The association between Dietary total antioxidant capacity with Rheumatoid Arthritis in adults: A case-control study

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Abstract

Objective

Dietary total antioxidant capacity (TAC) has been assumed as a useful tool to assess the relationship between the cumulative antioxidant food capacity and several chronic disorders. However, the relationship between the total antioxidant capacity of the diet (TAC) and the risk of RA has not been previously examined. The aim of this study was to evaluate the association between DTAC and risk of RA in a case-control study.

Methods

This case-control study was carried out among 100 patients with RA and 200 healthy subjects aged 18–55 years. Dietary data were collected using a validated 147- items quantitative food frequency questionnaire. DTAC was calculated based on the ferric reducing-antioxidant power (FRAP) values that reported by US Department of Agriculture.

Results

The mean age and BMI of the study participants were 49.4 years and 25.6 Kg.m2.. The energy, protein, fiber, MUFA, *n*-3 fatty acid, vitamin B9, vegetable, and fruit were significantly increased across tertiles of DTAC. Also, Compared with participants in the lowest tertile of DTAC, those in the highest terrtile had a significantly lower OR for rheumatoid after adjustment for BMI; physical activity; waist circumference; smoking; and dietary intake energy and fat (model 3: OR, 0.19; 95% CI, 0.07–0.51; p for trend, 0.001).

Conclusions

Our findings showed that a high DTAC was associated with a reduced risk of RA in adult, suggesting that promoting a naturally elevated antioxidant capacity might help prevent the development of RA. Further prospective studies should be conducted in this regard.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by dryness, swelling, stiffness and pain in the joints of the body as a result of inflammation and causes damaged joints, muscle erosion, atrophy and pain. (1–3). It is estimated that about 1% of the world's adult population is affected by RA. (4). The disease is more common in women than men (5). RA can have a significant economic impact on patients, families, and society by increasing the cost of health care, loss of productivity, and disruption of routine life individual. (6–9).

Although the main cause of RA is not clearly elucidated. however, genetic factors, female hormones, smoking, oxidative stress, obesity, unhealthy life styles, and dietary risk factors, may contribute to pathogenesis of the disease (10).

Studies suggest that systemic inflammation or excessive levels of free radicals and also disrupting the antioxidant balance in the body, in other words oxidative stress, may play a key role in the pathogenesis of RA (10–12). Thus, impaired antioxidant and anti-inflammatory defenses may cause or exacerbate a chronic condition of RA. On the other hand, various aspects of the effect of diet on the modulation of oxidative stress and disorder in the antioxidant system have been studied. One of the components of the diet that can affect these symptoms is the natural antioxidants in foods, and interventional studies using antioxidant supplements (vitamins C and E) have shown that supplementation with antioxidants may have a positive effect on these symptoms and diseases (11, 12). However, the evaluation of an antioxidant compound alone cannot reflect the total antioxidant potency of the diet and reflect the synergistic and potential effects of dietary antioxidant interactions. Thus, the term total antioxidant capacity for diet (DTAC)has been developed and is used as a suitable tool to evaluate the effects of dietary antioxidants that is a strong correlation with serum total antioxidant capacity (13) And it is closely related to the quality of the diet to determine the risk of chronic diseases (14).

Several evidences have suggested the potential link between DTAC and reduce the risk of chronic diseases such as diabetes (15), metabolic and oxidative stress markers (16), ulcerative colitis (17), and cardiovascular disease (18), which share common metabolic parameters with RA. However, to our knowledge, the association between DTAC and risk of development RA have not yet been investigated. Only, a number of studies have shown the ability of nutrients rich in antioxidant to reduced oxidative stress and subsequently reduced risk of RA including garlic, ginger, quercetin, green tea and pomegranate (3, 19–22). However, the synergistic effects of different antioxidant nutrients, which also found in DTAC and other chemical ingredients utilized in the growing or preparation of food have not been discussed.

Considering the lack of convincing evidence regarding the association of DTAC with RA, in this study we aimed to investigate the association between DTAC and risk of RA in Iranian population in order to improve and reduce the burden of diseases.

Subjects And Methods

Participants

This study was a case-control design. The based on a hypothetical odds ratio of 0.41 (15), a power of 80%, a two-sided confidence interval of 5% and a case/control sample ratio of 1:2, sample size was calculated. Finally, 100 RA patients (case group) and 200 age, gender and body mass index (BMI) matched healthy individuals (control group) were participated in the study. The patients were selected from a rheumatology clinic of Isfahan University of Medical Sciences, Isfahan, Iran.

Inclusion criteria included diagnosis of RA by a rheumatologist based on 2010 Rheumatoid Arthritis Classification Criteria (23), absence of other pathological conditions such as diabetes, hepatic and thyroid disorders, cancers, food allergies and nutritional deficiencies, absence of adherence to specific diets and consumption of dietary supplements. Exclusion criteria included extreme energy intake reporters (women reporting energy intake less than 600 or higher than 3500 kcal day-1 and men with energy intake less than 800 or higher than 4200 kcal day-1) (24). Also, pregnant and lactating women and subjects with an arbitrary special diet were excluded. In the present study, the nutritionists were used as interviewer. So, all the patients responded completely to the survey questions. Control participants were selected from healthy individuals who attended the clinic with the patients as companions. Also, in order to assess physical activity levels of participants, we used the General Practice Physical Activity Questionnaire (GPPAQ), a simple questionnaire reflecting an individual's current physical activity(25). All participants were signed written informed consents. This study was approved by the research council and ethics committee Isfahan University of Medical Sciences, Tehran, Iran.

Anthropometric Assessment

Anthropometric measurements were conducted by a trained dietician. Weight was measured using a standard digital Seca scale (made in Germany), while participants wore minimum clothes and without shoes and recorded to the nearest 100 g. Height was measured using a mounted tape in a standing relaxed shoulder position with no shoes to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight (kg) divided by height in square meters (m^2).

Dietary Assessment And DTAC Calculation

Dietary assessment and DTAC calculation

Nutritional status of individuals was assessed by a 147- items FFQ. The questionnaire has a standard size for each food item designed according to the Willett method (26). Study participants were asked to indicate their frequency of consumption of each food item according to their consumption in the past year. Depending on the type of food consumed, the frequency of consumption per day, week or month was questioned. Previous studies using this questionnaire have provided acceptable results and validity of the questionnaire indicates that the questionnaire has acceptable validity. The values listed for each food item were converted to grams daily using the Home Scale Handbook. Then, the amount of nutrients obtained by each individual was obtained using Nutritionist IV software. The total antioxidant capacity of the diet was obtained from previous articles based on the ferric reducing-antioxidant power (FRAP). The FRAP is defined as the ability of dietary antioxidants to reduce ferric to ferrous ions. The FRAP was expressed in milligrams per 100 grams of food(27). For similar foods in Iranian culture (for example, different types of bread), the average total values will be calculated. Finally, the frequency of consumption of each food item is multiplied by the amount of iron-reducing antioxidant power

associated with it, and then the diet is collected for each participant.to obtain the total antioxidant capacity.

Statistical analysis:

Statistical analysis was conducted using Statistical Package Software for Social Science, version 21 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov's test and histogram chart was used for testing the normality of the data. Baseline characteristics and dietary intakes were expressed as mean ± SD or median (25–75 interquartile range) for quantitative variables, and number and percentages for qualitative variables. Comparison of the data between two groups was done using independent sample t-test and chi square for continuous and categorical variables, respectively. Also, using analysis of covariance (ANCOVA), the differences of nutrients intakes and Baseline characteristics were compared across DTAC tertiles.

Binary logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for multiple covariates in different model. The data were presented as mean ± standard deviation and odds ratio with 95% confidence interval, and in all results, the significance level was determined as $P < 0.05$.

Result

The mean ± SD for age and BMI of the study participants were 49.4 ± 10.5 years and 25.6 ± 3.5 Kg.m2. Table 1 demonstrates anthropometric and characteristics among case (rheumatoid patients) and control groups. There were no significant differences between cases and controls in age and BMI; however, rheumatoid patients had higher weight and waist circumference compared with controls. Also, compared with the control, the rheumatoid cases have a higher level of physical activity. There were no significant differences in all other characteristics between case and control groups.

The participants' characteristics and dietary intake across the tertiles of DTAC are presented in Tables 2 and 3. The women percent, energy, protein, fiber, monounsaturated fatty acid (MUFA), *n*-3 fatty acid, vitamin B9, vegetable, and fruit were significantly increased across tertiles of DTAC ($p < 0.05$). While, the history of disease, drug use, smoking, carbohydrate, and fat were significantly decreased across tertiles of DTAC (p trend < 0.05). There were no significant differences in all other characteristics and dietary intake across tertiles of DTAC.

Table 1. Basic characteristics and physical activity Among the Case and Control Groups

variables	Groups, mean ± SD		P value[a]
	Case (n = 100)	Control (n = 200)	
Women, n (%)	81(81.0)	164(82.0)	0.366
Age, y	49.26 ± 12.6	49.08 ± 9.4	0.06
Weight, kg	67.64 ± 11.4	63.91 ± 8.46	0.002
BMI [b], kg/m^2	26.20 ± 4.3	25.38 ± 3.0	0.061
Waist- circumference (cm)	89.19 9.4	84.55 ± 7.3	< 0.001
Physical Activity (Met.min/wk)	4512.2 ± 6160.9	1632.3 ± 946.6	< 0.001
Smoking (yes), n (%)	6 (6)	12 (6)	0.91
Family size	4.27 ± 1.6	4.07 ± 1.5	0.300
Drug use (yes), n (%)	10 (10.0)	36 (18)	0.065
SES [c], n (%)			0.625
Low	32 (31.0)	73 (36.5)	
Middle	18 (18.0)	35 (17.5)	
High	51 (51.0)	92 (46.0)	

[a] Obtained from independent sample t-test for continuous variables and Chi-square for Categorical variables.

[b] BMI: body mass index.

[c] SES: socioeconomic status.

Table 2

Participants' characteristics across tertiles of dietary total antioxidant capacity (DTAC) among the study population

		Tertiles of dietary total antioxidant capacity			
		T1	**T2**	**T3**	P [a]
Women, n (%)		77 (92.8)	87 (84.5)	81 (71.1)	0.002
Age, y		47.0 ± 9.7	49.4 ± 10.2	50.4 ± 11.2	0.075
Weight, kg		66.2 ± 9.6	65.4 ± 9.9	63.2 ± 9.2	0.086
BMI [b], kg/m^2		25.6 ± 3.5	25.8 ± 3.6	25.4 ± 3.4	0.744
Waist- circumference (cm)		86.6 ± 8.3	86.4 ± 8.9	84.9 ± 7.8	0.313
Physical Activity (Met.min/wk)		2097.1 ± 2722.1	2843.7 ± 4286.2	2725.8 ± 4191.6	0.384
Smoking (yes), n (%)		13 (11.4)	5 (4.9)	0 (0.0)	0.018
Family size		4.0 ± 1.5	4.3 ± 1.7	4.0 ± 1.4	0.424
Drug use (yes), n (%)		25 (21.9)	17 (16.5)	4 (4.8)	0.004
SES [c], n (%)					0.274
	Low	23 (27.7)	38 (36.9)	43 (37.7)	
	Middle	12 (14.5)	18 (17.5)	23 (20.2)	
	High	486 (57.8)	47 (45.6)	48 (42.1)	

[a] P-value from one-factor ANOVA test or $\chi 2$ test, for continuous or categorical variables, respectively.

Table 3
Dietary intakes of the study population according to the tertiles of dietary total antioxidant capacity (DTAC) among the study population

	Tertiles of dietary total antioxidant capacity			
	T1	**T2**	**T3**	P
Nutrient Intake				
Energy(Kcal/d)	1880.6 ± 529.2	2107.0 ± 533.6	2424.5 ± 628.1	< 0.001
Carbohydrate(g/d))	338.4 ± 98.1	285.8 ± 81.1	252.2 ± 74.4	< 0.001
Protein(g/d)	63.1 ± 22.6	67.2 ± 20.5	74.9 ± 21.6	0.001
Fat (g/d)	92.0 ± 30.1	82.4 ± 26.7	72.7 ± 29.2	< 0.001
Saturated fatty acid (g/d)	24.0 ± 9.0	24.5 ± 8.3	26.8 ± 9.4	0.056
Total fibre(g/d)	34.4 ± 14.1	38.9 ± 14.3	40.1 ± 15.5	0.024
MUFA(g/d)	30.0 ± 10.7	30.5 ± 9.5	33.7 ± 10.9	0.022
n-3 fatty acid (g/d)	1.1 ± 0.66	1.2 ± 0.64	1.3 ± 0.66	0.043
Vitamin D (mcg/d)	1.5 ± 1.2	1.6 ± 1.5	1.4 ± 1.2	0.667
Vitamin B9	455.8 ± 132.9	490.1 ± 133.9	529.0 ± 156.6	0.002
Vitamin B12	3.6 ± 2.8	3.6 ± 1.8	4.0 ± 3.2	0.384
Food groups				
total dairy (g/d)	351.0 ± 327.6	3404.1 ± 281.7	367.4 ± 213.0	0.385
legumes(g/d)	21.6 ± 22.0	26.4 ± 22.1	29.2 ± 26.6	0.091
Refined grain(g/d)	331.9 ± 189.5	298.4 ± 157.4	309.3 ± 148.8	0.328
Whole grain(g/d)	58.9 ± 107.8	62.1 ± 95.0	81.5 ± 105.7	0.233
Red and processed meat(g/d)	46.5 ± 34.8	43.1 ± 29.0	44.0 ± 29.0	0.709
fish(g/d)	7.8 ± 7.9	8.4 ± 7.3	8.9 ± 8.0	0.597
Fruits(g/d)	186.7 ± 115.1	289.0 ± 150.7	401.7 ± 302.2	< 0.001
Vegetables(g/d)	233.1 ± 128.0	264.2 ± 160.2	297.3 ± 133.7	0.008
P-value from one-factor ANOVA test.				

The ORs and 95% CIs for rheumatoid in the tertiles of DTAC are shown in Table 4. Compared with participants in the lowest tertile of DTAC, those in the highest terrtile had a significantly lower OR for rheumatoid (crude model: OR, 0.36; 95% CI, 0.19–0.70; p for trend, 0.003), which remained significant

after further adjustment for BMI; physical activity; waist circumference; smoking; and dietary intake energy and fat (model 3: OR, 0.19; 95% CI, 0.07–0.51; p for trend, 0.001).

Table 4
The association between Tertiles of dietary total antioxidant capacity (DTAC) and risk of rheumatoid among the participants of study.

	Tertiles of dietary total antioxidant capacity			*P for trend*
	T1	**T2**	**T3**	
DTAC				
Case/Total	22 / 100	37 / 100	91 / 100	
Crude	1.00 (Ref)	0.47 (0.24–0.93)	0.36 (0.19–0.70)	0.003
Model 1*	1.00 (Ref)	0.46 (0.23–0.91)	0.34 (0.17–0.67)	0.002
Model 2†	1.00 (Ref)	0.46 (0.19–1.14)	0.19 (0.07–0.51)	0.001

* Model 1: adjusted for age, sex.

† Model 2: adjusted for model 1 and BMI, waist circumference, physical activity, smoking, dietary intake of energy and fat.

Discussion

This case-control study investigates the related between DTAC and Rheumatoid Arthritis. Our study suggests that DTAC may potentially reduce the risk of RA. In the present study, participants in the lowest tertile of DTAC had a significantly OR for rheumatoid, compared with those in the highest tertile and this result persisted after adjustment for potential confounders including BMI; physical activity; waist circumference; smoking; and dietary intake energy and fat.

To our knowledge, this is the first attempt to evaluating associated between DTAC and risk of RA in new diagnosis patients, although evidence have suggested that oxidative status affects the severity and activity of RA. Several previous studies have shown an inversely association between the Dietary TAC and inflammatory diseases such as MS, ulcerative colitis, cardiovascular diseases (18), cancer (28), diabetes, metabolic disorders (16) which share common metabolic parameters with RA.

Several studies showed an inverse relation between intake of antioxidant micronutrients and foods rich in antioxidants with risk of RA(29, 30). The healthy diet and Mediterranean diet are rich in natural antioxidants, which are determined by abundant amounts of plant foods including whole grains, fruits, vegetables, olive oil, legumes, herbs and spices, demonstrated an inverse relationship with risk of RA, as well as an inverse association in chronic diseases associated with RA (31–34). However, in a cohort study, this inverse relationship was found only in vegetables and citrus fruits (29). Also, a number of [illegible] ntioxidant to reduced oxidative stress and

subsequently reduced risk of rheumatism including garlic, ginger, quercetin, green tea and pomegranate (3, 19–22). Also, in our study, several nutrients that have antioxidant activity have shown an inverse relationship with risk for RA. Fruit, vegetable, n-3 fatty acid, MUFA, fiber and folic acid can be mention. However, in a prospective cohort of older women, there was no relation between coffee as an antioxidant-rich nutrient and incident RA(35). This may be due to the lack of precise control of potential confounders such as tea in this study. So that, decaffeinated tea was associated with an increased risk of developing RA that his increased risk could be due to a lack of caffeine .also, it is possible that other chemical ingredients utilized in the growing or preparation of tea are responsible for this observation(35). In addition, when considering the effects of antioxidant-rich nutrients, one should pay attention to their various synergistic effects, which are also present in DTAC. Also, this suggests that a natural balance between dietary antioxidants can be used to prevent RA compared to certain supplements that may lead to an imbalance of the complex antioxidant system through excessive antioxidant consumption and its side effects, be more effective.

One of the mechanisms that seems to play a role in preventing the onset of RA by receiving dietary antioxidants is the prevention of the production of 8-hydroxydeoxyguanosine from DNA damage by inhibiting the production of ROS(36). In addition, in various studies, antioxidant compounds such as α-tocopherol, β-carotene, and ascorbic acid have been implicated in blocking the activation of the nuclear transcription factor kB (NF κB), which is involved in the regulation of several "pre-inflammatory" genes, decreases the inflammatory response(37). On the other hand, some antioxidant compounds, such as vitamin E, can reduce anti-inflammatory response by inhibiting the arachidonic acid pathway, which is responsible for synthesizing pre-inflammatory prostaglandins and leukotrienes(38). Fruits and vegetables are rich in antioxidants and also major sources of fiber(39). Increased fiber intake reduces the time spent in the intestine and lessens the absorption of harmful compounds in the gut, thereby reducing serum levels of these harmful compounds in RA. By reducing the amount of these toxic compounds, patients' health can improve(40). On the other hand, inflammatory condition such as obesity and the consumption Western diet can increase the risk of rheumatism. They exert their effects through the production of cytokines and chemokine which increased risk of RA.

Strengths and Limitations

To the best of our knowledge, this is the first study that evaluated the association between evaluating dietary total antioxidant capacity and newly diagnosed RA patients. Additionally, we have selected new diagnosed patients to reduce the likelihood of diet changes. We controlled the effects of several potential confounders in the statistical analyses.

Also, our study encounters a number of limitations, including: relatively small sample size and evaluating dietary patterns by using a self-reported 1-year FFQ which may increase the possibility of error in measuring dietary intake The subjects we studied were only from Isfahan, thus we cannot extend these results to all Iranians or the worldwide peoples. It should be mentioned that results may have been influenced by some potential confounders that were not assessed, such as genetic and stress level.

Conclusion

The present study observed an inverse association between dietary total antioxidant capacity and risk of incidence Rheumatoid arthritis. Further studies with a larger population are warranted to confirm our findings.

Declarations

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Disclosure statement

None of the authors had any personal or financial conflicts of interest.

Authors' contributions

S.N, and Mh.S contributed in conception, design, and statistical analysis. S.N, and B.Bcontributed in data collection and manuscript drafting. R.GH and Mh.S supervised the study. All authors approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors of this manuscript declared their consent for publication.

Competing interests

The authors declare that they have no competing interests.

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