably geared towards glycolysis. Therefore, cancer cells depend on glucose more than normal cells [1,4]. As dietary carbohydrates can elevate serum insulin and insulin-like growth factor-1 (IGF-1) levels, therefore they can stimulate tumor cell proliferation. Consumption of LCD induces hypoglycemia, which can reverse the aggressive metabolic pathways in tumor cells [10]. Therefore, LCD, via suppressing the tumor cell proliferation and inducing apoptosis, through attenuating insulin-activated Akt/mTOR and Ras/MAPK signaling pathways, can prevent the initiation of malignancies in brain cells [1,10]. Moreover, LCD induces metabolic stress in brain cells, via suppressing glycolysis and pentose–phosphate pathways and consequently decreasing ATP and NADPH levels. This would in turn lead to “starvation-induced sensitization” in brain malignant cells and ultimately to apoptosis [24–26].

This study had several strengths. This work was the first study that examined the association between adherence to LCD and odds of glioma. In addition, several confounders were taken into account in the current study and therefore the findings are independent of other variables. Moreover, were recruited patients who were newly diagnosed with glioma during the past month. Therefore, dietary

habits of patients enrolled in the study did not change so much. However, some limitations need also to be considered. First is the case-control design of the study with its adherent recall and selection biases that would not allow us to confer causality. Second, we did not consider glioma grades in the current study which might affect our findings. Third, we used FFQ for dietary assessment of participants, in which probable misclassification of subjects is unavoidable. To minimize this, we defined LCD score based on percent of energy derived from carbohydrates. Forth, we used the conventional imaging techniques including magnetic resonance imaging (MRI) and computed tomography (CT) scan to diagnose and evaluate glioma. Whereas, molecular imaging like positron emission tomography (PET) scan provides metabolic information such as glucose metabolism and expression of amino acid transporters which are useful for noninvasive grading and management of tumor [27]. Despite the unique features of MRI, including excellent soft tissue contrast and dynamic contrast which is helpful in primary diagnosis and follow-up of patients [28], the use of combination of PET/MRI scan should be considered in future investigations. In addition, assessment of glioma in the current study was done based on morphology of tumors; however, the latest WHO classification of CNS tumors has suggested the use of molecular parameters along with tumors' morphology [29]. Moreover, blood glucose is an important factor in glioma. Examining plasma glucose levels of patients might help interpreting the findings. Although we excluded patients with self-reported diabetes from the study, no blood samples were taken in the current study to examine glucose levels. Although the generalizability of the findings should be done cautiously, participants were recruited from a referral hospital in Iran. Therefore subjects were socio-economically diverse.

In conclusion, findings from this case-control study revealed that adherence to LCD was inversely associated with odds of glioma among Iranian population. However, prospective cohort studies are warranted to confirm these findings.

Author contributions

SE, MS, SBK, MMS, GS and AE contributed to the conception, design, data collection, statistical analyses, data interpretation, manuscript drafting, approval of the final version of the manuscript. AE supervised the study.

Conflicts of interest

All authors declared that they have no personal or financial conflicts of interest.

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