Nutrition and Food Sciences Research Vol 9, No 4, Oct-Dec 2022, pages: 19-26

Original Article

Possible Roles of Low-Fat Yogurt and Cheese with in Further Side Effects of COVID-19 Vaccination: A Case-Control Study

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Received: January 2023 **Accepted:** April 2023

ABSTRACT

Background and Objectives: Morbidity and mortality caused by sever acute respiratory syndrome 2 (SARS-CoV-2) can decrease with effective vaccination. The current study assessed relationships between the food intakes and nutritional habits before vaccination and the severity of vaccination-linked symptoms.

Materials and Methods: Totally, 586 participants (377 cases with moderate to severe symptoms after COVID-19 vaccination and 209 controls with no clinical symptoms after vaccination) were investigated in a case-control study. Food frequency questionnaire was used to investigate dietary food group intakes during a year. Food habits were assessed using general questionnaires. Logistic regression models were used to estimate strength of the associations between the history of food intakes and the odds ratios (ORs) of side symptoms after vaccination.

Results: After considering energy intake, gender, vaccine type, type of dairy products and BMI in the logistic regression models, consuming yogurt and cheese during the year before the vaccination significantly increased the occurrence of side effects after vaccination with COVID-19 vaccine (OR = 4.153; 95% confidence interval (CI) = 2.182–7.902; $p < 0.001$), (OR= 1.556; 95% CI = 1.007–2.404; $p = 0.047$), respectively. In the group with side effects after vaccination, more participants consumed low-fat dairy, compared to the control ($p = 049$).

Conclusions: It seems that intake of yogurt and cheese can increase the odds of side effects after COVID-19 vaccination.

Keywords: Low-fat yogurt, Low-fat cheese, Side effects, COVID-19 vaccination

Introduction

Since 2019, a dangerous pandemic has occurred worldwide known as sever acute respiratory syndrome 2 (SARS-CoV), which has been caused by novel coronaviruses (1). Up to 23 February 2022, there were 426,624,859 verified cases of COVID-19, resulting in 5,899,578 deaths, according to World Health Organization (WHO) (2). For preventing coronavirus spread, mass vaccinations were the most effective public health measure. The COVID-19 vaccination programs were launched in several countries in December 2020, primarily targeting health care workers (3). The goal of vaccine development is to verify that vaccines are effective at protecting humans. The most important endpoint effect, protection against severe illness and death are not always easy to assess in phase-3 clinical trials (4); however, some vaccines may be more effective than others. By providing SARS-CoV-2 vaccines, mortality and morbidity decreased (5). Global vaccination and vaccine development are accelerating, increasing the importance of research to enhance immunity and immune responses to vaccines (5, 6).

After COVID-19 vaccination, the most common adverse reaction includes local pain followed by swelling (7). Nearly half of the surveys reported pain, joint pain and headache after receiving the first vaccine. Some of the vaccinated people developed symptoms that usually included flu-like illnesses, including fever, chills, headache, myalgia and sore throat. Less common side effects included nausea and diarrhea (8, 9, 10). The European Food Safety Authority states that "a proper nutritional status of the host is essential for an effective immune response"; hence, it may be helpful to pay further attentions to the history of nutritional intakes before vaccination (11, 12). As a result of the current epidemic, a relatively high number of COVID-19 vaccines are used

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[DOR: 20.1001.1.23830441.2022.9.4.3.4]

daily and concerns have increased about the efficacy of vaccines in malnourished individuals (13, 14). Nowadays, no human study has investigated relationships between the food intakes and nutrition habits prior to vaccination and vaccination symptoms. The present study investigated the history of food intake for the participants, who divided into two groups of cases (moderate to severe side effects) and controls (no side effects) after vaccination with a second dose of four vaccine types (Astrazeneca, Sputnik, Sinopharm and Barekat), Khuzestan Province, Iran, December 2021 to March 2022.

Materials and Methods

Participants

In total, 586 participants (377 cases with moderate to severe symptoms after COVID-19 vaccination and 209 controls with no clinical symptoms after vaccination) were investigated in the current case-control study. Between December 2021 and March 2022, participants were recruited from vaccination centers located at Khatam Al-Anbia Hospital, Shoushtar, Khuzestan Province, Iran. Medical Ethics Committee within Shoushtar Faculty of Medical Science approved the study protocol following the guidelines of 2013 Helsinki Declaration (registration no. IR.SHOUSHTAR.REC.1400.026). Consent forms were signed by the participants prior to the commencement of the study.

Demographic data of the participants, including age, sex, allergy history, ethnicity, occupation, education, chronic diseases, smoking history, marital status, nutritional supplement intake history and physical activity level, were collected using general information questionnaires. Family incomes below six million tomans were considered as lower-middle, incomes of less than 11 million tomans were considered as middle income and incomes greater than 11 million tomans were considered upper-middle income. Women and men over 18 years old who received a second dose of one of Astrazeneca, Sputnik, Sinopharm or Barekat vaccines and wished to participate in the study were eligible for participation in the study. Exclusion criteria included diabetes, high blood pressure, heart disease, anemia hyperthyroidism, hypothyroidism, kidney diseases and cancers. Moreover, participants who failed to complete the questionnaires appropriately, under or over-reported their energy intakes (energy intakes out of 800–4200 kcal/d), did not cooperate in anthropometric measurements, were pregnant or lactating, had malignancies within the past 5 y and/or used immunosuppressive medications were excluded from the study.

The participants' phone numbers were collected in the first visit. In the consecutive eight days after vaccination, participants were contacted every two days to investigate whether systemic (whole-body) and/or local side effects were experienced. Participants who did not have symptoms were questioned via phone calls. Participants with symptoms were referred to a physician at Khatam Al-Anbia Hospital for further verifications. Participants with local or systemic vaccine symptoms were included in the case group after verification by the physician. The most common adverse effects included headaches, fatigue, tiredness, sleepiness, chills, shivering, diarrhea and fever. The most common local side effects included myalgia, arm soreness, tenderness, redness, itching, painful rash and swollen lymph nodes. Participants were offered with the option of reporting additional side effects. A physician verified side effects after vaccination in the case group based on clinical symptoms. It was tried to select participants in two similar groups in terms of age, sex, weight, type of COVID-19 vaccine, ethnicity and level of physical activity.

Anthropometry and physical activity assessments

Stadiometer was used to measure height (m) with an accuracy of 0.10 cm. To measure the weight of participants (kg), calibrated balance was used with an accuracy of 0.5 kg. The body mass index (BMI) was calculated as follows: body weight (kg) divided by squared height (m^2). To assess the physical activity level, short version of the international physical activity questionnaire (IPAQ) was used. The metabolic equivalent of task (METs) was calculated based on the participants' usual physical activities. Then, participants were divided into three groups based on their levels of activity of active, minimally active and inactive. Twelve countries have verified IPAQ validity and reliability (15). Furthermore, it has been verified as a reliable and valid questionnaire in Iran (16).

Dietary assessments

Researchers used a 146 item food frequency questionnaire (FFQ) for the Iranian population that was validated previously (17–19). Foods consumed by the participants in the last year were asked by the interviewers. In addition to the questionnaires, interviewers used booklets to explain the household measurements as well as the portion sizes for each food group (20). Number of units consumed from each food group (as recorded through a food pyramid) was recorded as daily, weekly, monthly and yearly or as not consumed at all. These were converted to units consumed per day. Cereals and breads (including bread, pasta and rice), meat and alternatives (including various meats and legumes), dairy products (including milk, yogurt, ice cream and cheese), fruits and vegetables were included in these food groups. Moreover, survey asked about the number of fatty foods (fried foods), types of oils (olive oil, animal oil, sunflower, canola, corn and frying oil) and types of dairies (high-fat dairy with more than 2.5% of fat, medium-fat dairy with 2.5% of fat and

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low-fat dairy with less than 1.5% of fat). The questionnaire recorded number of biscuits, cakes, fast foods and soft drinks consumed on daily, weekly and monthly bases. Then, these were assigned with a qualitative rating (low, medium and high).

Statistical analyses

To assess the normality of data distribution, Kolmogorov-Smirnov test was used. The mean ±SD (standard deviation) and median (25 and 75 percentiles) respectively presented for data with normal or non-normal distribution. Independent t-test was used when data included normal distribution and Mann-Whitney U test was used when it did not. Total energy intake was adjusted using residual method (21). Chi-squared test was used to compare categorical variables. To estimate strength of the associations between the history of food intakes and the odds ratios (ORs) of side symptoms after vaccination, logistic regression models were used. These associations were investigated in a crude OR model and then adjusted for factors such as energy intake, gender and vaccine type using additional models. Statistics were analyzed using SPSS software v.17.0 (SPSS, Chicago, IL, USA.). Data were considered statistically significant when $p < 0.05$.

Results

There were 600 enrolled participants in this study and seven were excluded due to incomplete questionnaires (two in the case and five in the control groups). Moreover, three participants were excluded from the controls and four participants from the cases due to over-reporting of food groups. Therefore, 586 participants (377 cases and 209 controls) were analyzed. Table 1 shows demographic characteristics of the participants. The participants had a median age of 27.75 years (range, 18–65 years) and a BMI of 23.99 (17.41–33.12) kg/m2. In general, 494 (84.3%) of the participants were females and 92 (15.7%) were males. A total of 237 participants (43.6%) were from lower-middle economic class, 235 (41.4%) from middle class and 86 (15%) from upper-middle-class backgrounds. On average, 187 (31.9%) of the participants reported low levels, 328 (60.1%) reported moderate levels and 45 reported high levels (8%) of physical activities. The study included 135 (26%) job administrative, 93 (16%) self-employed and 340 (58%) unemployed individuals. In the past nine months, 361 (61%) participants consumed nutritional supplements and 225 (39% of participants) did not consume any supplements. No significant differences were seen in age, weight and height between the case and control groups. Furthermore, no significant differences were observed between the two groups in BMI categories, educational level, income, marital status, allergy history, smoking history, vaccination type, physical activity level and occupation. In the group with side effects after vaccination, a fewer participants reported nutritional supplements, compared to the control group ($p = 0.049$).

Group with side effects and the control group did not differ significantly in their median energy intakes [2451.5 kcal (1512.4, 3731.6) against 2513.6 kcal (1293.1, 3845.4), respectively]. Table 2 reveals that the intake of yogurt was significantly different between the group with side effects after vaccination and the controls ($p = 0.031$).

Table 1. Comparison of the case and control groups' basic characteristics and anthropometric measurements

Characteristics	No side effects after vaccination (Controls) n=209	Side effects after vaccination (Cases) n= 377	*P*-value
Age (years)[£]	28.17 (18, 65)	27.02(18, 65)	0.354
Weight (kg) [€]	64.56± 15.60	63.02 ± 13.90	0.236
Height (cm)[€]	162.90± 14.96	163.52± 7.64	0.575
BMI category[&] (kg/m^2) n (%)			0.286
BMI<25	141(67.46)	226(59.94)	
25<BMI<29.9	48(22.96)	101(26.79)	
BMI>30	20(9.58)	50(13.27)	
Gender[&] n (%)			**0.039***
Female	184(88)	309(82)	
Male	25(12)	68(18)	
Ethnicity[&] n (%)			0.295
Persian and others	140 (66.98)	230 (61)	
Arab	10 (4.78)	23(6.10)	
Lor, Turk and Kurd	59 (28.24)	124 (32.9)	
Physical activity level [&] n (%)			0.748
High	17(8.13)	38(10.07)	
Medium	123(58.85)	213(56.49)	
Low	69(33.02)	126(33.44)	
Occupation[&] n (%)			0.129
administrative jobs	38(18.18)	101(26.79)	

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Characteristics	No side effects after vaccination (Controls) n=209	Side effects after vaccination (Cases) n= 377	*P*-value
Self-Employed	40(19.15)	60 (15.92)	
Unemployed	131(62.67)	216 (57.29)	
Allergy history [&] **n (%)**			0.381
No	138 (66.02)	261(69.24)	
Yes	71(33.98)	116 (30.76)	
Smoking[&] **n (%)**			0.272
No	197 (94.26)	345 (91.52)	
Yes	12 (5.74)	32 (8.48)	
Vaccine type[&] **n (%)**			0.051
AstraZeneca	25 (11.96)	28 (7.42)	
Sputnik	17 (8.13)	18 (4.79)	
Barekat	19 (9.1)	41 (10.87)	
Sino pharm	148 (70.81)	290 (76.92)	
Educational level [&] **n (%)**			0.699
Elementary	95(45.45)	183 (48.54)	
Diploma	86(41.14)	151 (40.05)	
College	28(13.39)	43 (11.41)	
Income[&] **n (%)**			0.459
Upper-middle	32(15.32)	62(16.45)	
Middle	80(38.27)	160(42.44)	
Lower-middle	97 (46.41)	155(41.11)	
Marital status [&] **n (%)**			0.986
Married	71(33.97)	129(34.22)	
Single	138 (66.02)	248(65.78)	
Nutritional supplement consumption in last 6 month[&] **n (%)**			**0.049***
No	59 (28.2)	165(43.7)	
Yes	150 (71.8)	212(56.3)	

[&]Data are shown as n (%) and assessed by *chi-squared* test.
[€] The data are shown as mean ± standard deviation (mean ±SD) and analyzed using the *Independent t*- test.
[£] The data are shown as median (25 [th], 75 [th] percentiles) and analyzed by *Mann-Whitney U* test.
P-values less than 0.05 were considered significant (*p < 0.05).

Table 2. Comparison of daily food consumptions (per unit) between the cases and controls

Daily food intake (per unit)	No side effects after vaccination (Controls) n=209	Side effects after vaccination (Cases) n= 377	P-value
Rice (30 g cooked/ 1.05 Oz)	1.53(0.14, 10.00)	1.47(0.14, 8.00)	0.796
Pasta (30 g cooked/ 1.05 Oz) [&]	0.28(0.03, 2.55)	0.23(0.03, 2.55)	0.072
Bread (30 g/ 1.05 Oz)	1.89(0.0, 6.0)	1.93(0.01, 7.0)	0.638
Milk (240 cc/ 8.12 Oz)	0.35(0.0, 3.0)	0.322(0.0, 2.0)	0.516
Yogurt (180 cc/ 6.09 Oz)	0.47 (0.0, 3.0)	0.69(0.0, 7.05)	**0.031***
Cheese (45 g or 1.5 Oz)	0.93(0.0, 4.5)	1.04(0.0, 15.0)	0.256
Ice cream (180 cc/ 6.09 Oz)	0.205(0.0, 4.0)	0.17(0.0, 2.0)	0.322
Fish (60-90 g/ 2-3 Oz) [&]	0.135(0.0,0.42)	0.138(0.0,0.42)	0.898
Poultry (60-90 g/ 2-3 Oz) [&]	0.38 (0.0, 1.0)	0.405(0.0,1.0)	0.304
Red Meat (60-90 g/ 2-3 Oz) [&]	0.38 (0.0, 3.0)	0.42(0.0, 3.0)	0.326
Egg (one number)[&]	0.54 (0.0, 4.0)	0.39(0.0, 3.0)	0.512
Legumes (30 g cooked/ 1.05 Oz) [&]	0.31 (0.0, 3.0)	0.30 (0.0, 2.0)	0.689
Fruits (Apples, bananas, oranges, 1 A medium size number; Apricots, plums: 2-3 pcs) [&]	1.64(0.0, 3.5)	1.63(0.0,3.5)	0.909
Vegetables (Cucumber, tomato, onion, etc., half a glass chopped)	0.83(0.0, 4.0)	0.98(0.0,4.5)	0.140

[&] The data are shown as median (25 [th], 75 [th] percentiles) and analyzed by *Mann-Whitney U* test.
P-values less than 0.05 were considered significant (*p < 0.05).

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In the case group, yogurt intake was higher than that in the control group. In Table 3, results of logistic regression models are reported, testing relationships between the food intake and vaccine-induced side effects after vaccination with odds ratios (OR) and confidence intervals (CI). As a part of Model 1, energy intake and sex were assessed, while as a part of Model 2, vaccine type, dairy products type and BMI were added to Model 1 and then adjusted. Results of logistic regression in Model 2 showed that consumption of yogurt and cheese during the last year before vaccination significantly increased the occurrence of side effects after vaccination [(OR= 4.153; 95% CI = 2.182–7.902; p < 0.001) and (OR = 1.556; 95% CI = 1.007–2.404; p = 0.047), respectively]. Table 4 shows that most participants consumed low quantities of cakes, biscuits, fast foods and soft drinks with no significant differences between the cases and controls. Significant differences were reported in dairy types between the two groups (p = 0.049). In the group with side effects after vaccination, more participants consumed dairy products with low fat contents. Within the participants, sunflower, corn, olive and frying oils were most commonly consumed. The usual types of the oils between the two groups were not significantly different (Table 5).

Table 3. The odds ratios (ORs) [§] based on the intakes of various food groups with 95% confidence intervals (CIs)

	OR(Crude)	P-value	Model 1 of Adjusted OR	P-value	Model 2 of Adjusted OR	P-value
Rice	1.967(0.836, 1.120)	0.657	1.019(0.877, 1.185)	0.804	1.460(0.956, 1.186)	0.080
Pasta	0.527(0.258,1.074)	0.078	1.392(0.829, 2.203)	0.914	1.479(0.957, 2.267)	0.077
Bread	1.017(0.896, 1.153)	0.796	1.014(0.894, 1.15)	0.831	1.156(0.794, 1.68)	0.445
Milk	0.744(0.470, 1.179)	0.208	0.881(0.601, 1.292)	0.516	1.470(0.957, 2.266)	0.078
Yogurt	**1.359(1.023, 1.806)**	**0.034**	**1.836(1.239, 2.720)**	**0.002**	**4.154(2.182,7.902)**	****<0.001**
Cheese	0.817(0.656, 1.018)	0.072	0.906(0.762, 1.076)	0.259	**1.557(1.007, 2.404)**	***0.047**
Ice cream	0.785(0.480, 1.284)	0.335	0.907(0.456,1.805)	0.907	1.501(0.973, 2.318)	0.066
Fish	0.832(0.131, 5.299)	0.846	0.780(0.120, 5.070)	0.795	1.979(0.198, 3.255)	0. 8
Chicken	1.135(0.484, 2.662)	0.770	1.129(0.477, 2.669)	0.783	1.472(0.985, 2.267)	0.078
Red Meat	1.310(0.860, 1.995)	0.209	1.293(0.808, 2.068)	0.248	1.424(0.920, 2.202)	0.111
legumes	1.112(0.662, 1.868)	0.689	1.132(0.593, 2.160)	0.708	1.482(0.962, 2.276)	0.075
Egg	0.962(0.838, 1.104)	0.962	0.958(0.800, 1.149)	0.646	1.462(0.950, 2.252)	0.083
Fruit	0.992(0.861, 1.143)	0.909	1.005(0.854, 1.183)	0.949	1.476(0.955, 2.270)	0.080
Vegetables	1.090(0.962, 1.234)	0.177	1.104(0.961, 1.269)	0.163	1.472(0.954, 2.272)	0.081

[§] *Logistic regression* model for calculating odds ratios (OR). Energy intake, gender and vaccination type were included in the model as covariates. Energy intake and gender are adjusted in Model 1. In Model

Table 4. Comparison between the case and control groups for cake, biscuit, soft drink and fast food consumptions

Index		Total N=586 Number (%)	(Controls) n=209 Number (%)	(Cases) n= 377 Number (%)	*P*-value[#]
Cakes and biscuits	High	76(13)	32(12.4)	44(11.7)	0.226
	Medium	232(39.5)	83 (41.7)	149(39.5)	
	Low	278(47.5)	94 (45.9)	184(48.8)	
Soft drinks	High	57(9.7)	22(10.5)	35(8.2)	0.445
	Medium	155(26.4)	56(26.8)	99(27.6)	
	Low	374(63.9)	131(62.7)	243(64.2)	
Fast foods	High	58(9.9)	21(10)	37(9.8)	0.231
	Medium	196(33.4)	78(37.3)	118(31.3)	
	Low	332(56.7)	110(52.7)	222(58.9)	

[#] Data are shown as n (%) and assessed by *chi-squared* test.

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Table 5. Comparison between the case and control groups for dairy types and fat contents in foods and oils

Index		Total N=586 Number (%)	(Controls) n=209 Number (%)	(Cases) n= 377 Number (%)	*P*-value[#]
Dairy type	Low fat	191(32.6)	58(27.8)	133(35.3)	*__0.047__
	Medium fat	201(34.3)	73(34.9)	128(34)	
	High fat	194(33.1)	78(37.3)	116(30.8)	
Fat content in food	High-fat and frying	75(12.8)	28(13.1)	47(12.5)	0.305
	Medium fat	415(70.8)	143 (68.2)	272(72.1)	
	Low-fat and steamed	96(16.4)	38 (18.7)	58(15.4)	
The usual oil types consumed	Animal oil	35(5.9)	10(4.8)	25(8.7)	0.376
	Olive	46(7.8)	13 (6.1)	33(7.8)	
	Canola	31(5.4)	12(5.8)	19(5)	
	Sunflower and corn	237(40.5)	85(40.7)	152(40.3)	
	Olive and frying oil	237(40.4)	89(42.6)	148(38.2)	

[#] Data are shown as n (%) and assessed by *chi-squared* test.

Discussion

The aim of this study was to investigate dietary food groups and nutritional habits of participants with clinical side effects after vaccination with COVID-19 vaccine, compared to asymptotic controls. Additionally, associations between the food intakes and clinical side effects following vaccination with COVID-19 vaccine were assessed. Based on the authors' best knowledge, this is the first case-control study in this field. Lactose intolerance is mostly common in the population; thus, consumption of milk is usually low. In contrast, yogurt and cheese are the primarily consumed dairy products. Products derived from dairies are excellent sources of riboflavin, probiotics and high-quality proteins. Yogurt and cheese, as well as fermented milk, may increase immune responses against viruses. Based on the studies probiotics may play roles in increasing immune responses against viruses, (9, 10, 22, 23). The current study detected that consumption of low-fat dairy products was significantly higher in the group with clinical complications after the vaccination, compared to the control group. Similar to these results, She et al. recently reported in an animal study that low-fat dairy was significantly associated with a higher production of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 2 (IL-2) and interferon γ (IFN-γ). They revealed that low-fat dairies increased T-cells and body immune functions, compared to that the high-fat dairies did (24). It is noteworthy that improved immune systems are not necessarily associated with increased complications from vaccines. Immune systems are largely dependent on vitamins and minerals such as vitamins A, C, D and E and zinc and iron (25).

Low consumptions of meats, fruits and vegetables were reported in case and control groups in this study. If these food groups were inadequately consumed as good sources of micronutrients and macronutrients, damaging effects might occur in the population. People living in low and middle-income populations are more likely to suffer from malnutrition and micronutrient deficiency (26). Since booster doses of the vaccine have been recommended for the population, consumption of adequate quantities of foods is essential based on the United States Department of Agriculture (USDA) recommendations and food standard pyramids. In the present study, it was not clear that yogurt and cheese could increase the clinical complications after vaccination. Moreover, the exact mechanisms were unclear either. Validity of these findings need comprehensive clinical studies.

Strengths and limitations

In this study, two strong highlights were recorded. For the first time in this case-control study, food intakes and nutritional habits were assessed and compared between the participants with symptoms after COVID-19 vaccination and those in asymptotic control group. However, the present study included three limitations. 1) Validated food frequency questionnaire was used to ask about food group consumption history; however, the recall bias could not completely be eliminated; 2) Despite adjustment and minimization of the potential confounders in the present study, residual or unmeasured confounding factors might still be missed; and 3) the present study as a case-control study was unable to verify that a history of dietary food intake led to increases in side effects of COVID-19 vaccination. Therefore, further follow-up studies are strongly recommended.

Conclusions

In this study, further consumptions of yogurt and cheese over the previous year contributed to further side effects after vaccination with COVID-19. Although extensive

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studies are necessary to investigate mechanisms of these findings, it is secure to recommend populations, who experienced severe side effects after a dose of COVID-19 vaccine, booster doses and intakes of sufficient dairy products of milk. However, intake of dairies from yogurt and cheese is less recommended.

Author's contribution

Concept, design, analysis and interpretation of data and writing and revising of the manuscript were contributed by S.A. Moreover, Z.A. was involved in conceiving and designing the study, collecting data and drafting the preliminary version of the manuscript. S.E. contributed to design of the study and data collection. All authors approved the final version of the manuscript before submission.

Acknowledgement

The authors appreciate supports from the Vice Chancellor for Research Affairs at Shoushtar Faculty of Medical Sciences. The Medical Ethics Committee within Shoushtar Faculty of Medical Sciences approved the study protocol based on 2013 Helsinki Declaration (registration no. IR.SHOUSHTAR.REC.1400.026).

Financial disclosure

The authors declare no conflict of interest.

Funding/Support

This study was funded by the Vice-Chancellor for Research Affairs of Shoushtar Faculty of Medical Sciences (grant no. 400000036). Furthermore, Vice-Chancellor of Research Affairs of Shoushtar Faculty of Medical Sciences approved the study protocol.

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