Original Article

Dietary Total Antioxidant Capacity and Risk of Gall Stone: A Case-Control Study

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Abstract

Background: Since the relation between dietary total antioxidant capacity (DTAC) and the occurrence of gallstone disease (GSD) remains unclear, we conducted, for the first time, a case-control study to clarify this association in the Iranian population. **Methods:** In the present case-control study, convenience Sampling was performed. A total of 600 participants (300 case and 300 control) were included. Anthropometric, demographic, physical activity, and nutrient intakes data were obtained from each subject. DTAC was calculated using the US Department of Agriculture's database. The odds ratio (OR) and 95% confidence intervals were assessed using unconditional logistic regression. **Results:** The participants in the highest quartile of DTAC had a significantly lower OR for gallstone than the lowest quartile, which remained significant after further adjustment for age, sex, and education (model 2: OR, 0.34; 95% CI, 0.16–0.71). In addition, after adjustment for age, sex, education, BMI, physical activity, and energy, the results revealed that participants with the highest quartile of DTAC had 71% lower odds of gallstone than those with the lowest quartile (model 3: OR, 0.29; 95% CI, 0.11–0.78). **Conclusions:** The results of the present study demonstrated that the DTAC had an inverse association with GSD incident. However, interventional approaches are needed to confirm the relation between DTAC and GSD prevention.

Keywords: *Free radicals, gallstone, oxidative stress, total antioxidant capacity*

Introduction

Gallstone or cholelithiasis has been identified as the most common disorder of the biliary system requiring hospitalization.[1] Gallstones divided into three types depending on their main biochemical components: cholesterol gallstones, pigment gallstones, as well as mixed gallstones.[2] The majority of gallstones are contributed by cholesterol; yellow-gray stones made up of crystalline cholesterol monohydrate.[1] Gallstones are generally asymptomatic in the beginning stage of stones formation; then, symptoms become apparent when the size of rocks reaches more than 8 mm.[3] Gallstones can induce complications by inhibiting the flow of bile or digestive enzymes and causing acute and abrupt pain in the top right abdomen, nausea, vomiting, and inflammation.[4] The high morbidity of gallstones causes health economic burden highly in Western societies. This disorder is estimated to involve over 20 million adults, 20–74 years (6.3 million men, 14.2 million women) in the US.[5] The pathogenesis of gallstones is varied based on the type of gallstone and is figured to be multifactorial, deriving from interactions between genetic, dietary, and environmental factors.[6] A high rate of free radicals and oxidative stress, which are the consequence of a rising number of lipid and protein oxidation products and reduced quantity of antioxidant enzymes and vitamins, may be involved in the pathophysiology of gallstone disease (GSD).[7] Indeed, a number of bile elements, such as bile acids, cholesterol, and bilirubin, can interfere with free radicals and induce oxidative stress conditions.[8] Decreased antioxidant defense mechanisms as an aggravating pathological condition have been found locally in the gallbladder wall as well as in the circulation of patients with gallbladder disease.[9] These conditions may be resulted in a decreased activity of key enzymes in cholesterol and bilirubin metabolism in mucosal cells and lead to a disturbed gall bladder absorption and secretion of bile mucins and glycoproteins. The consequent increased risk of bile

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saturation would contribute more to the development of gallstone formation.[9,10] Animal models and theoretical considerations suggest a causal relationship between insufficient intake of micronutrient antioxidants and the progress of human gallstones. Most foods contain different antioxidant compounds.[11,12] Moreover, several clinical and experimental data have reported the role of dietary components in the induction and preventing of GSD.[13] To assess diet-disease relationships, dietary total antioxidant capacity (DTAC) is proposed as a score of antioxidant intake and potential marker of diet quality.[14] To our knowledge, the relationship between DTAC and the risk of gallstone formation has not been assessed. Since the association between DTAC and the occurrence of GSD remains unclear, we conducted, for the first time, a case-control study to clarify this association in the Iranian population.

Methods

Participants

The present case-control study was carried out on subjects who were admitted to the Research Institute for Gastroenterology and Liver Diseases of Taleghani Hospital in Tehran, Iran, in 2018. The study included 300 patients with gallstones (cases) and 300 individuals with no gallstone (controls). The inclusion criteria for cases were the age of 18 years and older, willing to participate in this study, approval of GSD, and ≤1 month passed since disease diagnosed. We excluded those with a history of other diseases and intestinal disorders, known autoimmune diseases, cancer, other inflammatory and infectious diseases, pregnancy or lactation in women, change the type and dosage of the patient's medications, and unwillingness to continue cooperation.

Controls were randomly selected age- and sex-matched subjects from the same clinic who had been undertaken an ultrasound showing no gallbladder disorders and liver problems. Data on each pair of cases and controls were collected simultaneously. All participants signed the written informed consent. The approval of the ethics committee is mentioned in the method section along with its number (IR.SBMU.RIGLD.REC.1396.159).

Anthropometric and physical activity assessment

Bodyweight and height were measured using a Seca scale with an accuracy of 100 g and a Seca stadiometer with an accuracy of 0.5 cm, respectively; and then, BMI was computed as body weight (kg) divided by the square of height (m). In order to assess the physical activity of individuals, the short form of the International Physical Activity Questionnaire was used via interviewing, and the results were expressed as metabolic equivalent hours per week.[15]

Dietary assessment and DTAC calculation

The usual food intake collected by trained dietitians during a structured interview. A valid and reliable 168-item semiquantitative food frequency questionnaire with standard servings was used to assess typical food intakes. The intake frequency of each food item was questioned on a daily, weekly, or monthly basis during the past year and converted to the gram. Total energy and nutrient intake were then calculated using Nut IV (the Hearst Corporation, San Bruno, CA) modified for Iranian foods. DTAC was estimated by considering the oxygen radical absorbance capacity of each food described by the US Department of Agriculture. It was stated as μmol of Trolox equivalents/100 g of food (mmol TE/100 g).[16]

Statistical analysis

All statistical analyses were fulfilled using IBM SPSS Statistics software (Version 24) (IBM SPSS Statistics, Armonk, USA). The normality of the variables was confirmed using the Kolmogorov–Smirnov test. Energy-adjusted DTAC was computed using the residual method and was categorized based on sex-specific quartiles.[17] The comparisons of the variables different between the groups were performed with the independent Student's *t*-test and Mann–Whitney test for variables with normal and nonnormal distribution, respectively. A Chi-square test was used for categorical data to identify significant differences across quartile categories of DTAC. ANOVA and the Kruskal–Wallis test were applied to compare the mean of the variables with normal and nonnormal distribution within the quartiles of DTAC, respectively. The odds ratio (OR) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression. Moreover, we used multivariable models to assess the relation between gallstone and DTAC. The analysis was adjusted for age, sex, education, BMI, marital status, physical activity, and energy. Tests for trend among DTAC quartiles were performed by using median DTAC for each quartile. A P value of less than 0.05 was regarded to be statistically significant.

Results

The characteristics of control and case participants and their dietary intake are presented in Tables 1 and 2. Participants with gallstone had a higher mean age, weight, BMI, energy ($P < 0.05$), and lower physical activity and DTAC scores ($P < 0.05$) than the control group [Table 1]. Additionally, there was a significant difference in the intake of several nutrients between the two groups [Table 2].

Significant difference was seen in daily intake of carbohydrate, fat, cholesterol, saturated fat, MUFA, PUFA, vitamin A, vitamin E, vitamin K, zinc, and iron between cases and controls; such that cases had a higher consumption of carbohydrate, fat, saturated fat, MUFA, PUFA, vitamin E, and iron ($P = 0.05$) and took a lower cholesterol, vitamin A, vitamin K, and zinc ($P = 0.05$).

Table 1: Characteristics of control and gallstone patient[a]

Variables	Controls (*n*=300) Mean±SD	Cases (*n*=300) Mean±SD	*P*[b]
Age (years)	54.50±12.48	56.82±16.67	<0.001
Weight (kg)	72.37±13.27	74.75±18.16	<0.001
BMI (kg/m^2)	26.59±4.10	27.44±5.89	<0.001
DTAC (mmol TE/100 g)	21,350.36±7199.35	20,087.58±9010.95	0.04
Physical activity (MET)	38.48±9.57	29.38±3.29	0.01
Marital status, *n* (%)			<0.001
Single	17 (5.66%)	11 (3.66%)	
Married	243 (81%)	54 (18%)	
Married-p[c]	40 (13.34%)	235 (78.34%)	
Education, *n* (%)			<0.001
Illiterate	48 (16%)	133 (44.33%)	
Low education[d]	208 (69.33%)	138 (46%)	
High education[e]	44 (14.67%)	29 (9.66%)	
Sex, *n* (%)			0.97
Male	159 (53%)	158 (52.66%)	
Female	141 (47%)	142 (47.34%)	
Smoking, *n* (%)			0.62
No	245 (81.66%)	233 (77.66%)	
Yes	55 (18.34%)	67 (22.34%)	

BMI=Body mass index; DTAC=Dietary total antioxidant capacity; MET=Metabolic equivalent task. [a]All values are mean±SD, [b]independent *t*-test was used for continuous variables and Chi-squared test for categorical variables, [c]married in past (widow), [d]nonacademic education, [e]academic education

Table 2: Daily macro- and micronutrients intakes in case and control group[a]

Variables	Controls (*n*=300) Mean±SD	Gallstone (*n*=300) Mean±SD	*P*[b]
Energy intake (kcal/day)	2401.23±724.12	2731.69±1354.21	0.004
Carbohydrate (g)	297.09±111.33	333.15±170.80	0.02
Protein (g)	79.03±27.9	82.44±36.89	0.38
Fat (g)	107.50±32.88	125.55±75.24	0.002
Fiber (g)	36.77±21.34	34.94±23.96	0.52
Cholesterol (mg)	240.58±131.22	209.24±99.4	0.05
Sat.fat (mg)	26.44±9.57	30.32±16.03	0.001
MUFA (mg)	41.62±12.91	48.81±40.16	0.001
PUFA (mg)	30.63±10.05	33.38±14.89	0.05
Vitamin A·REA (mg)	506.96±235.97	382.94±166.07	0.001
Beta-carot (mg)	3191.96+1945.62	1911.49+1206.89	0.001
Vitamin C (g)	122.05±62.07	105.66±75.42	0.10
Vitamin D (µg)	1.69±1.39	1.39±1.31	0.09
Vitamin E (mg)	27.93±8.51	28.43±12.67	0.001
Folic acid (µg)	466.33±168.93	477.35±264.19	0.65
Vitamin 12 (mg)	2.96±1.12	2.70±1.30	0.26
Vitamin K (mg)	140.45±76.18	99.52±77.49	0.001
Zinc (mg)	10.64±3.60	10.50±5.24	0.001
Calcium (mg)	886.34+323.53	854.52+361.58	0.43
Iron (mg)	14.92+5.82	15.70+9.79	0.001

MUFA=Monounsaturated fatty acid; PUFA=Polyunsaturated fatty acids; REA=Retinol activity equivalent. [a]All values are mean±SD, [b]*P* using *t*-test

The participants' characteristics across the quartiles of DTAC are presented in Table 3. There was no significant difference in age, weight, and BMI between DTAC quartiles, while the differences in physical activity and energy intake were significant. Across increasing DTAC quartiles, all participants had higher physical activity and energy intake ($P < 0.05$). Correlations between DTAC and food groups including fruits, vegetables, nuts, legumes, fruit juice, tea, and olive oil are presented in Table 4; [fruit ($r = 0.76$; $P < 0.001$), vegetables ($r = 0.59$; $P < 0.001$), nuts ($r = 0.42$; $P < 0.001$), legumes ($r = 0.36$; $P < 0.001$), fruit juice ($r = 0.32$; $P < 0.001$), tea ($r = 0.28$;

Table 3: Characteristics of participants across the quartiles of DTAC[a]

DTAC	Mean±SD				*P*-trend[b]
Variables	Q1 (*n*=150) <15,974.99	Q2 (*n*=150) 15,974.99-19,815.70	Q3 (*n*=150) 19,815.70-25,036.80	Q4 (*n*=150) >25,036.80	
Age (years)	53.13±16.01	54.84±12.91	56.41±12.30	55.34±11.61	0.39
Weight (kg)	72.63±15.54	74.35±14.45	72.31±13.74	76.92±13.18	0.10
BMI (kg/m^2)	27.02±5.38	26.53±4.23	26.20±4.08	27.28±4.20	0.36
Physical activity (MET)	34.43±5.70	36.96±7.75	38.07±14.09	37.58±7.62	0.03
Energy intake (kcal/day)	2163.50±651.10	2380.03±834.18	2468.69±1036.50	2842.45±849.91	<0.001

BMI=Body mass index; DTAC=Dietary total antioxidant capacity; MET=Metabolic equivalent task. [a]All values are mean±SD, [b]ANOVA for continuous variables

Table 4: Correlation between DTAC food groups

Food groups	Partial correlations (*r*)	*P*
Fruits	0.76	<0.001
Vegetables	0.59	<0.001
Nuts	0.42	<0.001
Legumes	0.36	<0.001
Fruit juice	0.32	<0.001
Tea	0.28	<0.001
Olive oil	0.16	<0.001

DTAC=Dietary total antioxidant capacity

$P < 0.001$), and olive oil ($r = 0.16$; $P = 0.001$)]. Moreover, food groups such as vegetables (32.8%), fruits (27.4%), tea (12.8%), legumes (9.4%), fruit juice (1.1%), and nuts (7.2%) were found to be the main contributors to DTAC.

Multivariable-adjusted ORs and 95% CIs for gallstone per each unit increase in DTAC, as well as across quartiles of dietary TAC scores, are shown in Table 5. The participants in the highest quartile of DTAC had a significantly lower OR for gallstone than the lowest quartile, which remained significant after further adjustment for age, sex, and education (model 2: OR, 0.34; 95% CI, 0.16–0.71). After adjustment for age, sex, education, BMI, physical activity, marital status, and energy, the results revealed that participants with the highest quartile of DTAC had 71% lower odds of gallstone than those with the lowest quartile (model 3: OR, 0.29; 95% CI, 0.11–0.78).

Discussion

The results of the present study, for the first time, indicated that the DTAC had an inverse association with gallstones incident. The participants in the highest quartile of DTAC had a significantly lower OR for gallstone than the lowest quartile, which remained significant after adjusting for age, sex, and education. Moreover, after adjustment for age, sex, education, BMI, physical activity, and energy, the results showed that participants with the highest quartile of DTAC had a lower odd of gallstone than those with the lowest quartile.

It has been observed that stress oxidative has a demonstrated role in the pathogenesis of gallstones. A high level of oxidative stress in gallbladder mucosa has been found in gall stone patients.[7] Regarding the cholesterol gallstones, it is confirmed that the free radicals are involved in the formation of cholesterol gallstone by the change of lipids and proteins in bile. Low intake of vitamin C or melatonin, through interfering with free radicals, can rise or alleviate the risk of gallstone generation, respectively.[18] Cell and membrane damage and pigment polymerization can be caused by the interaction of reactive oxygen species with bilirubin, leading to pigment gallstone generation and related inflammatory events. In the latter type of gallstone, also, some factors, such as iron or melatonin, can increase or lessen the oxidative stress process, respectively.[7,9] Sipos *et al*. showed a correlation between the free radical reactions, the number of stones, and the degree of cholecystitis.[8] Vitamin E, the carotenes, vitamin C, and selenium are the best-known antioxidant micronutrients; the latter two act as a protective agent in the aqueous phase beside the sulfur amino acids and their final product GSH.[19,20] Waniek *et al*. detected an inverse correlation between plasma levels of γ- and α-tocopherol levels and the probability of having GSD in a community-based sample. Potential explanations for this inverse association are higher protection from oxidative stress in individuals with higher vitamin E levels and emulsification of dietary lipids, including fat-soluble vitamins by bile acids.[21] However, Phillips *et al*. stated other than the deficiency of vitamin A, the occurrence of fat-soluble vitamin deficiencies is uncommonly in patients with primary biliary cirrhosis.[22] A small study by Worthington *et al*. showed that the lack of dietary antioxidants, specially α-tocopherol, may be related to human GSD.[23] In another study by the same researcher, it was found that cholesterol GSD is accompanied by micronutrient antioxidant lack, sulfur amino acids, folate, and vitamin B6-PLP deficiency and disturbed glutathione homeostasis.[24] Data from large studies indicate that serum ascorbic acid level has an inverse association with the prevalence of clinical and asymptomatic gallbladder disease.[25,26] It is shown that the individuals that regularly take vitamin C supplements have less risk for GSD than those not using vitamin C (4.7% vs. 8.2%).[27] Data from animal experiments show that ascorbic acid affects the activity of cholesterol 7α-hydroxylase, the rate-limiting step enzyme in the change of cholesterol to bile acids.[11] Moreover, suppression of oxidative functions within the

Table 5: Crude and multivariable-adjusted odds ratios and their 95% confidence interval of the associations between gallstone and dietary total antioxidant capacity

DTAC (µmol TE/100 g)	Q1 (*n*=150) <15,975	Q2 (*n*=150) 15,975-19,816	Q3 (*n*=150) 19,817-25,037	Q4 (*n*=150) >25,037	*P*-trend
Model 1	1	0.25 (0.12-0.55)	0.36 (0.18-0.73)	0.34 (0.16-0.69)	<0.001
Model 2	1	0.27 (0.12-0.59)	0.37 (0.18-0.76)	0.34 (0.16-0.71)	<0.001
Model 3	1	0.31 (0.14-0.76)	0.39 (0.17-0.98)	0.27 (0.12-0.75)	<0.001

BMI, Body mass index; DTAC=Dietary total antioxidant capacity; OR=Odds ratio; Q=Quartile, Model 1: Crude, Model 2: Adjusted for age, sex, education, Model 3: Adjusted for age, sex, education, BMI, marital status, physical activity, energy

gallbladder by ascorbic acid may reduce mucoprotein formation and gallstone generation. Mucin is a glycoprotein that is released by the epithelium of the gallbladder. It is worth noting that excess of mucin secretion by hydroxyl and oxygen radicals has been established to introduce cholesterol destabilization and gallstone production.[28] High intake of dietary antioxidants from plant foods, as part of a healthy balanced diet, may confer health benefits through protection from oxidative damages.[17] Jessri *et al*., in a case-control study, investigated the association of dietary patterns with the risk of GSD among Iranian women. The authors identified two discrete dietary patterns among study participants: healthy dietary patterns and unhealthy dietary patterns. A healthy dietary pattern consisting of high consumption of vegetables, fruits, fruit juice, legumes, whole grain, nuts, low-fat dairy products, and spices was associated with decreased gallstone.[29] These findings were in line with previous studies displaying vegetables and fruits to have a protective effect versus GSD via their high antioxidants.[30,31] Observational studies reported a significant difference in the prevalence of GSD among nonvegetarians than vegetarians after adjusting for age and BMI in women.[30-32] Findings of a study by Makiuchi *et al*. suggested that increased vegetable/fruit intake may reduce the risk of extrahepatic bile duct cancer, and folate, vitamin C, and insoluble fiber might be the principal agents to the detected protective effect.[32] However, another study showed that in Taiwanese vegetarians, types of vegetarians and the duration of vegetarianism are not associated with GSD development.[33] The inconsistency in the findings of the relation of specific dietary constituents on the risk of gallstone could be attributed to the ethnic variations, differences in lifestyle, and the problems in evaluating particular nutritional components in individuals.[29-32]

Our study has some limitations. First, we applied a case-control approach; then, we couldn't establish the causality relationship between DTAC and GSD. Moreover, the frequency of food consumption and quantification of this questionnaire may have been exposed to recall bias. Besides, the antioxidants content of the foods might be affected by some factors such as food preservation, agriculture conditions, and so on. Despite these limitations, this is the first study investigating the association between DTAC and GSD in a case-control design.

In conclusion, the findings of the present study demonstrate that the DTAC had an inverse association with gallstones incident. However, interventional approaches are needed to confirm the relation between DTAC and GSD prevention.

Informed consent

Informed consent was obtained from all participants before enrolment into the study.

Author's contributions

SS contributed in the data acquisition, analysis, and interpretation; wrote the manuscript and critically reviewed it; and participated in the final approval of the version to be published. AS participated in the data acquisition and interpretation, reviewed the article critically and made important intellectual contributions, and participated in the final approval of the version to be published. FH and VA contributed substantially to study conception and design, participated in the data analysis and interpretation, wrote the manuscript and critically reviewed it, and participated in the final approval of the version to be published. MR contributed substantially to study conception and design; participated in the data acquisition, analysis, and interpretation; wrote the manuscript and critically reviewed it; and participated in the final approval of the version to be published. BA and AS contributed substantially to study conception and design, participated in the data analysis and interpretation, wrote the manuscript and critically reviewed it, and participated in the final approval of the version to be published.

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Conflicts of interest

There are no conflicts of interest.

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