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Relationship Between Dairy Intake and Hospitalization Risk and Disease Severity in Patients With COVID-19

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ABSTRACT

The aim of this study was to investigate whether dairy intake was associated with the severity of coronavirus disease 2019 (COVID-19) disease and the probability of hospitalization of patients. This cross-sectional study was conducted on 141 patients with COVID-19 with an average age of 46.23 ± 15.88 years. The number of men (52.5%) participating in this study was higher than that of women. The association between dairy intake and COVID-19 was evaluated by multivariable logistic regression analysis. The risk of hospitalization in the highest tertile of dairy intake was 31% lower than in the lowest tertile (odds ratio [OR], 0.69; 95% confidence interval [CI], 0.37–1.25, p trend = 0.023). Higher milk and yogurt intake was associated with a reduced risk of hospitalization due to COVID-19. Patients in the third tertiles were about 65% (p for trend = 0.014) and 12% (p for trend = 0.050) less likely to be hospitalized than those in the first tertile, respectively. Dairy consumption, especially low-fat ones, was associated with a lower risk of hospitalization due to COVID-19 and lower severity of COVID-19.

Keywords: COVID-19; Diary; Hospitalization; Healthy diet

INTRODUCTION

In December 2019, a new form of respiratory disease was detected in the city of Wuhan, China. The new virus was named severe acute respiratory syndrome coronavirus-2, briefly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease was called coronavirus disease 2019 (COVID-19) [1]. COVID-19 mainly affected the respiratory system with slight damage to other organs. Fever, cough, fatigue, dyspnea, gastrointestinal discomfort, nausea, vomiting, anosmia, and muscle pain were the most common symptoms of illness onset [2]. The initial SARS-CoV-2 prevention includes social distancing, face mask

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Conflict of Interest
The authors declare that they have no competing interests.

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wearing, and getting vaccines. However, the lack of a vaccine, in all age groups or all parts of the world, or curative treatment for COVID-19 highlights the necessity for other treatments and prevention strategies. One of the non-pharmacological interventions in the management of COVID-19 is lifestyle and dietary modification. On the other hand, patients with chronic diseases appear to be more vulnerable to SARS-CoV-2 [3]. The coexistence of risk factors such as hypertension, overweight and obesity, impaired blood glucose, and dyslipidemia can be associated with severe infection and poor prognosis [4,5]. Unhealthy dietary habits can be a reasonable explanation for this association [6].

Nutrition can play an important role in the treatment and prevention of COVID-19 due to its association with both immunity and inflammation [7,8]. Micronutrients, especially vitamins A, C, D, as well as zinc and selenium, are important modulators of the immune system [9]. Dairy is one of the rich sources of these micronutrients. The zinc and selenium content of dairy has a protective role against inflammation, oxidative stress, and free radical damage. Also, vitamins B_6 and B_{12}, along with zinc and selenium, in dairy products can improve innate and adaptive immune responses through upregulating differentiation and proliferation of T and B cells. These nutrients also contribute to cell-mediated immunity and stimulate antibody production and function. Antimicrobial and anti-inflammatory activity are other features of these micronutrients. The importance of these micronutrients in maintaining the structural and functional integrity of physical barriers including the intestinal lining and the respiratory tract has also been proven [10]. Fermented milk consumption has also been shown to be associated with a reduced risk of mortality from COVID-19 [11]. These effects have been attributed in part to dairy peptides that, in addition to their antioxidant effects, have inhibitory activity on the angiotensin-converting enzyme [12].

Given the conflicting reports regarding the intake of dairy products in disease conditions, due to the exacerbation of lactose intolerance, diarrhea, and the possibility of allergy occurrence due to the absorption of dairy peptides with the reduction of intestinal integrity despite its numerous benefits [13], so far as we know, no study has been published on the relationship between dairy consumption and COVID-19. Therefore, the present study aimed to assess the association of dairy consumption and the severity of COVID-19 and the related hospitalization risk.

MATERIALS AND METHODS

Participants

The current study was designed as a case-control study to assess the association between dairy consumption and the severity of COVID-19 and the related hospitalization risk. In total, 141 patients with COVID-19 participated, of which 53 were hospitalized and 88 were outpatients. Patients were recruited from Emam Khomeini Hospital in Tehran, Iran by simple consecutive sampling technique. Outpatients were recruited from Simorgh Clinical Laboratory. The method of sampling was entirely explained in another study [14]. Briefly, the diagnosis was made based on the results of nasopharyngeal swabs for SARS-CoV-2 reverse transcription polymerase chain reaction and chest computed tomography scans. Patients admitted to the intensive care unit (ICU) or needing of invasive respiratory support were not included in the study. Those who received noninvasive ventilation masks were categorized as the severe group. The exclusion criteria were as follows: (1) the presence of comorbidities including hypertension, cardiovascular diseases, diabetes, kidney disease, inflammatory diseases, and cancer, (2) being pregnant or lactating, (3) following special diets over the past year. Inpatients were those admitted to the ward, not the ICU, who did not require invasive respiratory support and received oxygen support with antibiotics. On the other hand, patients who did not need to be hospitalized, and could be treated at home were considered outpatients. After a comprehensive explanation of the study protocol, written consent was obtained from all participants.

Dietary intake assessment

The dietary data of participants was collected by a valid and reliable 147-item semi-quantitative food frequency questionnaire [15]. Consumption of food items was questioned on a daily, weekly, or monthly basis over the past year by a trained nutritionist. Food items were summarized into 5 food groups including fruits, vegetables, grains, meats, and dairy foods (low-fat and high-fat). Low-fat dairy was generated as the sum of low-fat milk, regular cheese, and dough plus low-fat yogurt, and high-fat dairy was calculated as the sum of high-fat milk, cocoa milk, thick yogurt, high-fat yogurt, kashk (a traditional Middle East fermented dairy product), and ice cream. Absolute intakes of food groups were calculated in servings per day.

Clinical parameters

In this study, for measuring the height a wall-mounted stadiometer was used with 0.1 cm accuracy, also for weight measuring a digital scale with an accuracy of 0.1 kg was used. We calculate body mass index (BMI) by dividing weight (in kg) by height (in m^2). Biochemical parameters measured included white blood cells (WBCs), neutrophil-lymphocyte ratio (NLR), interleukin-6 (IL-6), and C-reactive protein (CRP). WBCs were measured by microscopy method with a BA310 microscope (MOTIC, Barcelona, Spain). Lymphocytes and neutrophils were assessed by Mindary BC-6800 and NLR was calculated accordingly. The enzyme-linked immunosorbent assay method was applied to measure IL-6 (Diaclone, Besançon, France) and CRP (Pars Azmoon Inc., Karaj, Iran).

Statistical analysis

The data were analyzed by the Statistical Package for Social Sciences (version 20.0; SPSS Inc., Chicago, IL, USA). The level that was considered statistically significant was < 0.05. For assessing the normality of variables, the Kolmogorov-Smirnov analysis was used. Quantitative data were reported as mean ± standard deviation or median (25–75), interquartile range and qualitative data as a percentage. Linear regression analysis was applied to comparing the basic characteristics of participants based on dairy intake tertiles. Logistic regression was carried out to evaluate the odds ratios (ORs) and 95% confidence intervals (CIs) of COVID-19 severity risk based on tertiles of dairy intake. In the current study, the first tertile of dairy intake was considered as the reference. The relationship between different dairy intakes with the risk of COVID-related hospitalization was evaluated as a crude model and multivariable-adjusted models with potential confounders, including sex, age, BMI, and daily energy intake.

Ethics approval and consent to participate

The Ethical Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.NNFTRI.REC.1399.046) approved the study protocol. Written consent was obtained from all participants.

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RESULTS

In the current study, 75 men and 66 women participated (**Figure 1**). The mean age of in-patients and outpatients was 50.17 ± 15.45 and 43.91 ± 15.77 years respectively. Outpatients were significantly younger than inpatients ($p = 0.024$). There was no statistically significant difference in BMI between the 2 groups, although the BMI of hospitalized patients was slightly higher (27.66 ± 4.57 vs. 26.53 ± 3.26 kg/m^2).

The basic characteristics of participants including dietary intake and biochemical parameters are shown in **Table 1**. Inpatients had lower energy intake, around 400 kcal per day, compared to outpatients. In terms of biochemical parameters, no significant differences were observed between the 2 groups. As can be seen, outpatients consumed significantly more servings of vegetables and dairy compared to inpatients, while no significant difference was observed in other food groups. Interestingly, high-fat dairy intake was significantly higher in hospitalized patients than in outpatients. **Table 2** presents the basic characteristics of participants across the dairy intake tertiles.

As shown in **Table 3**, higher milk intake was associated with a reduced risk of hospitalization due to COVID-19, accordingly patients in the second and third tertiles of milk intake were about 71% and 65% less likely to be hospitalized than those in the first tertile, respectively (p for trend = 0.014). The second tertile of low-fat milk intake was associated with an 11% increase and the third tertile of low-fat milk intake was associated with a 49% decrease in hospitalization risk, which was not statistically significant. Higher intake of yogurt (p for trend = 0.050) and low-fat yogurt (p for trend = 0.039) also showed a significant relationship with reducing the risk of hospitalization due to COVID-19. The second tertile of ice cream intake showed no association with COVID-19 severity, while the third tertile of ice cream intake, although associated with a 27% reduction in hospitalization risk, was not statistically significant.

Table 4 shows the association of dairy intake with the risk of COVID-19-associated hospitalization. Firstly, in a crude model it was indicated that higher dairy intake was associated with a reduced risk of hospitalization, although this relationship was not statistically significant. In the second model, after adjustments for age and sex, it is found

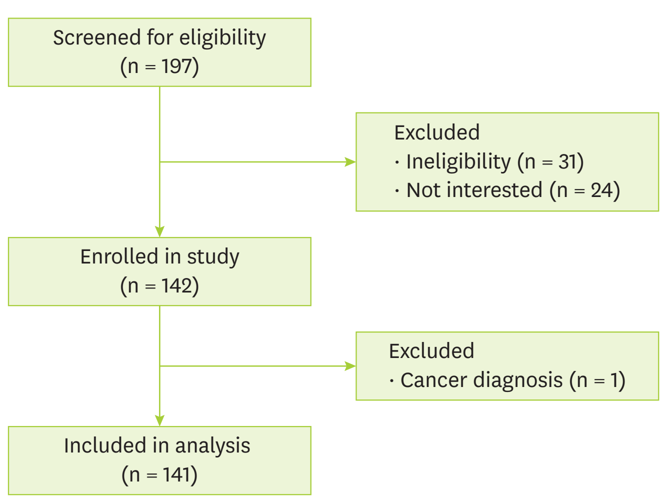

Figure 1. Flowchart of participant recruitment.

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Table 1. Basic characteristics of study participants based on coronavirus disease 2019 severity

Characteristics	In-patients (n = 53)	Out-patients (n = 88)	p value
Age (yr)	50.17 ± 15.45	43.91 ± 15.77	0.024
Female	24 (45.3)	42 (48.3)	0.862
BMI (kg/m^2)	27.66 ± 4.57	26.53 ± 3.26	0.089
Dietary intakes			
Energy (kcal/d)	1,542.83 ± 592.03	1,920.83 ± 648.07	0.001
Carbohydrate (%)	59.84 ± 8.98	60.44 ± 9.52	0.712
Protein (%)	13.68 ± 2.48	13.43 ± 2.43	0.563
Fat (%)	29.50 ± 8.00	29.68 ± 7.85	0.899
Cholesterol (mg)	210.48 ± 93.35	231.62 ± 110.66	0.247
Fiber (g per 1,000 kcal)	12.52 ± 3.82	13.41 ± 4.41	0.229
Simple sugar (g)	13.44 ± 7.52	15.52 ± 7.55	0.115
Biochemical parameters			
WBC (10^3/μL)	6.34 ± 1.97	6.14 ± 2.24	0.638
NLR	2.43 ± 2.06	1.95 ± 1.14	0.157
IL-6 (pg/mL)	7.59 ± 15.22	11.38 ± 30.99	0.582
CRP (mg/L)	6.26 ± 7.53	4.96 ± 6.22	0.294
Food groups (serving/day)			
Fruits	4.05 ± 2.46	4.66 ± 2.42	0.166
Vegetables	2.49 ± 1.85	3.64 ± 2.66	0.007
Grains	4.38 ± 2.58	4.57 ± 2.92	0.705
Meats	2.78 ± 1.33	3.04 ± 1.81	0.363
Dairy	1.05 ± 0.62	1.54 ± 0.95	0.001
Low fat	0.91 ± 0.61	1.11 ± 0.83	0.143
High fat	0.14 ± 0.38	0.45 ± 0.81	0.002

Data are presented as mean ± standard deviation for continuous variable and number (percent) for categorical variables.
BMI, body mass index; WBC, white blood cell; NLR, neutrophil-lymphocyte ratio; IL-6, interleukin-6.

Table 2. Basic characteristics of study participants based on dairy intake tertile

Characteristics	Tertiles			p trend
	T1 (n = 46)	T2 (n = 47)	T3 (n = 48)	
Age (yr)	47.89 ± 15.09	44.04 ± 14.21	46.75 ± 18.08	0.494
Female	23 (50.0)	21 (54.3)	22 (54.2)	0.894
BMI (kg/m^2)	27.29 ± 3.91	27.48 ± 3.94	26.11 ± 3.57	0.168
Dietary intakes				
Energy (kcal/d)	1,450.4 ± 472.2	1,795.87 ± 475.3	2,076.63 ± 796.6	< 0.001
Carbohydrate (%)	63.53 ± 10.12	60.13 ± 7.61	57.13 ± 9.07	0.003
Protein (%)	12.73 ± 2.57	13.20 ± 2.00	14.59 ± 2.39	< 0.001
Fat (%)	27.26 ± 8.66	29.91 ± 7.10	31.58 ± 7.34	0.027
Cholesterol (mg)	180.87 ± 93.90	211.37 ± 83.40	276.74 ± 112.00	< 0.001
Fiber (g per 1,000 kcal)	14.46 ± 4.29	12.49 ± 3.19	12.32 ± 4.73	0.023
Simple sugar (g)	14.36 ± 1.23	14.65 ± 7.29	15.19 ± 7.23	0.865
Food groups				
Fruits	4.38 ± 2.27	4.52 ± 2.43	4.33 ± 2.69	0.936
Vegetables	2.65 ± 1.61	3.08 ± 1.96	3.86 ± 3.28	0.050
Grains	4.51 ± 2.80	4.54 ± 2.22	4.44 ± 3.30	0.985
Meats	2.71 ± 2.15	2.72 ± 0.94	3.38 ± 1.59	0.077
Dairy	0.51 ± 0.29	1.29 ± 0.27	2.24 ± 0.80	< 0.001
Low fat	0.43 ± 0.31	0.96 ± 0.54	1.68 ± 0.74	< 0.001
High fat	0.08 ± 0.19	0.33 ± 0.51	0.59 ± 1.02	0.002

Data are presented as mean ± standard deviation for continuous variable and number (percent) for categorical variables.
BMI, body mass index.

that in comparison with the first tertile, the risk of hospitalization in the third tertile of dairy intake was 11% (OR, 0.89; 95% CI, 0.71–1.67) and in the second tertile of dairy intake was 15% (OR, 0.85; 95% CI, 0.69–1.45) lower.

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Table 3. 95% odds and confidence interval of the relationship between different dairy intake with the risk of hospitalization

Characteristics	Tertiles			p trend
	T1	T2	T3	
Milk	1.00 (ref.)	0.29 (0.11–0.72)	0.35 (0.13–0.95)	0.014
Low fat milk	1.00 (ref.)	1.11 (0.51–2.39)	0.51 (0.19–1.33)	0.141
Yoghurt	1.00 (ref.)	0.53 (0.19–1.27)	0.88 (0.22–1.58)	0.050
Low fat yoghurt	1.00 (ref.)	0.57 (0.16–1.14)	0.32 (0.11–0.94)	0.039
Ice cream	1.00 (ref.)	1.00 (0.99–1.01)	0.73 (0.27–1.47)	0.152

Table 4. Odds ratio (95% confidence interval) coronavirus disease 2019-associated hospitalization risk according to tertiles of dairy intake

Characteristics	Tertiles of scores			p trend
	T1	T2	T3	
Mean ± standard deviation	110.59 ± 60.75	275.96 ± 47.54	493.42 ± 88.73	
Model 1	1.00 (ref.)	0.92 (0.7–1.82)	0.83 (0.34–1.59)	0.102
Model 2	1.00 (ref.)	0.85 (0.69–1.45)	0.89 (0.71–1.67)	0.016
Model 3	1.00 (ref.)	0.74 (0.49–1.05)	0.69 (0.37–1.25)	0.023

Model 1: crude. Model 2: adjustment for age, sex. Model 3: adjustment for age, sex, body mass index, energy intake.

In the last model, all confounding factors including age, sex, BMI, and energy intake were adjusted, which showed that the risk of hospitalization in the highest tertile of dairy intake was 31% lower than in the lowest tertile.

DISCUSSION

The present study assessed the relationship between the consumption of dairy products and the severity of COVID-19. Dietary intake analyses showed that the inpatient group consumed lower amounts of dairy products compared to the outpatient group. On the other hand, higher intakes of dairy products including milk, yogurt, and low-fat yogurt showed a significant relationship with lower severity of the disease. Based on our knowledge this is the first study to report the relationship between dairy products and the severity of COVID-19.

So far, the relationship between dairy consumption and the risk of the severity of COVID-19 has not been investigated, and only limited studies have been conducted on the relationship between dairy consumption and the risk of contracting COVID-19 [16-18]. The association between food groups (including dairy products) and the risk of COVID-19 has been investigated in a few studies [17,19]. In agreement with the findings of the present study, Cobre et al. [17] stated that animal protein, including milk, could have protective effects against COVID-19, based on their study of the effects of foods and nutrients on COVID-19 recovery. Contradictorily, a study of the relationship between dietary factors and mortality and infection rates of COVID-19 in 158 countries found that higher milk intake was associated with increased infection rates [19].

Nutrition plays an important role in human health status. It has been shown that the body needs adequate macronutrients and micronutrients for optimal function [20]. Following a healthy and balanced diet is one of the crucial strategies for stimulating the immune system against viral infections and reducing the burden of infectious diseases [21]. It has been demonstrated that consuming foods rich in antioxidants is beneficial for our immune system, for instance, fresh fruits, vegetables, nuts, omega-3 fatty acids, and foods with low saturated and trans fatty acids content [22-24]. Vitamins A, B_6, B_{12}, folate, C, D, and E play an important role in promoting immunity and reducing the risk of infection. Moreover, other nutrients such as zinc, copper, selenium, and iron, as well as amino acids and fatty acids support the immune system. Vitamin A stimulates the expression of immunogenic genes through retinoic acid receptors [25]. It has been shown that vitamin B_{12} has an important role in antiviral defense by supporting the natural killer cells and CD8+ cytotoxic T lymphocyte activity, additionally, the deficiency of vitamin B_{12} can reduce the capacity of the phagocytic and bacterial killing of the neutrophils and decrease the number of CD8+ T lymphocytes and the activity of the natural killer cells [26]. Zinc, in addition to being a cofactor for many enzymes, plays an important role in the function of immune cells [27].

The role of gut microbiota in immunity has also been proven [28]. Several studies demonstrated that probiotics have beneficial impacts on reducing the severity of the disease and also in preventing respiratory infections [29,30]. The probiotics in yogurt may play a modulatory role in the immune system against the virus. The findings of the present study showed that consumption of yogurt, especially low-fat yogurt, is associated with a reduced risk of hospitalization due to COVID-19. Consistently, in a recent case-control study conducted by Mohseni et al. [18] in Iran, after adjusting for physical activity, yogurt consumption was significantly associated with a decrease in the occurrence of COVID-19, which can be mainly attributed to its probiotic properties.

Dairy products contain high biological value proteins, minerals, vitamins, and fatty acids which possess many health benefits. It has been proposed that the dairy content of conjugated linoleic acid (CLA) has gut anti-inflammatory properties, which may improve immune activity [31]. In addition, casein and whey derived from milk proteins can also have anti-viral, antioxidant, and anti-inflammatory properties in lung cells and regulate immune responses [32].

In the present study, milk showed the greatest effect in reducing the risk of hospitalization due to COVID-19, which was in line with the study of Darand et al. [16], in which the relationship between dairy products and the risk of COVID infection was investigated. In this study, it was reported that the consumption of low-fat dairy has a protective effect against COVID-19, while a variety of high-fat dairy products are associated with an increased risk of infection. In contrast, in another study, higher milk consumption was associated with an increased rate of COVID-19 infection [19]. The presence of some high-biological value proteins such as caseins and whey proteins in milk plays a role in reducing oxidative stress and inflammation [33]. The association of fatty acid called CLA with the reduction of inflammatory markers has also been shown [31]. It seems that the anti-inflammatory, antioxidant and immune-boosting effects of dairy products reduce the risk of contracting COVID-19 [17,33].

In this study, unlike usual case-control studies, outpatients and inpatients were compared and the relationship between dairy intake and the risk of hospitalization due to COVID-19 was assessed. The main limitation of this study was that we were not able to verify the causal relationship between the consumption of dairy products and the infection, due to the cross-sectional design of the study. Another important limitation was that we could not adjust all potential confounders.

In conclusion, our data provide evidence that dairy intake was associated with a lower risk of hospitalization due to COVID-19 and less severe infection.

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