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The Association Between Obesity, Mediterranean Diet Adherence, Zinc, Depression and COVID-19 Susceptibility: An Observational Study

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ABSTRACT

Objective: Unhealthy lifestyle factors have been associated with COVID-19 susceptibility, but data for diet and related lifestyle factors are conflicting. The objective of this study was to identify whether obesity, Mediterranean diet, Zn or depression could be associated to the risk of COVID-19 occurrence.

Methods: This observational case-control study was conducted in Türkiye (between December 2020 – September 2021) with face-to-face interview. A total of 100 former COVID-19 subjects as case group and 100 healthy control group, aged 20-54 were included in the study. By semi-structured questionnaire; demographic characteristics and anthropometric measurements was collected. Adherence to the Mediterranean diet was assessed using the Mediterranean Diet Adherence Screener and Mediterranean Diet Score. Daily dietary zinc intake was calculated using a 25-item food frequency questionnaire and blood samples for zinc levels was obtained from each participant. The level of depression was evaluated by Center for Epidemiologic Studies Depression Scale.

Results: No differences were found between the anthropometric characteristics of two groups (p>.05). Average adherence to the Mediterranean diet were lower in the case groups compared to controls (p<.05). While the total zinc intake showed a significant difference between the groups (12.6±13.0 vs 12.8±7.2 mg, respectively, p=.003), no difference was observed in the food sources related to zinc intake (9.4±5.71 vs 10.1±9.45 mg, p=.052). Case group had significantly lower zinc levels (64.7±17.6 µg/dL vs 76.1±16.7 µg/dL, p<0001) in both genders (for male p=.009 and female p<.001, respectively). The majority of case group subjects (76.1 vs 23.8%) had a serum zinc concentration below the reference ranges (p<.001).

Conclusion: Our findings suggest a negative relationship between Mediterranean diet adherence or serum zinc levels, and COVID-19 occurrence, however further studies are required to examine whether Mediterranean diet consumption or serum zinc status reduces the risk of COVID-19 causally.

Keywords: Mediterranean Diet, zinc, obesity, depression; COVID-19

1. INTRODUCTION

The worldwide coronavirus disease 2019 (COVID-19) pandemic has become the important global health emergency. Accordingly, World Health Organization (WHO) defined it as a global epidemic (pandemic) on 11 March 2020 (1).

The COVID-19 pandemic involved movement restrictions, also known as 'lockdown' or 'mass quarantine', to stop or limit the spread of the virus by restricting individual mobility and face-to-face interaction (2). These restrictions involved travel restrictions, stay-at-home orders, curfew enforcements, working-from-home advisories, self-quarantine, and also nationwide closure of schools, non-essential businesses and territorial borders (3). These measures have led to critical changes in lifestyle, resulting in high levels of stress, anxiety, and depression in addition to the risk of obesity (4).

Globally, virus-associated restrictions and lifestyle changes have led to adverse health consequences. It was highlighted the importance of maintaining a healthy lifestyle in fighting against COVID-19 pandemic (5). COVID-19 susceptibility may have been impacted by the eating, physical activity and other weight-related lifestyle behaviors. In this context, it was found that high body mass index (BMI) and insufficient physical activity associated with the risk of COVID-19 severe illness, with an implication that maintaining a healthy lifestyle could protect from COVID-19 susceptibility (6). It has also been identified that individuals with overweight and obesity increased as a result of virus-associated lifestyle

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changes. Body weight might increase as a result of unhealthy eating behaviors to cope with the pandemic (7). In addition to these, stress, depressive symptoms, financial strain, and loneliness exacerbated during the COVID-19 pandemic that might influenced the emotional state of individuals and lead to unhealthy eating behaviors like overeating (8-10).

Adherence to healthful dietary patterns may also protect from COVID-19 susceptibility. Data from 592 571 participants of the smartphone-based COVID-19 Symptom Study provide evidence that a healthy diet, characterized by healthy plant-based foods, was associated with lower risk and severity of COVID-19 (11).

Unhealthy lifestyle risk factors which might led to low grade inflammation have been associated with COVID-19 susceptibility (5). Obesity and other unhealthy lifestyle risk factors interactively impair immune function and increase the risk of severe infectious disease. It is currently not known whether patients with obesity are also more likely to have greater COVID-19 severity of illness (12).

Maintain a balanced function of the immune system and the redox system, zinc deficiency can probably be added to the factors predisposing individuals to infection and detrimental progression of COVID-19 (13). Numerous studies have demonstrated that zinc modulates immune response. Therefore, this possibility show the importance that zinc deficiency may have been associated with COVID-19 susceptibility (14-16).

Unhealthy lifestyle factors have been associated with COVID-19 susceptibility, but data for diet and associated lifestyle factors are conflicting (17). The present study aimed at examining the effects of the COVID-19 susceptibility on obesity, Mediterranean Diet adherence, zinc, and depression in a sample of adults.

2. METHODS

2.1. Study population and design

This observational (comparative) case-control study was conducted in Sarayköy District in Denizli, Türkiye, between December 2020 and September 2021. The sample size was calculated with a tolerable error of 2% and a confidence level of 95%, resulting in a minimum sample of 200. All individuals were selected through the simple random sampling process. A total of 200 individuals aged 20-54, 100 in the former COVID-19 case group and 100 in the control group (individuals with no COVID-19 occurrence) were included in the study. Individuals with any chronic disease, regular medication users, BMI<19 kg/m^2, elite athletes, pregnant and lactating women were excluded from the study.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the EMU Scientific Research and Publication Ethics Committee with the decision dated 07.04.2021 and numbered 2021/0068. Written informed consent was obtained from all subjects. This study funded and supported by the C-Type Scientific Research Project (date: 08.04.2021, decision: BAPC-OD-21-02). In order to carry out the study and to evaluate the serum zinc level, an application was made to the Private Denipol Hospital in Denizli and written permission was obtained. In this study, it was planned to evaluate the impact of obesity, adherence to the Mediterranean Diet, zinc and depression on COVID-19 susceptibility.

2.2. Demographic characteristics

A semi-structured questionnaire containing questions for collecting data on socioeconomic and demographic characteristics (gender, age, alcohol and cigarette consumption, cigarette and alcohol consumption, meal skipping) was used. Questions including whether or not to have COVID-19, the number of cases of contracting COVID-19, and the status of being vaccinated against COVID-19 were asked. All questions were filled in by the researcher dietician in a face-to-face interview according to the pandemic rules, by following the social distance, mask and hygiene rules.

2.3. Anthropometric measurements

Anthropometric measurements, including weight, height, and waist circumference (WC), were questioned according to individual declaration. Body mass index **(**BMI) was calculated by dividing the weight in kilograms by the square of the height in meters.

2.4. Zinc intake

Daily dietary zinc intake was calculated using a 25-item food frequency questionnaire, which includes foods rich in zinc. Questioned foods were developed based on the data from a short food frequency questionnaire including 18 items (18). The daily zinc intake (mg) of the participants was calculated by using the Nutrition Information Systems Package Program (BEBIS) version 8.2.

2.5. Serum zinc level

Serum zinc levels of all individuals were evaluated. 1 mL of blood was taken from the participants with a injector and transferred to a sodium EDTA tube. After the blood taken into the tube was kept for 30-60 minutes, it was centrifuged and the serum zinc level was determined in the Spectrophotometer device. According to the Private Denipol Hospital, the reference range for serum zinc was accepted as 68-115 µg/dL for women and 70-125 µg/dL for men, according to gender.

2.6. Adherence to the Mediterranean diet

Adherence to the Mediterranean diet were assessed using the Mediterranean Diet Adherence Screener (MEDAS) and Mediterranean Diet Score (MedDietScore).

2.7. Mediterranean Diet Adherence Screener (MEDAS)

The 14-item MEDAS questionnaire was indicated to be a moderate and reasonably valid tool for the rapid estimation of MD adherence (19). Turkish Validation and Reliability of Mediterranean Diet Adherence Screener conducted by Pehlivanoglu et al (20).A total score of 7 and above indicates that the individual has an acceptable degree of compliance with the Mediterranean diet (moderate), and a score of 9 or above indicates that the individual has a strict adherence to the Mediterranean diet (high) (19).

2.8. Mediterranean Diet Score (MedDietScore)

MedDietScore questionnaire has been validated for assessing Mediterranean diet adherence and providing dietary modification advice for primary prevention purposes. According to the rationale of the Mediterranean dietary pattern, the weekly consumption of the following 9 food groups: non-refined cereals (whole grain bread and pasta, brown rice, etc), fruit, vegetables, legumes, potatoes, fish, meat and meat products, poultry, full fat dairy products (like cheese, yoghurt, milk), as well as olive oil and alcohol intake have included in the diet score. A total score ranging from 0 to 55 was calculate/ed that higher values of this diet score indicate greater adherence to the Mediterranean diet (21). Accordingly, 0-20 points of adherence to the Mediterranean diet are considered low, 21-35 points of adherence to the Mediterranean diet are considered high, and 36-55 points of adherence to the Mediterranean diet are considered high (22).

2.9. CES Depression Scale (CES-D)

The Center for Epidemiologic Studies Depression Scale (CES-Depression Scale) was developed by The American National Mental Health Institute (23). It is a short self-report scale that has been found sensitive in measuring depressive symptoms in general population. The Adaptation of the CES-Depression Scale into Turkish was performed by Tatar and Saltukoglu (24).There are 20 items in the scale, and these items include questions to determine one-week feelings and thoughts. The items in the questionnaire are evaluated according to a 4-point Likert scale. (0: Never-Rarely, 1: A little-A few times, 2: Sometimes-Sometimes, 3: A lot-Most of the time). Among the questions, items 4, 8, 12 and 16 are scored in reverse. Participants receive points between 0 and 60 in line with their answers. CES-D Scale classified as <15 points not depression, 16-20 points as mild depression, 21-30 points as moderate depression, and >31 points as severe depression (23, 24).

2.10. Statistical analyses

All statistical analyses were performed using the statistical software package Statistical Package for the Social Sciences (SPSS) Statistics for Windows version 24.0 and p values were considered to be statistically significant if less than .05. Data are expressed as means ± standard deviation (SD) for continuous variables, and as number (percentage) for categorical variables. Variables were tested for normality using the Kolmogorov-Smirnov test. It was determined that the data set were not follow a normal distribution. For this reason, non-parametric hypothesis tests were used in the study. Comparisons of the basic and anthropometric measurements of the participants were performed. Mann Whitney U-test was used to determine the differences between former COVID-19 case group and control group. Differences between categorical variables were tested by Chi-square test. Binary logistic regression was applied to get the factors potentially related to COVID-19 occurrence.

3. RESULTS

3.1. Baseline characteristics

In this study, 100 patients with COVID-19 history were confirmed as a case group, and 100 healthy individuals with no COVID-19 occurrence were included as the control group. There was no chronic disease (non-included in the study) in any of the participants. The average age of the participants were 37.7±10.2 and 68% of the participants were women (Table 1).

Table 1. *Baseline characteristic of participants based on COVID-19 occurrence.*

Characteristics	All	Former COVID-19 case group	Control group	*p* value
Participants n (%)	200 (100)	100 (100)	100 (100)	
Gender (male) n (%)	64 (32)	38 (59.4)	26 (40.6)	
Gender (female) n (%)	136 (68)	62 (45.6)	74 (54.4)	
Age (years), X±SD [a]	37.7±10.2	37.7±9.9	37.7±10.4	.927
Age (years), X±SD (male) [a]	38.1±10.1	38.2±10.3	38.1±10.0	.978
Age (years), X±SD (female) [a]	37.5±10.2	37.5±9.9	37.6±10.6	.962
Vaccinated against COVID-19, n (%)[b]	124 (62.0)	63 (63.0)	61 (61.0)	.771
Current smoker n (%)[b]	57 (28.5)	30 (30.0)	27 (27.0)	.638
≤10 cigarettes/day n (%)[b]	25 (44.6)	13 (46.4)	12 (42.9)	.788
>10 cigarettes/day n (%)[b]	31 (55.4)	15 (53.6)	16 (57.1)	
Alcohol abstainers n (%)[b]	149 (74.5)	78 (78.0)	71 (71.0)	.256
2 drinks or more for men/1 drink or more in a day for women n (%)[b]	23 (11.5)	11 (47.8)	12 (52.2)	.98
Skipping meals n (%)[b]	69 (34.5)	34 (34.0)	35 (35.0)	.893

[a] *Data are presented as mean (standard deviation), X±SD. P: Mann Whitney U test ; p <.05*

[b] *n, number of participants; % , percentage of participants. P: Chi-squared test ; p<.05*

The comparative analysis of former COVID-19 patients and healthy controls showed no significant difference between lifestyle modifications in terms of age, vaccination, alcohol consumption, smoking status and meal skipping rate ($p>.05$) (Table 1). Regarding lifestyles, similar conclusions were obtained after stratifying by gender categories between case and control groups ($p>.05$) (Table 1)

3.2. Assessment of anthropometric measures

Mean BMI upon admission to the study was 26.4±4.4 kg/m^2. Distribution of mean values of weight (kg), height (cm), WC (cm) and BMI (kg/m^2) did not differ between case and control groups. In other words, there was no statistically significant difference between the anthropometric variables specified according to the state of infection in either gender ($p>.05$) (Table 2).

Table 2. *Comparison of mean (X±SD) anthropometric variables in former COVID-19 patients with control group.*

	All	Former COVID-19 case group	Control group	*p* value
Anthropometric measurements				
Weight (kg)	74.6±14.9	73.7±13.7	75.5±16.1	.532
Weight (kg) male	85.9±14.7	83.8±11.6 (38)	88.9±18.1 (26)	.356
Weight (kg) female	69.3±11.8	67.5±11.0 (62)	70.7±12.3 (74)	.112
Height (cm)	167.5±9.2	167.7±8.6	167.4±9.8	.675
Height (cm) male	175.4±7.4	174.3±6.2 (38)	177.1±8.8 (26)	1.00
Height (cm) female	163.8±7.5	163.7±7.4 (62)	163.9±7.6 (74)	.715
WC (cm) male	99.9±12.8	2.4±0.9 (38)	2.4±0.9 (26)	1.00
WC (cm) female	86.6±12.8	1.8±0.9 (62)	1.9±0.9 (72)	.302
BMI (kg/m^2)	26.4±4.4	1.8±0.7 (100)	1.8±0.8 (100)	.732
BMI (kg/m^2) male	27.7±3.7	2.1±0.7 (38)	2.0±0.8 (26)	.595
BMI (kg/m^2) female	25.8±4.6	1.6±0.7 (62)	1.8±0.8 (72)	.185

X, mean values; SD, standard deviation. P: Mann Whitney U test ; p <.05
BMI, body mass index; WC, waist circumference.

We classified our study participants based on different adiposity risk categories, adopting WCas an indicator of abdominal fat distribution and BMI as an indicator of body fatness. The clinical characteristics of patients with low, moderate, high risk abdominal obesity or with normal weight, with overweight and with BMI-based obesity are shown in Table 3. No patients was underweight and 39.5% (n=79) had a BMI of between 25 and 29.9 kg/m^2, while 20.5% (n=41) had a BMI over 30 and above kg/m^2 (Table 3). There were no significant differences between participants with normal weight, with overweight or with BMI-based obesity and COVID-19 occurrence ($p>.05$). By way of explanation, there were no differences in between case-control groups and BMI classes ($p=.321$) (Table 3). Likewise, no significant COVID-19 occurrence differences were found between participants with or without abdominal obesity risk for men or women ($p=.431$, $p=.169$; respectively), although the rate of the male participants is higher in high risk waist category, overweight or who suffered from BMI-based obesity than those with normal weight.

Table 3. *Difference in BMI and WC risk categories between groups.*

	All	Former COVID-19 case group	Control group	*p* value
BMI classes				
BMI category, n (%)	200 (100)	100 (50)	100 (50)	
Normal weight*	80 (40)	39 (48.8)	41 (51.2)	.321
Overweight**	79 (39.5)	44 (55.7)	35 (44.3)	
Obesity***	41 (20.5)	17 (41.5)	24 (58.5)	
BMI category for genders				
BMI category male, n (%)				
Normal weight*	15 (23.4)	7 (18.4)	8 (30.8)	.431
Overweight**	30 (46.9)	20 (52.6)	10 (38.5)	
Obesity***	11 (28.9)	8 (30.8)	19 (29.7)	
BMI category female, n (%)				
Normal weigh*	65 (23.4)	32 (51.6)	33 (44.6)	.169
Overweight**	49 (36.0)	24 (38.7)	25 (33.8)	
Obesity***	22 (16.2)	6 (9.7)	16 (21.6)	
WC classes for genders				
WC category for male, n (%)				
Low risk*	19 (29.7)	11 (28.9)	8 (30.8)	.704
Moderate risk**	1 (1.6)	1 (2.6)	-	
High risk***	44 (68.8)	26 (68.4)	18 (69.2)	
WC category for female, n (%)				
Low risk*	68 (50)	35 (56.5)	33 (44.6)	.205
Moderate risk**	12 (8.8)	3 (4.8)	9 (12.2)	
High Risk***	56 (41.2)	24 (38.7)	32 (43.2)	

*n, number of participants; %, percentage of participants. P: Chi-squared test; p <.05; *18.5-24.9 kg/m²; **25-29.9 kg/m²; ***≥30 kg/m²; *male ≤ 94 cm, female ≤ 80 cm; **male 95-102 cm, female 81-82 cm; ***male ≥ 102cm, female > 88 cm; BMI, body mass index; WC, waist circumference.*

3.3. Adherence to the Mediterranean diet and CES-D scale

Table 4 shows the levels of the adherence to the Mediterranean diet; in the total sample the mean±SD of the MedDiet and MEDAS scores among the study participants are 28.2±7.3 and 7.6±2.5, respectively. Average adherence to the Mediterranean diet scores are lower in the case groups compared to controls, even stratified by in both genders (Table 4). However only the cases of total and female MedDiet scores ($p<.001$) , total and MEDAS male scores ($p<.05$) showed a significantly lower mean±SD values compared to controls (Table 4).

In Table 5, the statistical relationship between the groups according to the gender and scale scores of MEDAS, MedDiet and CES-D of the participants, whether they had COVID-19 or not, has been examined. The vast majority (81.6%) of men who have had COVID-19 have adapted moderately to the Mediterranean diet (MEDAS adherence). But there is no such clear distinction for women. Of women who had COVID-19, 61.3% had good (moderate) adherence to the diet, while 38.7% had high compliance. In addition, the difference between the scale scores of the women, only MedDiet scores showed a difference with the cases of having COVID-19 (*p* <.05) while It was determined that MedDiet and MEDAS scores showed a difference in men who had COVID-19 (*p* <.05) (Table 5).

There was no difference between the scale groups according to gender of people who did not have COVID-19. Being female or male who did not have COVID-19, did not affect the scale scores (*p*>.05) (Table 5).

3.4. Serum zinc and COVID-19 occurrence

While the total zinc intake (food sources and supplements) showed a significant difference between the former case and control groups (12.6±13.0 vs 12.8±7.2 mg, respectively, *p*=.003), no statistically significant difference was observed in food sources related zinc intake mean values between groups (9.4±5.71 vs 10.1±9.45 mg, *p*=.022) (Table 6).

Table 4. *Comparison of mean (X±SD) CES-D scale, MedDietScore and MEDAS score values among groups.*

Score values	All	Former COVID-19 case group	Control group	*p* value
CES-D scale	18.6±10.9	19.4±10.6	17.9±11.2	.241
CES-D scale male	17.9±10.8	17.5±9.7	18.6±12.5	.945
CES-D scale female	18.9±10.9	20.5±11.0	17.6±10.8	.119
MedDietScore	28.2±7.3	26.3±6.1	30.1±7.9	**<.001***
MedDietScore male	27.5±7.9	26.2±6.1	29.2±9.8	.092
MedDietScore female	28.6±7.0	26.4±6.1	30.4±7.2	**.001***
MEDAS score	7.6±2.5	7.2±2.4	7.9±2.5	**.035***
MEDAS score male	7.5±2.4	6.9±1.9	8.2±2.8	**.032***
MEDAS score female	7.6±2.5	7.3±2.6	7.9±2.4	.316

*X, mean values; SD, standard deviation. P: Mann Whitney U Test ; *Denotes significant difference (p<.05) cases vs .control MEDAS, Mediterranean Diet Adherence Screener; MedDietScore, Mediterranean Diet Score; CES-D scale, The Center for Epidemiologic Studies Depression Scale.*

Table 5. *Adherence to the MEDAS , MedDietScore and CES-D scale of the participants.*

Characteristics	Former COVID-19 case group Male n (%)	Control group Male n (%)	*P* value male	Former COVID-19 case group Female n (%)	Control group Female n (%)	*p* value female	Difference in COVID-19 occurrence between genders
MEDAS Adherence							
Moderate	31 (81.6)	11 (42.3)	**0.001***	38 (61.3)	38 (51.4)	.245	0.427
High	7 (18.4)	15 (57.7)		24 (38.7)	36 (48.6)		
MedDietScore Adherence							
Low	9 (23.7)	6 (23.1)	**0.003***	12 (19.4)	6 (8.1)	**<.001⍰**	0.066
Average	26 (68.4)	9 (34.6)		47 (75.8)	41 (55.4)		
High	3 (7.9)	11 (42.3)		3 (4.8)	27 (36.5)		
CES-D scale							
No depression	14 (36.8)	14 (53.8)	0.067	17 (27.4)	26 (48.6)	.060	0.733
Possibility of mild depression	8 (21.1)	2 (7.7)		16 (25.8)	10 (13.5)		
Possibility of moderate depression	14 (36.8)	5 (19.2)		17 (27.4)	18 (24.3)		
Possibility of severe depression	2 (5.3)	5 (19.2)		12 (19.4)	10 (13.5)		

*%, percent of participants. P – value: Pearson's Chi-square test. *Denotes significant difference (p< .05) between male cases vs .control. ⍰Denotes significant difference (p<.05) between female cases vs. control. MEDAS, Mediterranean Diet Adherence Screener; MedDietScore, Mediterranean Diet Score; CES-D scale, The Center for Epidemiologic Studies Depression Scale.*

In addition, women in former COVID-19 case group had an average of 11.3±11.2 mg/day total zinc intake, while women who were in control group had 12.6±6.8 mg/day total zinc intake. While the serum zinc level of women who had COVID-19 was 60.6±15.7 mg/dL, it was 74.4±14.2 mg/dL for those who did not. A statistically significant difference was found between total zinc and serum zinc levels according to the COVID-19 transmission status of the women included in the study ($p<.05$). However, according to COVID-19 infection status, there was no statistically significant difference found between the men's average zinc intakes ($p>.05$) (Table 6).

Meanwhile, average serum Zn levels for all participants are as follow, 70.4±18.0 µg/dL. Accordingly, former COVID-19 patients had significantly lower zinc levels in comparison to the healthy controls (64.7±17.6 µg/dL vs 76.1±16.7µg/dL, $p<.001$). Consistently, in both genders, in case groups significantly lower serum zinc levels were observed (for male p=.009 and female $p<.001$, respectively) (Table 6).

Additionally, serum zinc level and MedDiet score were found to be significant variables explaining the status of COVID-19 occurrence ($p<.05$). When the serum zinc level and MedDiet score increase, the occurrence of COVID-19 decreases (Table 7).

Table 8 shows the distribution of the serum zinc level based on the reference value of the individuals, according to whether they had COVID-19 or not. The serum zinc level of 52.5% (n=105) of the total participants, 76.1% (n=80) of those who had COVID-19 and 23.8% (n=25) of those who did not have COVID-19, was below the reference value.

A significant difference was found between the cases of COVID-19 occurrence and the distribution of serum zinc levels. While the serum zinc value of the majority of those who had COVID-19 is below the reference value, it is between and/or above the reference value of the majority of those who did not have COVID-19. (Table 8)

Tablo 6. *Difference in mean (X±SD) serum zinc levels (µg/dL) and zinc intake (mg) values in former COVID-19 patients and healthy controls.*

	All	Former COVID-19 case group	Control group	*p* value
Total Zinc intake (mg) (food sources and supplements)	12.7±10.5	12.6±13.0	12.8±7.2	**.003***
Total Zinc intake (mg) (min.-max) male	14.05±11.85	14.6±15.4 (1.6-75.0)	13.5±8.3 (2.4-34.3)	.187
Total Zinc intake (mg) (min.-max) female	11.95±9.0	11.3±11.2 (2.4-62.2)	12.6±6.8 (3.6-35.9)	**.002***
Zinc intake (food sources) (mg)	9.8±5.38	9.4±5.71	10.1±9.45	.052
Serum Zinc levels (µg /dL)	70.4±18.0	64.7±17.6	76.1±16.7	**<.001***
Serum Zinc levels (µg /dL) (min.-max) male	16.15±29.55	71.3±18.6 (35.0-120.0)	81.0±21.9 (60.0-177.0)	**.009***
Serum Zinc levels (µg /dL) (min.-max) female	97.8±14.95	60.6±15.7 (36.0-142.0)	74.4±14.2 (41.0-126.0)	**<.001***

*X, mean values; SD, standard deviation. P: Mann Whitney U test ; *significant results (p<.05)*

Table 7: *Binary logistic regression analysis for the factors that are associated with COVID-19 occurrence.*

Variables	Regression coefficient (β)	Standard error (SE)	Wald	df	Sig	Odds ratio (Exp(β))	95% CI for Odds ratio Lower	Upper
Age (years)	-0.002	0.017	0.008	1	0.927	0.998	0.966	1.032
Weight (kg)	-0.008	0.015	0.259	1	0.611	0.992	0.964	1.022
Serum Zinc levels (µg /dL)	**0.043****	0.011	15.520	1	0.000	1.044	1.022	1.067
Total Zinc intake (mg)	0.006	0.015	0.130	1	0.718	1.006	0.976	1.036
CES-D scale	-0.004	0.015	0.064	1	0.402	0.996	0.967	1.026
MEDAS score	0.061	0.073	0.703	1	0.015	1.063	0.922	1.225
MedDiet Score	**0.062****	0.026	5.879	1	0.024	1.064	1.012	1.118

*Cox & Snell R^2= 0.171; Nagelkerke R^2= 0.227; – 2 Log Likelihood = 239.861; Chi Square= 37.398**; CI: Confidence interval, bold values were statistically significant at *: p≤.05; **: p<.01*

Table 8. *Difference in Serum Zinc Intake and Zinc status based on reference values.*

	All	Former COVID-19 case group	Control group	*p value*
Zinc intake below reference n (%) (male < 9.4 mg , female < 7.5 mg)	84 (42.0)	55 (65.5)	29 (34.5)	**.001***
Serum Zinc levels below reference n (%) (male < 70 µg /dL, female < 68 µg /dL)	105 (52.5)	80 (76.1)	25 (23.8)	**<.001***

*n, number of participants; %, percentage of participants. P: Chi-squared test; *significant results (p <.05)*

4. DISCUSSION

Although it was emphasized that there is a limited number of evidence to determine whether obesity increases the susceptibility of virus infection, several reports including meta-analysis and systematic reviews have confirmed the correlation between increased BMI and worse clinical outcome (ICU admission, use of mechanical ventilation, hospital admission and mortality) of COVID-19 in adult patients (25-28). Moreover, it was stressed that obesity defined by BMI could be an independent risk factor for COVID-19 (29). However, as opposed to BMI which poorly describes actual body fat excess, WC is shown to be more associated to chronic low-grade inflammation (30-32). Besides that, patients with high visceral fat measurements observed to have elevated inflammatory cytokine levels which linked to elevated obesity-associated morbidity in infections (30). Indeed, it recently stressed that visceral fat and upper abdominal circumference specifically increased the likelihood of severity of COVID-19 (32, 33).

In the current study no significant association was observed between COVID-19 occurrence, BMI and the mean WC values of participants. The subgroup analyses of participants with normal weight, overweight and those with BMI-based obesity also showed no significant difference in the COVID-19 occurrence. In addition, no significant effect of WC on COVID-19 cases in any (low, medium and high risk) subgroups found. This results is compatible with the finding of a recent study where it was proposed that apart from BMI, body fat distribution, in particular visceral adiposity, plays no direct causal role regarding COVID-19 severity and susceptibility (29). It is proposed that because of the single centered observational study design, including residual confounding and reverse causality, correlations of BMI and visceral fat accumulation with COVID-19 can be subjected to biases (29).

It is noteworthy that we could slightly underestimate the BMI and weight lost in COVID-19 patients. First of all, large cohort studies (34, 35) showed that self-reported weight upon admission cause underestimation of weight. Due to the given COVID-19 pandemic restrictions to prevent viral spread self-reported weights used in this study. Moreover, neither body weight at hospital discharge nor body composition at the base line were recorded and were missing for the analysis. It has been proposed that COVID-19 might negatively impact body weight and nutritional status. In many COVID-19 patients, independent of hospitalization, a weight loss of >5% which defined as the threshold used to diagnose cancer cachexia was observed (36). Additionally, it was emphasized that in COVID-19 patients weight loss even in patients with obesity in the hospital setting should be taken carefully because of the malnutrition risk which is known not only by low body mass but also unhealthy body composition and loss in the skeletal muscle mass (37).

Taken together, a cohort study presented that in COVID-patients weight loss may occur in a relatively short time period (32 days) and the patients could not return at the initial body weight at the follow up visits easily (a median of 23 days since discharge). This highlights the importance of questioning the disease duration and the length of hospitalization where both of the factors found as significant independent variables of weight loss by reflecting the disease severity and inflammation (34). With regards, another possible underestimation reason for the study could be that the evaluated patients was COVID-19 survivors whose prevalence of weight loss and the risk of malnutrition among seriously ill patients were lower.

Furthermore, taste/smell disturbances and other emotional factors such as fear, sadness, frustration, anxiety and anger may reduce the desire to eat or limit the access to food and/or the variety of food choices which having direct implications for nutrition and weight status of COVID-19 patients (38). Above all, the sample size was statistically representative of the population. However, trials with an increased number of participants should be evaluated (39).

The increased Mediterranean Diet score values were associated with a lower risk of COVID-19 occurrence (40). Furthermore, two recent observational studies showed an inverse correlation between the adherence to the Mediterranean diet and COVID-19 cases in selected European countries (41, 42). Similar to referred studies when adjusted for factors of well-being and physical activity, there was a negative association examined between the status of having COVID-19 and adherence to Mediterranean diet through two different tools in this study. However, the preventive role of Mediterranean diet in COVID-19 solely could not be completely approvable due to the limitations of the study. First of all, the observational study design does not lead to causative conclusion to be reached based on results. Secondly, although the adherence to the Mediterranean diet showed a significant negative association with depression score in adjusted models. Other life satisfaction factors which could have influence on viral infection occurrence and Mediterranean diet adherence such as income, education, age, gender, genetics and other sociodemographic characteristics should also be considered in the assessment models (40, 41). Additionally, not collecting data on medications and other nonpharmacological preventive measures (masks, hand washing etc.) could be the possible confounding factors of the study (42).

A number of review articles (43, 44) have examined Zn deficiency could be associated to the risk of infection or severe complication of COVID-19. Zn adequacy is needed to support anti-oxidant, anti-inflammatory, immune-boosting and other protective effects in COVID-19 patients (45). Notably, Zn is referred as a common subject in both prophylactic and curative for COVID-19 (43).

A recent case control study showed that serum zinc levels in COVID-19 patients are lower than control groups (39). Moreover, a prospective study data clearly demonstrated that a significant number of COVID-19 patients were zinc deficient compared to healthy controls (46). On the similar lines, in the current study former COVID-19 patients had a significantly lower zinc levels. Moreover, amongst them significant number were found zinc deficient in both genders. However, it is unclear whether low status zinc levels is simple causation or an epiphenomenon of COVID-19. We should be cautious about the interpretation of the results in this scenario.

In other words, serum zinc level is highlighted as one of the most important recommended method to estimate dietary zinc status in individuals (47). So far, it was observed that Zn absorption could be influenced by some foods. Particularly animal proteins result a greater Zn absorption, while phytates reduce its absorption (43). Moreover, according to the existing evidence, Zn deficiency could be highly prevalent in Türkiye secondary to high phytate consumption (48). Given that, only questioning the zinc-rich foods could be a possible limitation of the study. Dietary constituents (content) and physiological conditions that affect the bioavailability of Zn should also be evaluated. Furthermore, clinical studies have revealed that cellular Zn intake can be improved by ionophores including chloroquine and some of its derivatives such as hydroxychloroquine (43). Interestingly, hydroxychloroquine, a drug used initially in the management of COVID-19, is an ionophore that transports zinc across the hydrophobic cell membrane. Additionally, study results generally recommends that zinc supplements with antiviral drugs containing zinc ionophores precisely target and bind to SARS-CoV-2 preventing its replication within the infected host cells. Intracellularly, zinc binds with RNAdependent RNA polymerase causing elongation inhibition and decreased template binding of the viral mRNA (28, 46). On the other hand, a concern had arisen that long term (over 6 week) large doses (300 mg/day) Zn treatment can cause suppression of the immune system (43).

In the present study we failed to follow up and assess patients Zn levels and Zn supplementation in different stages of disease as we only collect the serum Zn levels and question Zn intake once after recovery. On this basis, before concluding we should have data clarifying which patients were zinc deficient and which were not before COVID-19. Furthermore, the baseline clinical and treatment characteristics as well as supplementation should be taken into consideration at initial assessment, throughout the course of disease, and after clinical remission. This could have been probably yield a better explanation for future studies.

5. CONCLUSION

In conclusion, even though our findings suggest a negative relationship between Mediterranean diet adherence or serum zinc levels, and COVID-19 occurrence, further studies are required to examine whether Mediterranean diet consumption or serum zinc status reduces the risk of COVID-19 causally. Also, future research is necessary to investigate the underlying mechanisms linking obesity and zinc status with COVID-19. In particular, as an integral part within the treatment and management of COVID-19 patients; nutritional and anthropometric evaluation, nutrition counselling and nutritional treatment should be applied at initial assessment, during the course of the disease, and after clinical remission.

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