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The Association between Non- Enzymatic Dietary Total Antioxidant Capacity and Phytochemical Index with Semen Parameters: A Cross-Sectional Study in Isfahan Infertile Men

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ABSTRACT

Background: Infertility affects about 15% of the population and male factors only are responsible for ~25–30% of cases of infertility. Oxidative stress is an imbalance between the production of free radicals and the capacity of the body to counteract their harmful effects through neutralization by antioxidants. This study aims to access the relationship between non-enzymatic dietary antioxidant capacity and male infertility. **Methods**: In this cross-sectional study, 270 infertile men aged 18-55 years were selected from Isfahan province in 2018. Semen assessment was performed according to the fifth edition of the WHO laboratory manual and a 168-item food frequency questionnaire (FFQ) questionnaire was used to determine the amount of dietary intakes of participants. P-value < 0.05 was considered statistically significant. **Results:** There were no significant association between sperm parameters and dietary total antioxidant capacity (DTAC) tertiles in the crude model and after adjustment for potential confounders. The participants in the highest tertile of DTAC had a higher risk of abnormal density and motility in crude model (OR=1.30; 95% CI: 0.65, 2.59; *P* = 0.46 and OR=1.69; 95% CI: 0.83, 3.44; *P* = 0.99) and risk of abnormal density decreased in the adjusted model (OR=0.99; 95% CI: 0.39, 2.50; *P* = 0.99) and (OR: 1.43; 95% CI: 0.51, 4.01; *P* = 0.5). **Conclusion:** In this cross-sectional study there was no significant relationship between semen parameters and DTAC tertiles in the crude and adjusted model. Therefore, it is required to conduct more research studies to determine the clear benefits and risks of antioxidant therapy for infertility.

Keywords: *Antioxidants; Semen analysis; Male infertility; Phytochemical index*

Introduction

A commonly experienced problem by females and males is infertility worldwide, remaining on the boundaries of people's healthiness and medicinal procedures in situations

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with lower resources (Bornstein *et al.*, 2020). Over 180 million people worldwide suffer from infertility, in which one is not capable of conceiving a gestation during 1–2 years of attempts to become pregnant (Inhorn and Patrizio, 2015). Besides, being a medical condition in itself, infertility can have a significant impact on well-being and quality of life (Maroufizadeh *et al.*, 2018).

The semen quality is the main determinant of male healthful reproduction. In the last two decades, because of elevated infertility rate and azoospermia in males, concerns about semen quality parameters, particularly concentration and morphologic features of sperm have grown up (Najafpour *et al.*, 2020). Oxidative stress is deemed to be responsible for the pathophysiology of subfertility (Smits *et al.*, 2018).

In the process of transformation of spermatogonia to mature sperm, the combined loss of cytoplasm, formation of mitochondrial reactive oxygen species (ROS), and preferred accretion of a very oxidizable substratum in sperm cell membrane cause its high susceptibility to oxidative injury. This increased vulnerability has been enormously interesting with regard to the contribution of antioxidants to the administration of subfertile males (Nassan *et al.*, 2018). The sperm morphologic features and tasks are negatively affected by excessive ROS via lipid peroxidation, DNA fragmentation, and apoptosis, thereby compromising the viability, count, motility, and even fertilization ability of sperm, leading to male subfertility or, oftentimes, infertility. The main concerning issue in the present reproductive research area is to assess and manage oxidative stress caused men infertility (Agarwal and Sengupta, 2020). High concentrations of ROS may result from either endogenic or exogenic agents. The commonest exogenic inducers of oxidative stress in reproductive cells are environmental contamination, smoking, alcohol, poor nutritional status, and obesity. Besides, infections and chronic and autoimmune diseases are the reputed endogenic inducers (Tremellen, 2008). Antioxidants can have effects beyond their capability of preventing oxidation (Young *et al.*, 2008).

As a dietary factor, a lower intake of some antioxidant nutrients, such as vitamins A, C, and E, folate, zinc, and selenium, has been associated with sperm quality (Agarwal and Said, 2004). For instance, in a cross-sectional study of 97 healthy male volunteers, a higher nutrient intake of vitamins C, E, and b-carotene was associated with higher sperm count and motility (Wong *et al.*, 2002).

Dietary antioxidant capacity as a priori index indicates the content of antioxidants intake from diet. ROS can be reduced by antioxidants, including carotenoids, flavonoids, phytochemicals, and vitamins (E and C), to avoid oxidative injury (Daneshzad *et al.*, 2020). Phytochemicals are the huge group of compounds, which can be responsible for therapeutic effect as well as color, flavor, and aroma of foods. These phytochemicals have different classes (phenol, flavonoid, alkaloid, carotenoid, nitrogen-containing, and organosulfur compounds). A study proposed that dietary total antioxidant capacity (DTAC) and some dietetic quality indices (e.g., the Mediterranean Diet Score, Healthy Eating Index, and Diet Quality Index) were positively correlated, but DTAC and energy and concentration were negatively correlated. DTAC associations with these dietetic quality indicators result from the fact that DTAC and the use of healthy food groups, including fruits, vegetables, fish, and nuts, are positively correlated (Puchau *et al.*, 2009).

Antioxidant system of body includes two parts of enzymatic and non-enzymatic system. Currently, there is limited high-quality evidence to show the association between the dietary antioxidant intake and the semen parameters in Iranian infertile men. Therefore, the purpose of this cross-sectional study was to access the relationship between non-enzymatic dietary antioxidants intake and some semen quality parameters in infertile men.

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Materials and Methods

Participants: The present study was conducted in Isfahan in 2018. Totally, 270 participants referred to the main infertility clinic, with either history of primary or secondary infertility and aging between 18 and 55 years were selected. Ten participants with missing information or caloric intake of above 4200 kcal/day were excluded. Finally, 260 participants fulfilling the study signed an informed consent form. Subjects with the following criteria were not included in the study: (history of testicular atrophy, urinary tract infection, azoospermia, testicular torsion, genital surgery, and other genital diseases, endocrine, and anatomical disorders), metabolic diseases, psychiatric and physiological disorders, alcohol and drug abuse and supplement use (Biswas *et al.*, 2010).

The detailed report of methods and data collection have been previously published (Shirani *et al.*, 2020).

Semen parameters assessment: In order to collect semen samples, the participants were asked to abstain for 3 days. The samples were collected in sterile containers and placed at 37 °C for half an hour before final analysis to liquefy. Semen assessment was performed according to the fifth edition of the WHO laboratory manual (World Health Organization, 2010).

Dietary intakes assessment: A validated 168-item food frequency questionnaire (FFQ) was utilized to evaluate individuals' dietary intakes. Previously, it has been shown that this questionnaire is valid for the assessment of Iranian food intakes (Mirmiran *et al.*, 2010). The participants' mean frequency of food consumption during the last 12 months was determined in this questionnaire. (More detailed dietary assessment is provided in a previously published article) (Shirani *et al.*, 2020).

Non-enzymatic dietary total antioxidant capacity evaluation: DTAC value from the ferric reducing–antioxidant power test of every food was added to calculate the dietetic TAC scores based on a previous report and was presented as DTAC in mmol/100 g of food. If not reported previously, a value was assigned to TAC-bearing foods using the data for the same food product (e.g. similar botanical group) as a representative. In cases of unpublished DTAC values for cooked foods, a DTAC score was calculated by TAC levels of fresh foods. The dietetic TAC score from the FFQ was calculated using the mean TAC value of the foods included in every product (Puchau *et al.*, 2009).

Phytochemical index evaluation: The phytochemical index (PI) was calculated based on the modified method previously developed by McCarty (McCarty, 2004); [PI = (phytochemical-rich foods g/d/ total food intake g/d) × 100]. Food included the whole grains, nuts, legumes, olives and olive oil, soy products, as well as, coffee, tea, and spices. Potatoes often consumed as a starch component, then were not considered as vegetables. Natural fruit and vegetable juices were included in the fruit and vegetable groups, since these are considered as rich sources of phytochemicals.

Other variables assessment: A structured questionnaire was used to collect demographic data, alcohol abuse or cigarette smoking, medical history, and supplements intake. The participants were interviewed directly. Their weight (considering 0.1 kilograms) and height (considering 0.5 centimeters) were measured. Next, their body mass index (BMI) was calculated in kg/m^2.

Ethical consideration: Before they entered the study, all participants signed the written consent. The Ethics Committee of Isfahan University of Medical Sciences (IUMS), Isfahan, Iran ethically approved the study (no.397387).

Data analysis: The data normality was assessed utilizing kolmogrove-smirnov test. Continuous variables are presented as mean (±Standard Deviation (SD)) and categorical variables are presented as percentage. The tertiles of the DTAC were applied to assess dietary intakes and sperm parameters' relationships. One-way ANOVA test was employed appropriately to access the general

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characteristics of the participants as well as their dietary intakes across different dietary intakes tertiles. Multiple logistic regressions (odds ratios (ORs) with 95% confidence interval (CI)) were utilized to investigate the association between the sperm parameters and DTAC tertiles. In the adjusted model, the potentially confounding variables, such as age, energy intake, BMI, physical activity, marriage time, educational status, smoking, and alcohol history were justified. In the whole model, the first tertile was used as a reference level. The statistical analyses were done using SPSS software (version 20), and the significance level was set at P-value < 0.05.

Results

Baseline features of members according to tertile of DTAC and PI are shown in **Table 1**. The mean age, waist circumference, BMI, and physical activity of infertile men were 31.24 years, 94.51 cm, 26.94 kg/m^2, and 29.27 Met.h/day, respectively. In the last tertile of DTAC, age was higher.

The dietary nutrients and food items intakes of members through tertiles of DTAC and PI are shown in **Table 2**. The participants in the last tertile of DTAC had higher intake of carbohydrate, vitamin C, and potassium, but lower intake of saturated fatty acid (SFA), calcium and selenium compared to the lowest tertile. Intakes of energy, protein, fat, fiber, mono unsaturated fatty acid (MUFA), poly unsaturated fatty acid (PUFA), cholesterol, vitamin A, E, B6, B9, B12, magnesium, zinc, and iron were not different in DTAC tertiles. Furthermore, intake of fat, SFA, MUFA, and cholesterol significantly reduced in the last tertile of PI.

Mean of sperm parameters in crude and adjusted models across tertile of DTAC and PI are shown in **Table 3**. Members in the highest tertile of DTAC and PI had no significant difference in comparison with the lowest tertile in the crude model. After adjustment for potential covariates, such as age, energy intake, BMI, physical activity, marriage time, educational status, smoking, and alcohol history, mean value of sperm density showed a significant difference across tertiles of PI.

Multivariable-adjusted odds ratio (OR) and 95% confidence intervals (CIs) for sperm parameters across tertiles of DTAC and PI are indicated in **Table 4**. There was no significant association between sperm parameters and DTAC tertiles in the crude model and after adjustment for potential confounders, including age, energy intake, BMI, physical activity, marriage time, educational status, smoking, and alcohol history. The participants in the highest tertile had a higher risk of abnormal density and motility in crude model (OR=1.30; 95% CI: 0.65, 2.59; P = 0.46 and OR=1.69; 95% CI: 0.83, 3.44; P = 0.99) and risk of abnormal density decreased in the adjusted model (OR= 0.99; 95% CI: 0.39, 2.50; P = 0.99) and (OR: 1.43; 95% CI: 0.51, 4.01; P = 0.5).

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Table 1. Basic characteristics of the participants across the tertiles of DTAC and phytochemical index.

Variables	Dietary total antioxidants capacity (DTAC)				Phytochemical index			
	T1 (N=84)	T2 (N=85)	T3 (N=85)	P-value[a]	T1 (N=85)	T2 (N=87)	T3 (N=86)	P-value
Quantitative variables								
Age (year)	31.16±3.93[b]	30.97±4.69	31.35±4.30	0.84	31.55±4.76	30.76±3.69	31.32±4.49	0.46
Body mass index (kg/m^2)	26.55±4.81	27.44±3.41	26.86±4.01	0.36	26.57±4.06	27.19±3.99	27.02±4.29	0.59
Waist (cm)	94.64±11.35	95.36±8.48	94.07±11.10	0.72	93.89±9.85	95.54±10.42	94.20±10.90	0.54
Marriage time (year)	5.39±3.27	5.68±2.64	5.44±3.20	0.79	5.48±30.7	5.51±2.56	5.67±3.57	0.91
Physical activity (Met.h/day)	29.10±2.30	29.55±2.03	29.08±2.01	0.38	29.27±2.16	29.09±2.11	29.46±2.10	0.63
Qualitative variables								
Smoking history								
Yes	34 (40.47)[c]	29 (34.11)	31 (36.47)	0.68	36 (42.4)	29 (33.3)	30 (36.8)	0.42
No	50 (59.53)	56 (65.89)	54 (63.53)		49 (57.6)	58 (66.7)	56 (63.2)	
Alcohol history								
Yes	18 (21.42)	20 (23.52)	15 (17.64)	0.63	13 (15.3)	20 (23.0)	20 (23.3)	0.34
No	66 (78.58)	65 (76.48)	70 (72.36)		72 (84.7)	67 (77.0)	66 (76.7)	
Supplement use								
Yes	25 (29.76)	31 (36.47)	24 (28.23)	0.47	23 (27.1)	31 (35.6)	26 (30.2)	0.46
No	59 (70.24)	54 (63.53)	61 (71.77)		62 (72.9)	56 (64.4)	60 (69.8)	
Education status								
Less than high school	15 (17.86)	16 (18.82)	25 (29.42)	0.14	22 (25.9)	12 (13.8)	24 (27.9)	0.09
High school diploma	25 (29.76)	24 (28.23)	29 (34.11)		24 (28.2)	26 (29.9)	29 (33.7)	
Bachelor degree or higher	44 (52.38)	45 (52.95)	31 (36.47)		39 (45.9)	49 (56.3)	33 (38.4)	

[a]: Using one-way ANOVA for continuous and Chi-square test for categorical variables; [b]: Mean ± SD; c: n (%).

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Table 2. Dietary intakes of the participants across the tertiles of DTAC and phytochemical index.

VariableS	Dietary total antioxidants capacity (DTAC)				Phytochemical index			
	T1 (N=84)	T2 (N=85)	T3 (N=85)	P-value	T1 (N=85)	T2 (N=87)	T3 (N=86)	P-value[b]
Energy (kcal/d)	2571.15±734.82[a]	2443.92±627.91	2543.46±712.90	0.45	2648.49±710.76	2529.03±707.45	2379.87±626.95	0.03
Carbohydrate (g/d)	358.91±120.10	350.12±93.28	374.26±100.98	0.03	360.70±103.33	370.58±108.63	352.63±102.91	<0.001
Protein (g/d)	97.57±29.54	93.10±23.35	92.80±28.08	0.20	98.95±25.07	96.48±29.22	87.40±25.41	0.17
Fat (g/d)	91.61±39.44	83.72±29.71	85.89±40.32	0.34	99.15±44.07	84.43±33.67	77.42±26.97	0.001
Dietary fiber (g/d)	39.18±18.55	38.89±13.64	43.82±16.80	0.05	37.90±17.64	41.03±15.00	43.76±16.75	<0.001
SFA (g/d)	29.86±12.20	26.67±9.48	26.60±12.20	0.02	32.40±12.81	27.21±10.22	23.55±9.04	<0.001
MUFA (g/d)	29.66±13.39	27.50±11.11	28.20±13.87	0.69	32.27±15.42	27.05±11.52	24.99±9.96	0.01
PUFA (g/d)	17.52±9.64	16.67±6.61	16.70±8.49	0.67	18.82±10.99	16.24±7.12	15.80±5.45	0.21
Cholesterol (mg/d)	344.19±245.98	285.32±137.97	317.24±219.14	0.34	367.51±222.27	327.03±237.30	248.85±119.55	0.009
Vitamin A (RAE/d)	778.27±358.32	819.95±431.09	822.62±432.66	0.36	789.01±368.12	857.93±417.55	765.98±427.49	0.16
Vitamin E (mg/d)	14.06±8.58	13.07±5.88	13.52±5.14	0.89	14.84±8.54	13.03±5.29	12.79±5.49	0.38
Vitamin B_6 (mg/d)	2.17±0.57	2.17±0.59	2.22±0.63	0.26	2.18±0.59	2.25±0.58	2.11±0.62	0.01
Vitamin B_9 (µg/d)	599.89±166.72	544.00±126.40	564.79±147.33	0.85	552.95±140.75	566.55±140.29	553.06±159.99	0.02
Vitamin B_{12} (µg/d)	6.43±3.38	6.21±3.37	5.74±3.24	0.24	6.84±3.82	6.33±3.19	5.08±2.63	0.02
Vitamin C (mg/d)	211.84±110.95	241.72±128.85	274.31±133.25	0.001	211.74±116.31	262.50±134.83	250.13±124.59	<0.001
Potassium (mg/d)	4260.34±1349.52	4450.40±1344.83	4747.00±1464.42	<0.001	4334.25±1312.49	4632.71±1454.62	4441.08±1416.02	<0.001
Calcium (mg/d)	1267.01±450.07	1224.74±447.88	1158.96±381.22	0.04	1278.38±410.24	1264.20±434.71	1101.12±412.51	0.09
Magnesium (mg/d)	449.84±151.91	445.47±129.39	462.29±148.12	0.30	446.38±141.97	458.48±143.65	452.27±146.61	<0.001
Selenium (mg/d)	125.61±52.48	111.49±38.29	110.56±43.49	0.03	119.68±43.55	118.05±46.66	110.87±466.61	0.82
Zinc (mg/d)	14.69±4.51	14.12±4.11	13.98±5.08	0.30	15.08±4.54	14.35±4.59	13.27±4.46	0.60
Iron (mg/d)	17.81±6.21	17.34±4.63	18.39±5.46	0.29	17.58±5.47	18.20±5.65	17.85±5.32	<0.001

FA: Saturated fatty acid; PUFA: Polyunsaturated fatty acid; MUFA: Monounsaturated fatty acid; [a]: Mean± SE; [b]: All values are adjusted for energy intake using ANCOVA.

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Table 3. Mean sperm parameters across tertiles of DTAC and Phytochemical index.

Variables	Dietary total antioxidants capacity (DTAC)				Phytochemical index			
	T1 (N=84)	T1 (N=85)	T2 (N=87)	P-value[e]	T1 (N=85)	T2 (N=87)	T3 (N=86)	P-value
Volume (ml)								
Model I[a]	3.96±2.26[d]	4.37±1.98	4.16±1.99	0.43	4.16±2.29	4.22±1.88	4.06±2.04	0.87
Model II[b]	3.96±2.26	4.37±1.98	4.16±1.99	0.36	4.16±2.29	4.22±1.88	4.06±2.04	0.93
Model III[c]	3.96±2.26	4.37±1.98	4.16±1.99	0.31	4.08±2.21	4.37±1.85	4.25±1.89	0.62
Density ($\times 10^6$/ml)								
Model I[a]	13.88±17.38	14.25±16.70	11.02±12.88	0.34	11.58±15.77	13.24±12.47	14.72±19.25	0.44
Model II[b]	13.88±17.38	14.25±16.70	11.02±12.88	0.33	11.58±15.77	13.24±12.47	14.72±19.25	0.33
Model III[c]	13.88±17.38	14.25±16.70	11.02±12.88	0.15	8.61±5.57	11.62±5.98	10.30±6.28	0.02
Total motility (%)								
Model I[a]	31.82±18.99	29.08±17.90	27.36±17.37	0.27	32.04±19.21	27.69±16.38	29.34±18.60	0.28
Model II[b]	31.82±18.99	29.08±17.90	27.36±17.37	0.27	32.04±19.21	27.69±16.38	29.34±18.60	0.36
Model III[c]	31.82±18.99	29.08±17.90	27.36±17.37	0.19	26.33±17.63	25.40±14.69	25.98±17.34	0.99
Normal morphology (%)								
Model I[a]	3.28±7.35	5.04±12.14	3.81±10.22	0.50	5.23±13.77	3.48±7.18	4.06±10.29	0.55
Model II[b]	3.28±7.35	5.04±12.14	3.81±10.22	0.50	5.23±13.77	3.48±7.18	4.06±10.29	0.62
Model III[c]	3.28±7.35	5.04±12.14	3.81±10.22	0.37	2.27±1.35	2.36±1.54	2.36±1.54	0.80

[a]: Crude; [b]: Adjusted for age and energy intake; [c]: Additionally adjusted for BMI, physical activity, marriage time, educational status, smoking, and alcohol history; [d]: These values are mean (SE).
[e]: Using ANCOVA.

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Table 4. Crude and multivariable-adjusted odds ratios and 95% CIs for abnormal sperm parameters across tertiles of DTAC and phytochemical index.

Variables	Dietary total antioxidants capacity (DTAC)				Phytochemical index			
	T1 (N=84)	T2 (N=85)	T3 (N=85)	P_{trend}[e]	T1 (N=85)	T2 (N=87)	T3 (N=86)	P_{trend}[e]
Volume (ml)								
Model I[a]	1.00	0.54 (0.28, 1.03)[d]	0.60 (0.31, 1.15)	0.12	1.00	0.91 (0.47, 1.76)	1.21 (0.64, 2.30)	0.54
Model II[b]	1.00	0.45 (0.20, 1.00)	0.51 (0.22, 1.19)	0.10	1.00	0.89 (0.46, 1.72)	1.13 (0.59, 2.17)	0.68
Model III[c]	1.00	0.41 (0.17, 0.94)	0.45 (0.18, 1.09)	0.06	1.00	0.71 (0.30, 1.67)	0.74 (0.31, 1.75)	0.55
Density ($\times 10^6$/ml)								
Model I[a]	1.00	0.96 (0.49, 1.86)	1.30 (0.65, 2.59)	0.46	1.00	0.55 (0.27, 1.11)	0.57 (0.28, 1.16)	0.13
Model II[b]	1.00	0.80 (0.35, 1.84)	0.86 (0.35, 2.10)	0.74	1.00	0.56 (0.28, 1.14)	0.58 (0.28, 1.18)	0.14
Model III[c]	1.00	0.80 (0.34, 1.88)	0.99 (0.39, 2.50)	0.99	1.00	0.30 (0.11, 0.79)	0.53 (0.19, 1.46)	0.26
Total motility (%)								
Model I[a]	1.00	1.07 (0.55, 2.09)	1.69 (0.83, 3.44)	0.14	1.00	1.30 (0.66, 2.54)	1.36 (0.69, 2.67)	0.36
Model II[b]	1.00	0.97 (0.40, 2.38)	1.35 (0.49, 3.72)	0.56	1.00	1.26 (0.64, 2.47)	1.29 (0.65, 2.57)	0.44
Model III[c]	1.00	0.98 (0.39, 2.46)	1.43 (0.51, 4.01)	0.50	1.00	0.81 (0.30, 2.15)	0.88 (0.32, 2.37)	0.80
Morphology (%)								
Model I[a]	1.00	0.42 (0.12, 1.42)	0.65 (0.17, 2.42)	0.57	1.00	1.02 (0.31, 3.31)	0.74 (0.24, 2.23)	0.58
Model II[b]	1.00	0.62 (0.11, 3.59)	0.57 (0.09, 3.61)	0.55	1.00	0.95 (0.28, 3.16)	0.77 (0.24, 2.38)	0.64
Model III[c]	1.00	0.67 (0.11, 4.09)	0.38 (0.05, 2.77)	0.33	1.00	1.11 (0.13, 8.99)	0.24 (0.03, 1.59)	0.11

[a]: Crude' [b]: Adjusted for age and energy intake; [c]: Additionally adjusted for BMI, physical activity, marriage time, educational status, smoking and alcohol history; [d]: These values are odd ratio (95% CIs); [e]: Obtained from logistic regression.

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Discussion

In this study, 260 infertile men were examined to determine the prevalence of infertility and its possible relationship with DTAC. The results of this study showed that intake of carbohydrate, vitamin C, and potassium were higher and intake of SFA, calcium, and selenium were lower in the last tertile of DTAC in comparison with the lowest tertile. Also, intake of fat, SFA, MUFA, and cholesterol significantly reduced in the last tertile of PI. The participants in the last tertile of DTAC had a higher risk of abnormal density and motility in crude model, but risk of abnormal density decreased in the adjusted model; however, there were no significant relationship between semen parameters and teriles of DTAC and PI.

Over the last decades, sperm quality has decreased and the most important reasons for this decrease are environmental factors, job stress, chemicals, heat, smoking, and nutritional factors (Akpinar *et al.*, 2007). For the first time, in 1943 stated that oxidative stress would reduce sperm viability and ultimately damage sperm DNA by altering sperm function (Agarwal *et al.*, 2008). Increased oxidative stress in the semen of infertile men could cause changes in the structure and functional capacity of sperm and by activating different pathways can have a negative role in sperm health. Therefore, increasing the level of ROS by disrupting the count, motility, shape, and health of sperm DNA, indicates the role of oxidative stress in male infertility (Türk *et al.*, 2010).

The study by Eskenazi *et al.* showed that, beta-carotene intake was directly related to sperm concentration and sperm motility (Eskenazi *et al.*, 2005). Another study by Mendolia *et al.* showed that receiving higher levels of lycopene was associated with better semen quality (Mendiola *et al.*, 2010). Also, the study by Minguez stated that, there was a positive correlation between lycopene consumption, sperm count and motility (Mínguez-Alarcón *et al.*, 2012). However, in the present study, the intake of vitamin C and potassium were significantly higher in the last tertile of DTAC.

Fruits and vegetables are good sources of folate, vitamin B6, and antioxidants, such as vitamin C, beta carotene and vitamin E, all of which can affect sperm quality. Oxidative stress is associated with an increase in ROS, which are inversely related to sperm concentration and motility (Ross *et al.*, 2010). Physiological amounts of ROS are naturally produced by sperm, but overproduction of ROS and lack of antioxidants lead to semen disturbance (Aitken, 2016). In addition, the beneficial effects of dietary antioxidants, such as vitamin C, vitamin E, and folate on sperm motility have already been demonstrated. For example, a randomized controlled trial (RCT) reported that after treatment with sulfate and folic acid, the number of normal sperm increased in infertile and fertile men (Wong *et al.*, 2002). Fruits and vegetables are rich in fiber and potassium, which can be beneficial for semen quality (Ross *et al.*, 2010).

SFAs and hormonal preservatives or residues, such as xenobiotics or anabolic steroids may alter sperm quality (Rambhatla *et al.*, 2016). High concentrations of SFAs and low levels of omega-3 PUFA are associated with decreased fertility parameters (Chavarro *et al.*, 2014). In animal studies, some dietary SFAs do not affect sperm quality parameters. However, various human studies have shown that higher levels of palmitic acid or stearic acid are present in sperm in infertile men (Eslamian *et al.*, 2017).

Some recent studies have pointed to the importance of selenium and other minerals, such as zinc on the maturation process and sperm quality. Selenium mainly in the form of selenoproteins affects male reproductive function. Sufficient selenium is required for normal spermatogenesis and sperm maturation (Ahsan *et al.*, 2014). In the present study selenium levels were lower in the last tertile of DTAC.

Oxygen poisoning is an inherent challenge to aerobic life, including sperm, the cells responsible for species reproduction. Increased oxidative damage to sperm membranes, proteins, and DNA is associated with changes in signal transduction mechanisms that affect fertility. Recent evidence suggests that sperm and eggs have an innate, but limited capacity to produce ROS to aid the

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fertilization process. A variety of defense mechanisms, including antioxidant enzymes (SOD, catalase, GSH peroxidase, and reductase), vitamins (E, C, and carotenoids), and biomolecules (OSH and ubiquinol) are available to balance the risks of ROS and antioxidants appear to be essential for sperm survival and function (Salas-Huetos *et al.*, 2017).

The availability of antioxidants in abnormally high concentrations, as well as the fact that they are commonly added to various food products, may put patients at risk of overdosing on these compounds, which may be toxic. Few studies evaluating antioxidant overdose and its side effects have shown that high doses of dietary antioxidant supplements - even if present - have different therapeutic effects even if free radicals are clearly present in the cells. Oxidative damage is a phenomenon called the "antioxidant paradox". In addition, excessive use of antioxidants, such as vitamin C, vitamin E, and N-acetyl cysteine may lead to reduced stress, which is reported to be as dangerous to cells as oxidative stress and can cause diseases, such as cancer or cardiomyopathy (Henkel *et al.*, 2019). Therefore, it is required to conduct more careful research to determine the clear benefits and risks of antioxidant therapy for male infertility.

A recent systematic review of 17 randomized trials of antioxidant supplementation showed an improvement in sperm motility in men assigned to antioxidant supplementation compared with placebo. A higher antioxidant dietary intake has been associated with higher sperm numbers and motility in healthy nonsmoker men (Agarwal *et al.*, 2008). A recent review of intervention studies about the effect of antioxidants on semen parameters concluded that vitamins A, C, E, carnitine, and glutathione improve semen quality in male factor infertility (Agarwal and Said, 2004).

Unfortunately, there are little data on the biological mechanisms by which these antioxidants affect semen quality and how dietary intake relates to their levels in the seminal plasma. It is possible that for some of these micronutrients, increasing intake within the range documented in the study does not result in an appreciable increase in their concentrations in the semen. It is also unclear whether different antioxidants are concentrated in different parts of the genital tract. This would explain why certain micronutrients would be associated with semen parameters (if they were concentrated in the epididymis).

The present study had several limitations that should be considered when interpreting the results. The research design was cross-sectional, so we were not able to identify the cause-and-effect relationship between dietary antioxidant consumption and infertility. Therefore, in order to confirm the findings of the present study, clinical trials or case-control studies in this field are required. Also, in this study, serum levels of nutrients and antioxidants were not measured, which in turn reduces the accuracy of the results. However, the food frequency questionnaire was used, which its validity and reliability was measured for the Iranian community. The strength of the study was the ability to simultaneously adjust several confounding variables, including age, energy intake, BMI, level of physical activity, and smoking status.

Conclusion

In this cross sectional study, there was no significant relationship between semen parameters and DTAC tertiles in crude and adjusted model. However, there was a significant distribution between mean values of sperm density across tertiles of PI in the adjusted model. Overall, it is required to carry out studies to determine the clear benefits and risks of antioxidant therapy for male infertility in different populations.

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Authors' contributions

Shirani M participated in study design, data collection and evaluation and writing the article. Ghaem Far Z participated in data collection and evaluation. Bagheri M; participated in statistical analysis and interpretation of the data. Nouri M contributed to all experimental work, and interpretation of data and writing the article.

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Conflicts of interest

The authors declare no conflict of interest.

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