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Dietary total antioxidant capacity and risk of ulcerative colitis: a case-control study

Antioxidant and ulcerative colitis

ABSTRACT

Background: Data on the association between the anti-oxidant capacity of diet and risk of ulcerative colitis (UC) are scarce.

Aims: The current study aimed to assess whether there exists any relation among dietary total antioxidant capacity (TAC) and odds of UC in Iranian adults.

Methods: In this case-control study, patients with UC and age-matched healthy controls were recruited from a hospital clinic. All subjects completed a validated 168 item food frequency questionnaire, the results of which were subsequently used to generate dietary TAC. Ferric reducing-antioxidant power (FRAP) values were used to calculate dietary TAC.

Results: Sixty-two patients with UC and 124 controls were enrolled. Controls had higher Vitamin C intake than the UC participants ($p < 0.01$). In a fully adjusted model, subjects who were in the highest quartile of the dietary TAC had lower risk of UC (OR = 0.11, 95% CI: 0.01–0.73).

Conclusion: A higher dietary TAC score was associated with lower odds of UC in this case-control study. Further elucidation of the role of key dietary elements is now warranted.

Keywords: dietary total antioxidant capacity, ulcerative colitis, TAC, diet

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disorder affecting the colon, which can be accompanied by various extra-intestinal features with significant morbidity [1]. The prevalence of UC has increased substantially over the past decades[2].

While the etiology of UC remains unclear, preclinical and clinical data suggest that diet and oxidative stress plays a pivotal role in the initial pathogenesis of the disease [3-8]. For instance, analysis of anti-oxidation related genes in a case-control study identified single nucleotide polymorphisms in the glutathione peroxidase gene that were highly associated with UC development [9]. Moreover, erythrocytes collected from individuals with UC contain increased

levels of oxidative stress related lipid peroxidation, catalase and superoxide dismutase [10]. **Lipid peroxidation inhibition and oxygen free radicals scavenging provide protective statuses against ulcerative colitis[11] and dietary antioxidants such as vitamin E and C can scavenge oxygen and superoxide anion radicals[12]. Furthermore, these anti-oxidants have anti-inflammatory effect that improve protection against inflammatory bowel diseases[13].** Finally, the total antioxidant capacity of blood in patients with UC has also been found to be significantly depleted when compared to assessments from healthy controls [14]. Taken together, these intriguing studies point towards a potential role of oxidative stress and anti-oxidative intervention in the development and treatment of UC, respectively. In line with this, a range of natural and synthetic antioxidant compounds have been proposed as candidate interventional agents for the prevention of UC [15, 16].

Interestingly, a multitude of observational clinical studies have highlighted a clear association between specific nutritional components and UC [17-19]. Studies have focused on animal protein, mono-unsaturated fatty acids and n-6 polyunsaturated fatty acids as important predisposing factors in the development of UC [20-22]. In contrast, there is indication that n-3 polyunsaturated fatty acids may confer a protective effect [23]. Indeed, n-3 polyunsaturated fatty acids have been known to affect oxidative stress [24, 25].

The dietary total antioxidant capacity (TAC) is a tool which predicts the free radical scavenging potential of a particular diet by utilizing food frequency questionnaire data[26]. The metric works by adding together the previously reported ferric reducing–antioxidant power (FRAP) value of each food component within a specific diet. This tool has previously been applied to several cohorts investigating the interaction between TAC and cardiometabolic [27], obstetric [28] and psychiatric outcomes [29]. Up to this point, however, little consideration has been given to the diet as a whole with respect to UC and whether the innately reduced antioxidant capacity which characterizes Western-style diets may have contributed to the exponential growth of the disease. Herein, this study aimed to apply this tool to ascertain the relation among dietary TAC and odds ratio of UC diagnosis using a case-control study design.

METHODS

Study participants

The current study protocol has been described previously [30]. During 2013, a case-control designed study based on UC patients who were newly diagnosed (<6 months) was conducted. All case and control participants were Caucasian and were recruited from a hospital-based clinic in Tabriz, Iran.

The medical records of all cases were reviewed to confirm the diagnosis of UC. History of any other gastrointestinal illness, carcinoma, autoimmune disease, and other inflammatory and infectious disorders were exclusion criteria.

Patients in orthopedic clinics were considered as Control group. Exclusion criteria for the control group were history of any gastrointestinal illness or symptoms **and other illness**.

Controls and cases were matched based on age (10-year groups). **Segments with 10 years' intervals were considered in case and control groups and individuals were selected based on these segments. For each person in each segments in case group, two individuals were added in the corresponding segments in the control group.** All subjects were interviewed by a trained interviewer. Weight was measured while subjects were standing without shoes and was recorded to the nearest kilogram. Height was measured in a standing position fixed to a wall without shoes and was recorded to the nearest centimeter by a non-stretchable tape meter. Informed consent was obtained from each participant prior to enrolment. The Shahid Beheshti University of Medical Science ethics committee approved the study protocol (1393/523).

Assessment of diet and calculation of dietary TAC

A semi-quantitative food frequency questionnaire (FFQ) was used to assess usual diet information in the last year [31]. The consumption food items was calculated on a daily, weekly, or monthly. Then, data were transformed into the average monthly intake. The USDA portion sizes and household measures were used for each food. The ferric reducing-antioxidant power (FRAP) values were used to calculate dietary TAC [32]. The FRAP assay measures the ability of dietary antioxidants to reduce ferric to ferrous ions and is reported as mmol per 100 grams of foods[33]. The nearest comparable food value was assigned to food items lacking TAC data. FRAP values of food items was multiplied by the food consumption volume and summed up to obtain the dietary TAC for each participant.

Statistical analyses

T test, χ^2 and ANCOVA analyses were used to evaluate the distribution of demographics and nutrient intake variables among case and control groups. The overall dietary TAC score was categorized into quartiles based on their distribution among participants. Logistic regression analysis was carried out for potential confounding variables models (i.e. age, sex, total energy intake, sodium intake, fiber intake, trans fat intake, vitamin D intake, caffeine intake, total fat intake, total protein intake, body mass index, smoking, and education level). The lowest category of TAC score assumed as the reference category and odds ratios (ORs) and 95 % confidence intervals (95 % CIs) were estimated. All analyses were completed using SPSS version 23. Significance level was set at $\alpha=0.05$ for all analysis.

RESULTS

Subjects

Sixty-two recently diagnosed UC patients and 124 healthy controls were recruited (**Table 1**). In each group, 56.5% of participants were women. The mean age and BMI for UC patients and healthy controls were 37.43 ± 13.55 and 36.23 ± 11.85 years ($p=0.53$) and 24.81 ± 4.07 and 25.68 ± 3.68 kg/m² ($p=0.14$), respectively. Ten percent of cases and eight percent of controls were active smokers ($p=0.91$).

Overall dietary patterns in cases and controls

The average dietary intake for case and control groups were calculated (**Table 2**). Mean total calorie intakes \pm SD were 2902.3 ± 643.3 and 2590.8 ± 585.2 kcal per day in case and control groups, respectively ($p<0.01$). UC participants consumed more mono unsaturated fatty acids (MUFA) ($p<0.01$), Vitamin B9 ($p<0.01$), and calcium ($p=0.02$) than controls. In contrast, the mean intake of vitamin C was greater in the control group compared to the UC group ($p<0.01$).

Dietary total antioxidant capacity score for cases and controls

The TAC score was used for classification of participants into quartile categories, with subsequent calculation of odds ratio for UC for each TAC quartile, with Q1 acting as the

reference category (**Table 3**). The highest quartile of the TAC score was not different to the lowest quartile in the crude model (OR = 1.39, 95% CI: 0.57–3.36). However, after adjusting for covariates, the highest quartile differed significantly from the lowest quartile (OR = 0.11, 95% CI: 0.01–0.73, $p=0.04$).

DISCUSSION

Chronic inflammation is a critical component of UC [34], with aetiology relating to a complex interaction between environmental, hereditary, and immunoregulatory factors [35]. Diet is purported to influence gut inflammation through antigen presentation, prostaglandin balance changes, and alteration of the microbiota [36]. Whilst oxidative stress has been recognized as one of the key elements of tissue injury in IBD [37], increasing TAC may conceivably help to ameliorate or protect against gut inflammation [14]. TAC is a tool that assesses the beneficial effects of dietary antioxidants. The key findings of this study were that individuals with the greatest dietary TAC score (quartile 4) were substantially less likely to have UC.

Oxidative stress and free radicals play pivotal roles in the etiology and exacerbation of UC [38-40]. Higher anti-oxidant levels may be able to reduce the reactive oxygen species (ROS) in the intestine. Further, therapeutic intervention in patients with UC results in reductions in colonic ROS [40, 41]. Indeed, in the present study, higher dietary TAC was associated with lower odds of UC, suggesting that it may offer a protective effect. Thus, high dietary TAC may conceivably protect against UC through reduction in ROS, resulting in less production of inflammatory cytokines and improvement of disease manifestations.

It seems that a primary defect renders the bowel mucosa susceptible to oxidative damage in the development of UC. Plasma or serum concentrations of antioxidants have been used as biomarkers of oxidative stress [42, 43]. Increased free radical production, of various free radical species, during colonic inflammation has been reported [44, 45]. On the other hand,

levels of the most important antioxidants have been found to be seriously impaired in UC patients. For example, the mucosal levels of copper/zinc-containing proteins (superoxide dismutase and metallothionein) have been found to be decreased in UC[46]. The that low levels of anti-oxidants in patients with UC could be attributed to several factors, and dietary intake is likely a major contributor. For example, Koutroubis et al. [14] showed that patients with UC consume less fruits and vegetables compared to control subjects. The authors asserted that whilst this may be an important cause of reduced TAC levels, a combination of other mechanisms could also be involved, such as malabsorption, increased vitamin requirements, and increased gastrointestinal losses, especially during active disease.

There have been attempts to examine the association between dietary intake and food groups with UC [47-49]. In a comprehensive systematic review, Hou et al [49] identified that there was an increased risk of developing UC with high intake of total fat, PUFAs, omega-6 fatty acids and meats. The results in the current study have shown the protective effects of high dietary TAC, following adjustment for multiple potential risks factors for UC, including age, sex, total energy intake, sodium intake, fiber intake, trans fat intake, vitamin D intake, caffeine intake, total fat intake, total protein intake, body mass index, smoking, and education. Moreover, the subjects with UC in the present cohort, consumed significantly more MUFA and oleic acid than the control group. However, the presented results must be interpreted with caution because risk reduction was significant only in quartile 4, with no dose-response relationship evident.

This study has several advantages. Foremost, this is the first study, to the authors' knowledge, to examine the relationship between dietary TAC and the risk of UC, utilizing a case-control study design and an accepted methodology to derive TAC. Furthermore, the study was conducted in a developing country where dietary intakes are various due to various cultures and socioeconomic status. However, this study was cross-sectional and is also limited by the

use of food frequency questionnaire data to derive scores. Biological variables, such as serum or tissue antioxidant and ROS levels, were not available. In addition, the data was limited to one population and may not be representative of other populations.

Conclusion

In conclusion, this case-control study found that high dietary TAC is associated with a significantly reduced risk of UC. Additional longitudinal cohort studies are needed to confirm the present results, along with concurrent assessment of key biological markers. These further studies are required to ascertain the clinical relevance of these data.

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Table 1. Selected characteristics of cases and controls participating in the study^a

Characteristic	Cases (n = 62)	Controls (n = 124)	P Value ^b
Age	37.43 ±13.55	36.23 ± 11.85	0.53
BMI^c	24.81± 4.07	25.68± 3.68	0.14
Sex			
Female	35 (56.5)	70 (56.5)	0.82
Male	27 (43.5)	54 (43.5)	
Education			
Primary	7 (11)	6 (5)	0.15
Secondary and high school	28 (45)	69 (55)	
University	27 (44)	49 (40)	
Smoking	6 (10)	10 (8)	0.91

a) Data are presented as mean ± SD or n (%).

b) Independent samples t-test was used for continuous variables and Chi-square test was used for categorical variables.

c) Body Mass Index (kg/m²)

Table 2. Distribution of dietary intakes of macro and micronutrients in cases and controls^a

Characteristic	Cases (n = 62)	Controls (n = 124)	P Value ^b
<i>Total calories (kcal/day)</i>	2902.3±643.3	2590.8±585.2	<0.01
<i>Total protein intake (g/day)</i>	100.79±33.43	88.49±23.82	0.76
<i>Total carbohydrate intake (g/day)</i>	381.54±86.25	353.25±88.05	0.08
<i>Total fat (g/day)</i>	113.81 ±34.95	96.92 ±25.46	0.08
<i>Cholesterol (mg/day)</i>	299.59 ±144.82	269.21 ±136.03	0.66
<i>SAFAs (g/day)</i>	32.92 ±11.83	28.19 ±9.78	0.46
<i>MUFAs (g/day)</i>	39.17 ±12.73	32.43 ±8.27	<0.01
<i>PUFAs (g/day)</i>	26.02 ±9.06	23.01 ±7.08	0.57
<i>Oleic acid (g/day)</i>	35.28 ±11.86	28.97 ±7.52	<0.01
<i>Linoleic acid (g/day)</i>	22.70 ±8.46	19.86 ±6.46	0.40
<i>Linolenic acid (g/day)</i>	1.65 ±0.76	1.50 ±0.70	0.54
<i>EPA (g/day)</i>	0.02 ±0.04	0.03 ±0.06	0.17
<i>DHA (g/day)</i>	0.09 ±0.13	0.11 ±0.19	0.14
<i>Trans-fatty acids (g/day)</i>	0.0135±0.01	0.0119 ±0.01	0.26
<i>Vitamin A (RAE/day)</i>	773.88± 593.73	682.23± 332.43	0.79
<i>Vitamin D (ug/day)</i>	1.90± 1.63	2.09± 1.54	0.09
<i>Vitamin E (mg/day)</i>	18.73± 8.41	17.54± 6.85	0.74
<i>Vitamin C (mg/day)</i>	126.34± 53.98	139.46± 70.25	<0.01
<i>Vitamin B6 (mg/day)</i>	2.09±0.55	1.92±0.56	0.05
<i>Vitamin B9 (ug/day)</i>	609.94±128.71	591.53±159.92	<0.01
<i>Vitamin B12 (ug/day)</i>	6.61±6.46	4.77±2.83	0.10
<i>Zinc (mg/day)</i>	14.55±5.29	12.12±3.45	0.06
<i>Copper (ug/day)</i>	2.12±0.70	1.87±0.56	0.74
<i>Magnesium (mg/day)</i>	434.79±103.19	399.27±106.77	0.66
<i>Iron (mg/day)</i>	20.08±4.96	18.31±5.03	0.28
<i>Calcium (mg/day)</i>	1173.44±372.58	1153.67±353.37	0.02

a) Data are presented as mean ± SD.

b) Obtained from ANCOVA. all values except energy intake are adjusted for age, sex and energy intake.

SAFAs: Saturated fatty acids, MUFA: mono-unsaturated fatty acids, PUFA: polyunsaturated fatty acids, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid.

Table 3: Odds ratios and confidence intervals for the association between dietary total antioxidant capacity and ulcerative colitis.

	Quartile1 <9.40	Quartile2 9.40-12.40	Quartile3 12.40-16.08	Quartile4 ≤16.08	P Value for Trend
Case/control	13/34	14/32	19/28	16/30	-
Crude	Ref	1.14 (0.46- 2.80)	1.77 (0.74- 4.21)	1.39 (0.57- 3.36)	0.30
Model 1^a	Ref	1.14 (0.46- 2.80)	1.73 (0.72- 4.15)	1.35 (0.55- 3.10)	0.35
Model 2^b	Ref	0.53 (0.16- 1.70)	0.60 (0.14- 2.56)	0.11 (0.01- 0.73)	0.04

a) Adjusted for age.

b) Adjusted for age, sex, total energy intake, sodium intake, fiber intake, trans fat intake, vitamin D intake, caffeine intake, total fat intake, total protein intake, body mass index, smoking, education