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Original Research

The relationship between the levels of anti-Müllerian hormone, vaspin, visfatin, and the patterns of nutrition and menstruation in non-polycystic ovary syndrome and non-obese young women

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Summary

Purpose of Investigation: The aim of this study was to investigate the relationship between the levels of anti-Müllerian hormone (AMH), vaspin, visfatin, and the patterns of nutrition and menstruation in healthy non-polycystic ovary syndrome (PCOS) and non-obese young women. *Materials and Methods:* A total of 77 medical faculty students aged between 18 and 28 years were included in the study. Blood levels of AMH, vaspin, and visfatin of individuals were examined by the enzyme-linked immunosorbent assay (ELISA) method. *Results:* There was no statistically significant relationship between the AMH, vaspin, and visfatin ($p = 0.712$), a statistically significant positive correlation was found between the vaspin and visfatin ($p < 0.001$). There was no relationship of AMH, vaspin, and visfatin with age, body mass index (BMI), and anthropometric body measurements. The levels of vaspin and visfatin increased ($p < 0.001$ and $p < 0.001$, respectively), as the nutritional quality decreased, in the group with regular exercise. The AMH levels were lower in the smokers and also in the group with irregular menstrual cycle ($p = 0.048$ and $p = 0.001$, respectively). *Conclusion:* Based on the present study results, the authors conclude that there is an interactive relation among the reproductive system, adipose tissue, and daily life habits of young individuals.

Key words: AMH; Vaspin; Visfatin; Nutrition; Obesity; PCOS.

Introduction

The traditional role attributed to adipose tissue is energy storage and fatty acids being released when fuel is required, but it was understood to be a multi-functional tissue by the identification of gene products of adipose tissue such as adipokines [1]. Adipose tissue is now accepted as a key endocrine organ containing several processes such as glucose homeostasis, steroid production, hematopoiesis, immune regulation and reproduction, and also plays a role in metabolic regulation [2].

Visceral adipose tissue-derived serine protease inhibitor (vaspin), is a novel adipocytokine, was identified in obese diabetic rats, reported to improve glucose tolerance and insulin sensitivity [3]. In 2005, Fukuhara *et al.* isolated a new adipocytokine called visfatin, which expression increases in obesity. Visfatin has an insulin-mimetic effect in mice and in vitro reduces plasma glucose levels [4].

Vaspin and visfatin, like most other adipokines, were considered as a link between obesity, insulin resistance, diabetes, and polycystic ovary syndrome (PCOS) in research on reproductive functions [5]. Tan *et al.* [6] showed that vaspin levels increased in obese PCOS patients and decreased with the use of metformin, and reported that the increase of vaspin might be a consequence of insulin resistance. Koiou *et al.* [7] also reported that vaspin levels were higher in both lean and obese PCOS patients, compared to the control group. In another study, Kowalska *et al.* [8] found that visfatin had a negative correlation with insulin sensitivity and increased in lean PCOS patients, whereas visfatin expression was suppressed in obese PCOS group. In a recent meta-analysis, it was reported that visfatin level was elevated in the PCOS group, and visfatin could be a potential biomarker for PCOS, but no correlation was found between visfatin and insulin resistance, body mass index (BMI), and hyperandrogenism [9].

The relationship between the reproductive system and adipokines has been studied in patients with PCOS, obesity, diabetes, or eating disorders in the literature to date. The aim of this study was to investigate these relationships through anti-Müllerian hormone (AMH), vaspin, and visfatin in non-PCOS and non-obese healthy young women, and the role of nutritional pattern, menstrual pattern, and other daily life habits among these relationships was also investigated in this study.

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Materials and Methods

This prospective and cross-sectional study included the medical faculty students between November 2015 and March 2016. Young healthy female students aged between 18 and 28 years were included in the study. Those with premature ovarian failure, PCOS, those undergoing surgery, chemotherapy or radiotherapy that may affect ovarian reserve, diabetes, hypertension or autoimmunity, chronic drug usage, eating disorders as anorexia nervosa or bulimia, and BMI ≥ 30 and ≤ 16 were excluded from the study. None of the individuals involved in the study had ever been pregnant and delivered a baby.

The individuals were asked to answer a questionnaire about nutrition, exercise habits, smoking and alcohol usage, and menstrual patterns. They were separated into three groups according to the nutritional qualities. The high-qualified nutrition group included individuals who have regular meals and breakfast, whose frequency of eating at home is high, who are balanced on vegetable, fruit, and meat consumption, and far from fried products and do not consume snack. The non-qualified nutrition group included individuals whose meals were irregular, who do not prefer to eat at home, do not have a balance between the foods, and often ate fried products and snacks. Other individuals were included in the standard nutrition group.

In the question of menstruation regularity, those who had cycles within the range of 21-45 days were included into regular menstruation group and individuals with dysfunctional uterine bleeding, prolonged bleeding, oligo-amenorrhea were included into irregular menstruation group.

A peripheral venous blood sample was taken from individuals to measure AMH, vaspin, and visfatin levels. In the literature, levels of both AMH and adipokines were shown to remain unchanged throughout the menstrual cycle [10, 11]. Therefore, a minimum of 10 cc blood samples were taken into heparinized tubes from the cubital vein after at least eight hours of starvation for a night without considering the cycle day. Blood samples were centrifuged at 3,000 rpm for 10 minutes immediately and plasma samples were stored at -80°C until the day of analysis. AMH, vaspin and visfatin measurements were performed after all blood samples were completed. All measurements were performed by standard enzyme-linked immunosorbent assay (ELISA) method. ELISA kits used in the study: human AMH, MIS/AMH ELISA kit, human visfatin ELISA kit, and human visceral adipose-specific serine protease inhibitor (vaspin) ELISA kit. All of the procedures were performed according to the manufacturers' instructions. The results are expressed in ng/ml for AMH, vaspin, and visfatin.

The study was approved by the local Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki. All participants were informed about the study and a written consent form was obtained from each of them.

Statistical analysis was performed using the SPSS 11.5 software. The quantitative data were expressed in mean ± standard deviation (SD) and median (minimum-maximum), while the qualitative data were expressed in number (percentage). The Mann-Whitney U test was used to identify whether there was a statistically significant difference between the categories of the categorical variables with two groups for quantitative variables, since the assumptions of normal distribution were not provided. The Kruskal-Wallis test was used to analyze whether there was a statistically significant difference between the categories of categorical variables with more than two groups for quantitative variables, since the assumptions of normal distribution were not provided. To examine the relationship between two quantitative variables, the Spearman's correlation coefficient was used, as normal distribution assumptions were not provided. A p value of less than 0.05 was considered statistically significant.

Results

A total of 77 young women were included in this study. The mean age was 23.6 ± 2.1 years. The mean BMI was 22.7 ± 4.6 kg/m^2. The mean age of the first menstruation was 13.3 ± 1.2 years. Overall characteristics of nutritional and menstruation patterns of the participants are shown in Tables 1 and 2.

All participants were divided into three groups according to the nutritional patterns. A total of 23 (29.9%) participants were included in the qualified nutrition group (good), 26 (33.8%) of them in standard nutrition group (moderate), and 28 of them (36.3%) in the non-qualified nutrition group (poor). Study participants were divided as regular and irregular menstrual pattern according to the menstrual cycle patterns. A total of 52 (67.5%) participants were included in regular group and 25 (32.5%) of them in irregular group.

No statistically significant relationship was found between the nutritional and menstrual patterns in the study participants (p = 0.070). In the qualified nutrition group, the menstrual pattern was regular in 13 (56.5%) participants and irregular in ten (43.5%) participants. In the moderate nutrition group, the menstrual pattern was regular in 22 (84.6%) participants and irregular in four (15.4%) participants. In the non-qualified nutrition group, the menstrual pattern was regular in 17 (60.7%) participants and irregular in 11 (39.3%) participants.

Table 3 shows the results of correlation analysis in which AMH, vaspin, and visfatin levels were not statistically significantly related to age, weight, and anthropometric body measurements of participants.

In this part of the study, the relationships among AMH, vaspin, and visfatin levels were investigated. A positive low correlation was found between AMH and vaspin, but this relationship was not statistically significant (p = 0.712, r = 0.043). A positive low correlation was found between AMH and visfatin, but this relationship was not statistically significant (p = 0.979, r = 0.003). There was a positive moderate correlation between vaspin and visfatin, and this relationship was statistically significant (p < 0.001, r = 0.623).

The authors investigated whether there was any difference in terms of AMH levels among nutritional groups, and median (minimum-maximum) levels of good, moderate, and poor nutritional groups were found to be 2.8 (1.0-5.6), 2.6 (0.9-4.2), and 2.2 (0.7-6.0), respectively.

There was no statistically significant difference in AMH levels among groups (p = 0.398). A statistically significant difference was found among good, moderate, and poor nutritional groups in terms of vaspin levels (p < 0.001). According to the comparison of the subcategories of the nutritional pattern, a statistically significant difference was found between the good and poor groups (p < 0.001), and moderate and poor groups (p = 0.016). The median (mini-

Table 1. — *Nutritional table.*

Variables		n	%
Meal regularity	Regular	36	46.8
	Irregular	41	53.2
Breakfast	Everyday	44	57.1
	3-4 per week	20	26.0
	1-2 per week	11	14.3
	Rarely	2	2.6
The frequency of eating at home	Everyday	44	57.1
	3-4 per week	19	24.7
	1-2 per week	12	15.6
	Rarely	2	2.6
Green, red, yellow, and vegetables	Everyday	13	16.9
	3-4 per week	42	54.5
	1-2 per week	17	22.1
	Rarely	5	6.5
Fruit	Everyday	19	24.7
	3-4 per week	21	27.3
	1-2 per week	26	33.8
	Rarely	11	14.3
Fried foods	Everyday	1	1.3
	3-4 per week	26	33.8
	1-2 per week	35	45.4
	Rarely	15	19.5
Snack	Everyday	19	24.7
	3-4 per week	26	33.8
	1-2 per week	18	23.3
	Rarely	14	18.2
Nutritional balance	Meat	11	14.3
	Vegetable	9	11.7
	Meat, vegetable and others	57	74.0
Alcohol	2-3 per week	2	2.6
	Never	68	88.3
	Rarely	7	9.1
Smoking	Yes	15	19.4
	Quit	8	10.3
	Never smoked	54	70.1

Table 2. — *Menstrual pattern table.*

Variables		n	%
Menstruation cycle (days)	14-20	3	3.9
	21-28	39	50.6
	29-35	28	36.4
	> 35	7	9.1
Days of menstruation	< 3	12	15.6
	3-7	48	62.3
	> 7	17	22.1
PMS	Yes	58	76.3
	No	18	23.7
Dysmenorrhea	Yes	55	71.4
	No	22	28.6
Number of pads/day	1-2	6	7.8
	3-4	37	48.1
	4-5	28	36.4
	> 5	6	7.7

PMS: premenstrual syndrome.

Table 3. — *The relation of AMH, vaspin, and visfatin. with age, BMI, and anthropometric body measurements.*

Variables	AMH		Vaspin		Visfatin	
	r	*p*	*r*	*p*	*r*	*p*
Age	0.012	0.920	-0.114	0.325	-0.091	0.432
Weight	-0.107	0.352	0.003	0.981	0.079	0.497
Muscle Weight	-0.112	0.334	0.062	0.590	0.153	0.183
Fat weight	-0.097	0.402	-0.051	0.663	0.003	0.979
Body water	-0.123	0.287	0.065	0.575	0.142	0.219
Fat-free weight	-0.125	0.278	0.067	0.565	0.150	0.192
BMI	-0.063	0.584	-0.048	0.679	0.042	0.717
PBF	-0.098	0.395	-0.105	0.364	-0.067	0.565
WHR	-0.054	0.638	-0.045	0.696	0.042	0.720
BMR	-0.125	0.277	0.072	0.534	0.152	0.186

AMH; anti-Müllerian hormone; BMI; body mass index; PBF: percent body fat; WHR: waist-hip ratio; BMR: basal metabolic rate.

mum-maximum) levels for good, moderate, and poor categories were found to be 1.5 (0.6-4.9), 2.9 (0.6-5.5), and 4.0 (1.3-8.1), respectively. A statistically significant difference was also found among good, moderate, and poor nutritional groups for visfatin levels ($p < 0.001$). According to the comparison of the subcategories of the nutritional pattern, a statistically significant difference was found by the difference between the good and moderate ($p = 0.001$), good and poor ($p < 0.001$), and moderate and poor ($p = 0.003$) groups. The median (minimum-maximum) levels for good, moderate, and poor categories were found to be 17.3 (10.2-56.3), 38.5 (18.1-87.1), and 77.6 (26.1-138.5), respectively.

There was no statistically significant relation between regular and irregular exercise groups in terms of AMH levels ($p = 0.327$). The median (minimum-maximum) levels of AMH in the groups of regular and irregular exercise were 2.6 (1.1-6.0) and 2.5 (0.7-5.6), respectively. In the group with regular exercise, vaspin levels were statistically significantly higher than the irregular exercise group ($p < 0.001$). The median (minimum-maximum) levels of vaspin in the groups of regular and irregular exercise were found to be 4.8 (3.4-8.1) and 1.8 (0.6-3.8), respectively. The visfatin level was also found to be statistically significantly higher in the group with regular exercise than the irregular exercise group ($p < 0.001$). The median (minimum-maximum) levels of visfatin in the groups of regular and irregular exercise were found to be 63.7 (27.4-138.5) and 26.1 (10.2-107.1), respectively.

AMH level was found to be statistically significantly lower in the group with regular menstruation than the group with irregular menstruation ($p = 0.001$). The median (minimum-maximum) levels of AMH in the groups with regular and irregular menstruation were 2.6 (0.7-4.8) and 1.5 (1.0-6.0), respectively. There was no statistically significant relationship between the regularity of the menstruation and the levels of vaspin and visfatin ($p = 0.870$ and $p = 0.918$, respectively).

There was no statistically significant difference between groups with and without premenstrual syndrome (PMS) in terms of AMH, vaspin, and visfatin levels ($p = 0.826$, $p = 0.595$, and $p = 0.253$, respectively). Similarly, there was no statistically significant difference between groups with and without dysmenorrhea in terms of AMH, vaspin, and visfatin levels ($p = 0.880$, $p = 0.634$, and $p = 0.931$, respectively).

All participants were also divided into three groups according to their alcohol use frequency (two to three per week, never, and rarely) and the groups were examined for any differences in terms of AMH, vaspin, and visfatin levels. The median (minimum-maximum) levels of AMH in the groups of "two to three per week", "never" and "rarely" were found to be 2.3 (2.0-2.6), 2.6 (0.7-6.0), and 2.2 (1.0-4.8), respectively, and a statistically significant relationship was not found among the three groups ($p = 0.880$). The median (minimum-maximum) levels of vaspin in the groups of "two to three per week", "never", and "rarely" were found to be 5.2 (3.8-6.5), 2.9 (0.6-8.1), and 2.8 (0.6-4.3), respectively, and a statistically significant relationship was not found among the three groups ($p = 0.634$). The median (minimum-maximum) levels of visfatin in the groups of "two to three per week", "never", and "rarely" were found to be 60.0 (44.2-75.7), 40.3 (10.2-138.5), and 38.8 (10.7-99.0), respectively, and statistically significant relationship was not found among the three groups ($p = 0.931$). Furthermore, all participants were divided into three groups according to the smoking status as smoking, quitted, and never smoked. There was a statistically significant relationship among smoking status groups in terms of AMH levels ($p = 0.048$). The median (minimum-maximum) levels in the groups of "smoking", "quitted", and "never smoked" were found to be 1.5 (1.0-5.6), 1.4 (1.2-1.5), and 2.6 (0.7-6.0), respectively. No statistically significant correlation was found among smoking status groups in terms of vaspin ($p = 0.164$). The median (minimum-maximum) levels in the groups of "smoking", "quitted", and "never smoked" were found to be 3.6 (1.3-5.7), 1.3 (1.3-1.5), and 3.0 (0.6-8.1), respectively. No statistically significant relationship was found among smoking status groups in terms of visfatin ($p = 0.114$). The median (minimum-maximum) levels in the groups of "smoking", "quitted", and "never smoked" were found to be 38.1 (15.2-112.5), 20.4 (12.2-21.9), and 47.8 (10.2-138.5), respectively.

Discussion

In this study, the relationships between AMH, vaspin, visfatin, and lifestyle characteristics such as nutrition, exercise, smoking, alcohol, and menstruation characteristics were investigated in non-PCOS, non-obese healthy young women. No relationship was found between the nutritional pattern and menstrual pattern in this study population. The relationship of AMH with vaspin and visfatin levels was not found, although there was a positive correlation between vaspin and visfatin levels. In smoking young women, the AMH levels decreased, and the menstrual irregularity increased in the participants with low AMH levels. The vaspin and visfatin levels were lower in subjects with the qualified nutrition, and higher in the group with regular exercise. However, no relationship was able to be shown between the menstrual pattern and the vaspin and visfatin levels.

In the literature, there are several studies showing the relationship of nutrition and BMI with the reproduction and menstrual pattern [12]. In a study with PCOS patients, a relationship between an increase in visceral adiposity and anovulation was established [13]. Mustageem *et al.* [14] published a study indicating that obesity leads menstrual irregularity in young women. Binge eating has also been associated with menstrual disorders [15]. In Korea, a study of 4,621 women aged between 19 and 54 years showed that there was a relationship between body weight changes and menstrual irregularity in the obese group, but this relationship could not be shown in the non-obese group [16]. In a study conducted with adolescents, a relationship between BMI and menstrual pattern was observed, and it was reported that periods were infrequent in the overweight group [17]. In a study of young athletes with menstrual irregularity showed that there was no change in the menstrual pattern when the diet was regulated for three months [18]. In a study conducted with young dancers and athletes, the menstrual regulation was achieved after nine months in subjects who applied regular diet for one year [19].

The relationship between the nutritional status and menstrual pattern in the literature was not observed in the present study. As either PCOS and obesity groups or eating disorders such as anorexia-bulimia or heavy physical exercise groups were included in this group of studies in the literature. However, women with obesity, PCOS, and eating disorders were not included in this study group. There were also no professional athletes with very intense exercise in this study group.

In this study, no relationship was found between AMH levels and nutritional status, BMI, and other anthropometric body measurements. In the literature, there has been no consensus on this issue. In a study of individuals with and without PCOS, it was reported that the main factor that influenced the circulating AMH level was nutritional status independently from PCOS, in which AMH levels were negatively correlated with BMI, and anthropometric parameters in both PCOS and non-PCOS groups [20]. Skalba *et al.* [21] did not show a relationship between AMH and BMI in both PCOS and non-PCOS groups. In a study by Lafebvre *et al.* [22], a negative correlation was shown between AMH and BMI in the PCOS group, but no relationship was found between AMH and BMI in the non-PCOS

group.

In the present study, AMH levels were found to be lower in the group with irregular menstruation than in the group with regular menstruation. The regularity of the menstrual cycles are formed by regular follicular growth, selection, and good quality ovulation, as well as accompanying endometrial preparations, and growth, maturation, and luteolysis of corpus luteum [23]. AMH blood levels are also one of the best indicators of ovarian reserve [24]. In this case, it is also expected that a decrease in AMH levels that indicates disorders of ovarian function will be accompanied by menstrual irregularities.

In the literature, the effects of diet and physical exercise on AMH were compared in overweight and obese PCOS groups, and it was found that the decrease in AMH levels was higher in the regulated diet group than the exercise group [25]. Another study reported that physical exercise increased the AMH levels in overweight and obese patients both with and without PCOS [26]. In the present study, there was no correlation between physical exercise and AMH.

In the present study, in the smoking groups including those who quit, AMH levels were lower than the non-smokers. Dafopoulos *et al.* [27] reported that AMH levels of women with normal reproductive history were not affected by smoking. A study conducted in subjects aged between 38 and 50 years reported that active smoking reduced AMH in this age group, and further investigations are needed in younger age groups [28]. In a study conducted with IVF patients, active smoking was reported to reduce AMH and negatively affect ovarian reserve [29].

In the present study, a positive correlation was observed between vaspin and visfatin levels in the participants, and it was observed that vaspin and visfatin levels increased as the nutritional quality decreased. Vaspin and visfatin were not associated with BMI and body measurements. The role of vaspin and visfatin in the development of obesity is not entirely clear in the literature. In a study in which vaspin was associated with obesity, body fat percentage was reported to be the strongest predictor of visceral vaspin. Insulin sensitivity has been reported to be the strongest determinant of subcutaneous vaspin expression [30]. Interestingly, visfatin levels have been reported to decrease in both weight reduction and over-nutrition related weight gain in visfatin studies [31-33]. Likewise, there are reports of both increased and decreased visfatin levels in obese subjects [34, 35]. In a study with obese and normal weight women, it was reported that vaspin levels were higher in obese women, and visfatin levels were not different between obese and normal weight women. This study also showed a positive correlation between carbohydrate intake and visfatin, but no relationship was found between vaspin and visfatin levels [36]. In a study that showed insulin sensitizing properties of vaspin and visfatin in the tissue, anti-atherogenic properties of vaspin and plaque destabilization effect visfatin were revealed, and both adipokines were referred as "links between obesity and atherosclerosis" [37].

In this study, vaspin and visfatin levels were observed to be higher in the regular exercise group. In the literature, there are studies reporting that the physical activity increases the level of vaspin [38, 39]. Studies of visfatin have reported that serum visfatin levels do not change, decrease, or increase with exercise [40-42]. In study by Frydenlund-Larsen *et al.* [43], it was shown that visfatin level in adipose tissue increased with exercise and but in the blood, the level did not increase. Despite the diversity of information in the literature, the fact that both vaspin and visfatin increased, when the nutritional quality decreased and increased with exercise, has brought this theory into question: these adipokines may play a protective role against atherosclerosis, diabetes, and obesity in the non-qualified nutritional status in younger bodies, elevations may be a compensatory mechanism, and exercise also supports this protective system. In the literature, obtaining very different information about this issue may be due to the poor functioning of this protective mechanism in PCOS, diabetes or obese groups.

In the present study, there was no relationship between levels of vaspin and visfatin and menstrual cycle pattern. In the literature, the study groups were PCOS patients, obese or anorectic women or athletes, and the relationship between menstrual irregularities and adipokines were not compared [44-46]. There was no relationship between both AMH and vaspin and visfatin levels and alcohol use, PMS, and dysmenorrhea, in the subjects of the present study. No data was found in the literature about these issues.

In the present study, a relationship between blood levels of AMH, vaspin, visfatin, nutritional status, daily life habits, and menstrual pattern were investigated in young women. In the literature, studies on this issue are focused on PCOS and patients with obesity. The present study is the first that was conducted in young, healthy non-PCOS and non-obese subjects, and in which all of these parameters were examined together. This is also the first study to show that smoking decreased AMH levels in young women. The fact that the number of smokers was low in this group suggests that this study should be supported by the studies with higher numbers. The low number of subjects in this study is an important limitation. Nutritional information was obtained by questioning the subjects while conducting the study. In addition, it would be better to examine lipid profile, liver function tests, insulin, and blood glucose levels which could reflect the nutritional pattern. In the ovarian reserve evaluation, the value of this study would be higher if there was data of antral follicle count in addition to AMH.

Conclusion

In this study including non-PCOS and non-obese young women, the authors investigated the possible relationship between the reproductive system and adipose tissue which is now accepted as an endocrine organ, and the role of daily life habits of young individuals on this relationship. In the present study, vaspin and visfatin levels were found to be correlated with each other, although the authors found no relationship between the AMH and these adipokines. The AMH levels decreased in smokers and menstrual irregularities were found to increase, as the AMH levels decreased. The fact that increased vaspin and visfatin levels with decreased nutritional quality suggests a possible protective compensatory mechanism against atherosclerosis, obesity, diabetes in younger bodies, and regular exercise were considered to be contributory factors in this direction. However, further studies are needed to confirm these findings in the future.

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