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ORIGINAL ARTICLE

Effects of Dietary-Like Amount of Arginine Supplementation on Fractional Exhaled Nitric Oxide (FeNO) Levels in Obese and Normal-Weight Individuals

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ÖZET

Amaç: Daha önce yapılan çalışmalarda arjinin-nitrik oksit yolağı obezite gibi bazı kronik hastalıklara özgü yolaklar ile ilişkilendirilmiştir. Bu çalışmanın amacı, obez ve normal ağırlıktaki bireylerde diyete benzer miktarda arjinin takviyesinin fraksiyonel ekshale nitrik oksit (FeNO) düzeyleri üzerindeki etkilerini incelemektir. **Yöntem:** Bu çalışma 40 katılımcı (20 obez ve 20 kontrol) ile gerçekleştirilmiştir. Katılımcılar bir gecelik açlığın ardından 4500 mg arjinin takviyesi ve düşük proteinli (41 mg arjinin/25 g toz ürün) çorba tüketmiştir. Dinlenme metabolizma hızı (DMH) ve 1., 2. ve 5. saat FeNO düzeyleri ölçülmüş ve 3 günlük besin tüketimleri kaydedilmiştir. **Bulgular:** Obez gruptaki katılımcıların ortalama başlangıç ve 1. saat FeNO düzeyi ile kontrol grubundaki katılımcıların ortalama başlangıç FeNO düzeyi arasında anlamlı bir fark yoktu. Kontrol grubundaki katılımcıların ortalama 2. ve 5. saat FeNO düzeyleri, obez gruptaki katılımcıların ortalama 2. ve 5. saat FeNO düzeylerinden anlamlı olarak daha yüksekti ($p<0.05$). **Sonuç:** Normal ağırlıktaki katılımcıların obez katılımcılardan daha yüksek FeNO düzeylerine sahip olması, muhtemelen hava yolu inflamasyonu ve obezite arasındaki ilişkiye işaret eden önceki çalışmaları desteklemektedir.

Anahtar kelimeler: Arjinin, Obezite, Solunum, Nitrik oksit, Vücut ağırlığı

ABSTRACT

Aim: In previous studies, the arginine-nitric oxide pathway has been associated with pathways specific to some chronic diseases such as obesity. The purpose of this study was to examine the effects of dietary-like amounts of arginine supplementation on fractional exhaled nitric oxide (FeNO) levels in obese and normal-weighted individuals. **Methods:** This study was conducted with 40 participants (20 obese and 20 control). The participants consumed 4500 mg arginine supplement and low protein (41 mg arginine/25 g powder product) soup after one-night hunger. Resting metabolic rate (RMR) and 1st, 2nd, and 5th hour fractional exhaled nitric oxide (FeNO) levels were measured and 3-day food consumptions were recorded. **Results:** There was no significant difference between the mean baseline and 1st -hour FeNO level of the participants in the obese group and the mean baseline FeNO level of the participants in the control group. The mean 2nd and 5th hour FeNO level of the participants in the control group were significantly higher than the mean 2nd and 5th hour FeNO levels of the participants in the obese group ($p<0.05$). **Conclusion:** The fact that normal-weighted participants had higher FeNO levels than obese participants probably support previous studies that pointed to the relationship between airway inflammation and obesity.

Keywords: Arginine, Obesity, Respiration, Nitric oxide, Body weight

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INTRODUCTION

Arginine, a conditionally essential amino acid with four nitrogen atoms in its chemical structure, is the most important nitrogen transporter in the body and works as a precursor in nitric oxide (NO) production which plays an important role in the inflammation process (1). Dietary protein, protein turnover and endogenous (de novo) synthesis are listed as sources of arginine in the body (2). The end metabolism products of arginine such as glutamate, prolamin, and NO which have various regulatory functions in the body (3). The arginine/NO pathway has been associated with pathways specific to some chronic diseases such as obesity (4). Obesity, as a chronic inflammation-related disease, is considered to increase the risk of respiratory diseases (5-7). Numerous studies have revealed that obesity is associated with a decrease in lung function (8, 9). In addition, increasing body mass index (BMI) in obesity could be harmful to lung functions via different mechanisms. Increased mechanical body load with an increase in adipose tissue reduces lung compliance, leading to a decrease in lung volumes (10).

Previous studies reported that there was no difference in FeNO levels in obese individuals compared to normal-weighted individuals (11, 12) or obese individuals had lower FeNO levels compared to normal individuals (13, 14). Some studies have even reported that body weight gain in children and adults increases FeNO production (15, 16). Therefore, investigating the impact of dietary-like amounts of arginine supplementation on FeNO levels in different weight groups could help discern potential associations between arginine intake, body weight, and FeNO regulation. The purpose of this study was to examine the effects of dietary-like amounts of arginine supplementation on FeNO levels in obese and normal-weighted individuals.

MATERIAL AND METHODS

This non-randomized and experimental study was derived from the doctoral dissertation titled "The Effect of Dietary L-Arginine on Nitric Oxide Levels, Resting Metabolic Rate and Anthropometric Measurements. The data was collected between June and September 2015 in Erciyes University Faculty of Health Sciences' anthropometry laboratory. Erciyes University Ethics Committee approved this study in accordance with the Declaration of Helsinki (2014/617). All participants' written consents were obtained. Participants were invited to the study via social media platforms or by calling directly. Anemics, alcohol, cigarette and multivitamin-multimineral, other herbal supplement and medication users, and current dieters with chronic diseases were excluded from the study. Nine of the 54 participants (obese=5, control=4) who were interviewed by giving detailed information about the study did not want to participate. The four participants (obese=3, control=1) were excluded from the study because they had anemia or acute infection. A participant in the control group

could not complete the study due to the development of hypotension and possible nausea caused by hunger on the intervention day. Finally, the study was conducted with 20 obese and 20 control group participants. The participants were assessed using the World Health Organization (WHO) adult BMI classification; those with a BMI ≥ 30.0 kg/m2 were classified as obese, and those with a BMI of 18.5-24.9 kg/m2 were classified as normal weight. All participants were above 18 years old.

Two weeks before the intervention day, the participants were asked to fill in a sociodemographic characteristics' questionnaire and 3-day food consumption records (two weekdays and one weekend) after each snack or meal consumed every day to calculate mean dietary arginine intake. Furthermore, the participants were asked not to consume foods containing high amounts of citrulline three days before the day of the study because of citrulline converted into arginine. The participants were informed about arginine and citrulline-rich foods via a brochure. According to the 3-day food consumption records, the types and amounts of the foods consumed daily were determined, and the energy and nutrients values were calculated using the computer program (BeBiS Version 7.1, Pacific Com., Istanbul, Turkey). The percentages of the participants' energy and nutrients intakes according to dietary reference intakes (DRI) were calculated. DRI percentages (DRI%) were calculated and evaluated as <67% insufficient, 67-133% adequate, and >133% excessive intake according to the level of DRI ±33% (17). The participants were informed on how to keep 3-day food consumption records using household measures. Also, the participants were encouraged to continue their routine nutritional habits, exercise and sleeping habits one week before the intervention day. Participants' diets were encouraged to be standardized to not affect FeNO levels the day before intervention and consume nothing after midnight.

On the intervention day, the body mass index (BMI) and body composition of the participants were determined using the bioelectrical impedance analysis (BIA) method. Anthropometric measurements were measured with the appropriate technique. The Resting metabolic rate (RMR) measurement of participants was measured by indirect calorimetry method using Fitmate Pro (Cosmed Corp., Italy) brand ergospirometer. Before starting the measurement, participants were allowed to rest for 15-20 minutes and placed in a semi-reclining position. The masks were fixed according to the face of the participants and in such a way that it does not leak air. Then, participants consumed 4500 mg arginine supplement (arginine mono hydrochloride, cat no. 1.01543.0250, Merck, Darmstadt, Germany) and low protein (41 mg arginine/25 g powder product) soup (FSM Form Limited Comp., Istanbul, Turkey). Consumption of low protein soup determined by analyzing has low arginine level was preferred. Arginine supplement and low protein soup in powder form consumed by participants were measured with a precision

balance sensitive to 0.0001 g (Pioneer Ohaus Corp., NJ, USA).

Participants first consumed a low protein soup (25 g powder product/portion), followed by 100 ml of water. They then consumed 100 ml of water again after the arginine dietary supplement dissolved in 50 ml of water. The duration of consumption of arginine supplement and low protein soup was standardized at five minutes.

FeNO level was analyzed with the NIOX-MINO (Aerocrine AB, Solna, Sweden) device, which is hand-held, non-invasive, easy to apply, provides fast results, and correlates with chemiluminescence methods. Measurements were made by the measurement techniques recommended by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) (18). FeNO levels of the participants were measured on the intervention day before arginine supplementation (baseline), first, second and fifth hours.

Data was analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL) package program, and were tested with Shapiro-Wilk for normal distribution. Data were expressed as mean ($\bar{x}$), and standard deviation (±SD). Student-t test was used to compare quantitative variables with normal distribution, and Mann Whitney U test was used for the comparison of non-normally distributed quantitative variables. Values were considered significant at $p<0.05$.

RESULTS

There were 11 men and 9 women in the obese group, and 9 men and 11 women in the control group. There was no significant difference between the groups in terms of other sociodemographic characteristics. (Data not shown in a table). There was no significant difference between the ages and heights of the obese and control groups' participants. Some characteristics and anthropometric measurements of the participants were presented in Table 1. Energy and nutrient intakes of the participants were also presented in Table 2.

Table 1. Some characteristics and anthropometric measurements of the participants

Variables	Obese group (n=20) $\bar{x}$±SD	Control group (n=20) $\bar{x}$±SD	p
Age (year)	31.5±8.3	27.5±6.2	0.128
Weight (kg)	95.2±11.1	65.7±8.7	≤0.001
Height (cm)	170.1±6.4	169.1±9.3	0.697
BMI (kg/m^2)	32.8±2.7	22.8±1.1	≤0.001
NC (cm)	40.9±3.5	35.5±3.4	≤0.001
WC (cm)	109.3±9.4	85.9±10.3	≤0.001

HC (cm)	116.6±8.2	102.6±5.6	≤0.001
Waist \ Hip	0.94±0.08	0.83±0.08	≤0.001
Waist \ Height	0.64±0.05	0.50±0.04	≤0.001
BFM (kg)	33.0±8.2	16.2±3.9	≤0.001
BFR (%)	38.1±4.01	23.7±6.1	≤0.001
TBW (kg)	44.8±6.7	37.5±7.6	0.005
TBWR (%)	47.0±4.7	53.3±4.1	0.001
RMR (kcal)	2087.4±345.6	1761.3±337.2	0.005

BMI: Body mass index. NC: Neck circumference. WC: Waist circumference. HC: Hip circumference. BFM: Body fat mass. BFR: Body fat ratio. TBW: Total body water. TBWR: Total body water ratio. RMR: Resting metabolic rate.

Table 2. Energy and nutrient intakes of the participants

Energy and nutrient intakes	**Obese group (n=20) $\bar{x}$±SD**	**Control group (n=20) $\bar{x}$±SD**	**p**
Energy (kcal)	3523.2±161.7	2625.8±121.8	≤0.001
Protein (g)	93.5±3.7	71.0±5.8	≤0.001
Protein (E%)	10.6±0.3	10.8±0.6	0.123
Plant protein (g)	37.2±4.7	25.4±1.8	≤0.001
Animal protein (g)	56.2±1.7	45.5±4.1	≤0.001
Animal protein (P%)	60.2±3.6	64.1±1.3	0.002
Arginine (mg)	4118.4±226.77	4060.8±168.92	0.224
Carbohydrates (g)	440.5±24.4	359.3±10.4	≤0.001
Carbohydrates (E%)	54.8±1.9	50.0±1.1	≤0.001
Fat (g)	154.1±7.8	100.5±9.8	≤0.001
Fat (E%)	39.4±1.0	34.3±1.8	≤0.001
MUFA (g)	53.6±2.6	42.7±1.7	≤0.001
PUFA (g)	44.5±3.1	38.3±2.3	≤0.001
SFA (g)	55.9±6.4	20.4±8.5	≤0.001
Linoleic acid (g)	39.4±2.7	33.0±1.6	≤0.001
Linolenic acid (g)	4.7±0.3	2.2±0.4	≤0.001
Cholesterol (mg)	413.0±23.4	299.3±50.6	≤0.001
Dietary fiber (g)	25.7±1.0	26.8±0.9	0.004
Soluble dietary fiber (g)	6.4±0.8	8.1±0.8	≤0.001
Insoluble dietary fiber (g)	19.3±1.1	18.7±1.0	0.147
Water (ml)	2640.0±356.0	2800.0±278.0	0.114

E%: Percentage of nutrient contribution to energy. MUFA: Monounsaturated fatty acids. PUFA: Polyunsaturated fatty acids. SFA: Unsaturated fatty acids

The comparison of the FeNO levels of the participants in the obese and control groups were shown in Table 3. There was no significant difference between the mean baseline FeNO level of the participants in the obese group (25.52±13.3 ppb) and the mean baseline FeNO level of the participants in the control group (30.74±17.4 ppb). There was no significant difference between the 1st hour FeNO level of the participants in the obese group (33.64±13.9 ppb) and the 1st hour FeNO level (40.02±20.3 ppb) of the participants in the control group. The mean 2nd hour FeNO level of the participants in the control group (40.02±19.1 ppb) was significantly higher than the mean 2nd hour FeNO level of the participants in the obese group (27.84±12.1 ppb) ($p<0.05$). The mean of the 5th hour FeNO level of the participants in the control group (35.96±19.7 ppb) was significantly higher than the mean of the 5th hour FeNO level of the participants in the obese group (23.20±12.1 ppb) ($p<0.05$) (Table 3).

Table 3. The comparison of the FeNO levels of the participants in the obese and control groups

FeNO (ppb)	**Obese group (n=20)** $\bar{x}\pm SD$	**Control group (n=20)** $\bar{x}\pm SD$	**p^{ϕ}**
Baseline	25.52±13.3	30.74±17.4	0.312
1st hour	33.64±13.9*	40.02±20.3	0.267
2nd hour	27.84±12.1	40.02±19.1	**0.025**
5th hour	23.20±12.1	35.96±19.7	**0.023**
p^{Ω}	**0.045**	0.423	

Ω: Indicates statistical significance within the group. ϕ: Expresses statistical significance between groups. *: Indicates statistical difference.

DISCUSSION

Demonstrating a relationship between FeNO level and BMI (15. 16) has led to an increase in studies examining the relationship between obesity and FeNO levels (19. 20). However. it was seen that studies examining the relationship between FeNO level and BMI gave inconsistent results.

It has been reported that the NO level measured in the breath is affected by some conditions such as respiratory tract infection. asthma. obesity. allergic diseases. exercise. smoking. use of some drugs. and consumption of nitrite/nitrate-rich diet (20. 21). Furthermore. it has been reported that the period in which the FeNO level is measured during the day affects the measurement result. and the morning measurements are at a lower level. especially when compared to the afternoon measurements (22). In a study. adults with BMI≥27 kg/m2. it was reported that the reliability of a single measurement was sufficient when the FeNO levels of individuals were measured once or three times (23). Another study conducted on 19 normal-weight and 15 overweight and obese individuals. it was reported that obesity did not affect the levels of breath NO. which is an indicator of airway inflammation (11). Similarly. in the study conducted by Gemicioğlu et al. (19). no significant relationship was found between individuals' BMI and FeNO levels. Contrary to these results. in a study by Holguin et al. (24). it was determined that there was a negative correlation between individuals' FeNO levels and BMI. This relationship was explained by the deterioration of the ratio of arginine and asymmetric dimethylarginine (ADMA). It has been reported that ADMA is a natural inhibitor of nitric oxide synthase (NOS) enzyme. which is involved in NO synthesis. and that an increase in ADMA level in obesity causes a decrease in FeNO levels (24). In this study. the mean FeNO levels of the participants in the obese group at the 2nd and 5th hours were significantly lower. This result suggests that dietary-like amount of arginine supplementation causes different FeNO levels in obese and normal-weighted individuals and this is thought to be related to inflammation.

In a clinical study conducted by Ogata et al. (25) with 11 individuals. it was revealed that when a single dose of 200 mg/kg arginine was added to the diet of individuals. plasma. and FeNO levels were measured at 30-minute intervals for 150 minutes. and breath NO reached its highest value in 60 minutes. In the current study. while the 1st hour FeNO levels of the participants in the obese group were found to be significantly higher than the baseline. 2nd. and 5th hour FeNO levels ($p<0.05$). there was no significant difference between the FeNO levels of the participants in the control group. This result shows that. approximately one hour after arginine supplementation to the diet of the participants in the obese group. the participants' FeNO levels increased significantly. In this study. the finding that the FeNO level increased significantly approximately one hour after arginine supplementation to the diet of the participants in the study group supports the results of the study by Ogata et al (25).

However. the lack of this effect in the control group may be because the conversion rates of arginine to NO in breath may differ depending on obesity.

CONCLUSION

FeNO levels of normal-weighted participants were higher than that of obese participants supporting that NO synthesis from arginine added to the diet occurs at different rates in obese and normal-weight individuals. It may be advised not to use commercially available arginine and NO dietary supplements without consulting a physician or dietitian. and to prefer food consumption instead of dietary supplements. Studies that reflect the intake level of arginine. which is an important precursor for the synthesis of NO. which is not essential in adult human nutrition but has many important metabolic functions and examining the relationship between nutrients and nutrients and NO. should be conducted in the future.

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Conflicts of interest: The authors have no conflicts of interest to declare.

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