

# Evaluation of Fetuin-A level and related factors in obese adolescents

**Gulin Karacan Kucukali** (✉ [gulinkucukali@gmail.com](mailto:gulinkucukali@gmail.com))

Ankara Doktor Sami Ulus Çocuk Hastanesi: SBU Ankara Dr Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi  
<https://orcid.org/0000-0001-7506-1711>

**Semra Çetinkaya**

Ankara Doktor Sami Ulus Çocuk Hastanesi: SBU Ankara Dr Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi

**Erdal Kumaz**

Ankara Doktor Sami Ulus Çocuk Hastanesi: SBU Ankara Dr Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi

**Elvan Bayramoğlu**

Ankara Doktor Sami Ulus Çocuk Hastanesi: SBU Ankara Dr Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi

**Şervan Özalkak**

Ankara Doktor Sami Ulus Çocuk Hastanesi: SBU Ankara Dr Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi

**Gülşah Demirci**

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

**Hasan Serdar Öztürk**

Ankara University Faculty of Medicine: Ankara Üniversitesi Tıp Fakültesi

**Şenay Savaş Erdeve**

Ankara Doktor Sami Ulus Çocuk Hastanesi: SBU Ankara Dr Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi

**Zehra Aycan**

Ankara Doktor Sami Ulus Çocuk Hastanesi: SBU Ankara Dr Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi

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## Research Article

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## Abstract

Inflammation is thought to be responsible for insulin resistance and fatty liver in obese cases. The contribution of fetuin-A to the inflammation process is not clear. We aimed to evaluate fetuin-A levels in obese adolescents and to evaluate its relationship with anthropometric data, insulin levels and high-sensitive CRP. We found that there was no difference in fetuin-A levels between obese and healthy cases in the whole group. However, hs-CRP levels of obese patients were found to be significantly higher than healthy subjects. There was no difference in terms of fetuin-A and hs-CRP levels between the insulin-resistance and non-resistance group. There was no correlation between lipid parameters and fetuin-A levels. There was no difference in terms of fetuin-A and hs-CRP in cases with and without fatty liver. This may suggest that although systemic inflammation starts in obese patients, fetuin-A is not involved in this process or that the negative effect of fetuin-A on inflammation with other factors is still balanced in the adolescent age group. As a conclusion, further studies are needed to evaluate at what stage and how fetuin-A participates in systemic inflammation physiopathologically.

## What Is Known

Chronic inflammation plays a role in the etiopathogenesis of insulin resistance. Fetuin-A is known as one of the mediators of inflammation.

**What is new:** High sensitive- CRP levels of obese cases were high but no difference in fetuin-A levels between obese and normal weight adolescents.

## Introduction

Childhood obesity is increasing day by day with the modern lifestyle in the world. Obesity is also associated with many comorbidities such as dyslipidemia, insulin resistance, type 2 diabetes mellitus (DM), nonalcoholic fatty liver disease (NAFLD) and hypertension [1]. It is thought that obesity triggers the inflammatory process in the body and endotoxemia in the body increases the risk of obesity-related diseases [2]. In particular, it is suggested that chronic inflammation plays a role in the etiopathogenesis of insulin resistance [3]. Fetuin-A,  $\alpha 2$ -Heremans-Schmid glycoprotein is a glycoprotein that inhibits the endogenous insulin receptor tyrosine kinase and is predominantly synthesized from the liver [4]. This hepatokin has many different functions due to its complex structure and its binding to different toll-like receptors (TLR) in different tissues [5]. Studies have reported that TLR4 is associated with obesity-related inflammation and insulin resistance, and fetuin-A acts as the endogenous ligand of TLR4 [6, 7, 8]. It also reduces the insulin response in muscle and adipose tissue by inhibiting the autophosphorylation of the insulin receptor [4, 9, 10]. Another possible mechanism is that it increases inflammatory cytokines and inhibits adiponectin [10]. Fetuin-A is known as one of the mediators of inflammation. In adult studies, fetuin-A is associated with many diseases such as infections, renal diseases, cardiovascular diseases, cirrhosis, cancer, insulin resistance and metabolic syndrome [6, 11, 12, 13]. There are a limited number of children studies [14, 15, 16, 17, 18]. Examining fetuin-A, a multifunctional protein, in different disease groups will contribute to our understanding of its pathophysiology. Therefore, in this study, we aimed to evaluate fetuin-A levels in obese adolescents and to evaluate its relationship with anthropometric data, insulin levels and high-sensitive CRP (hsCRP).

## Methods

The study was performed at the pediatric endocrinology outpatient clinic of our hospital. Informed consent form was taken from the families of volunteers participating in the study.

The Ethics Review Board of Ankara Numune Training and Research Hospital approved the study protocol (approval number: E-16-1134).

Forty-one obese (over BMI > 95 percentiles) and 30 healthy adolescent (BMI = 15–85 percentiles) who are without additional systemic diseases and drug-free included in the study. Anthropometric data, fasting glucose, insulin, hsCRP, fetuin-A were examined in both obese and healthy group. Obesity comorbidity assessment (dyslipidemia, hepatosteatosis) of obese adolescents were obtained from hospital records.

A SECA scale (SECA, Hamburg, Germany) and a Harpenden stadiometer (Holtain Ltd., Crymch, UK) were used to measure weight and height, respectively. Anthropometric data for the Turkish population, such as height, weight and body mass index (BMI), are available in an online database ([www.ceddczum.com](http://www.ceddczum.com)) [19].

Blood samples taken from the patient and healthy control groups before 9:00 AM following an overnight fast. Glucose, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels were measured with Architect C16000 auto-analyzer system, insulin levels were measured by the chemiluminescence method (Advia Centaur XP). Hs-CRP was assessed using the cassette test (Getein 1600 immunofluorescence quantitative analyser; Getein, Nanjing, China). A commercially available sandwich enzyme-linked immunosorbent assay kit (Elabscience Biotechnology Inc., Houston, TX, USA) was used to detect fetuin-A levels.

The following formula was used to calculate homeostatic model assessment estimated insulin resistance (HOMA-IR): fasting insulin ( $\mu\text{U/ml}$ )  $\times$  fasting glucose ( $\text{mg/dl}$ )/405 (cut-off was taken as 3,82 for pubertal girls and 5,22 for pubertal males) [20].

**Statistical analyses-** Descriptive statistics for the continuous variables (characteristics) were presented as mean and standard deviation. Normality assumption of the continuous variables was tested with Kolmogorov-Smirnov test. After normality test, Student t test was used for the comparison of means in normally distributed characteristics. Statistical significance level was considered as 5% and SPSS (IBM SPSS version 22.0; IBM, New York, N.Y., USA) statistical program was used for all statistical computations.

## Results

Forty-one pubertal obese and 30 healthy adolescents were included in the study. Anthropometric data and biochemical comparative analysis results of the cases were presented in Table-1.

There was no difference in fetuin-A levels between obese and healthy cases in the whole group; however, hs-CRP levels of obese patients were found to be significantly higher than healthy subjects ( $p = 0.012$ ). Fetuin-A levels were similar in boys and girls in the obese group. While the fasting glucose levels of the patients were similar, the insulin and HOMA-IR levels of obese patients were found to be significantly higher than the healthy ones ( $p = 0.087$ ;  $p = 0.000$ ;  $p = 0.000$ , respectively).

When the participants were grouped as insulin resistant and insulin non-resistant according to HOMA-IR; there was no difference between the two groups in terms of fetuin-A and hs-CRP levels.

In addition, no significant correlation was found between fetuin-A and hs-CRP in the obese and control groups. Oral glucose tolerance test (OGTT) was performed in 32 patients with additional risk factors in the obese group. In OGTT; plasma glucose level at 0 minute was found to be  $88.2 \pm 7.7$  (72–106) mg / dl and at 120. minute it was  $116.7 \pm 25.6$  (75–205) mg / dl. Glucose intolerance was detected in four cases, and diabetes mellitus in one case. When looking at the correlation between plasma glucose levels in OGTT at 0-30-60-90-120 minutes and Fetuin-A levels, no significant correlation was found (According to minutes, respectively;  $r = -0.02$ ;  $p = 0.88$ ;  $r = 0.16$ ,  $p = 0.36$ ;  $r = 0.15$ ,  $p = 0.39$ ;  $r = 0.19$ ,  $p = 0.28$ ;  $r = -0.06$ ,  $p = 0.71$ ). Eight of the obese patients had high cholesterol, 15 had high triglycerides, eight had high LDL, and 20 had low HDL. There was no correlation between lipid parameters and fetuin-A levels. While there was no difference in terms of fetuin-A levels when the groups with and without dyslipidemia were compared ( $p = 0.296$ ); hs-CRP levels were found to be significantly higher in the group without dyslipidemia ( $p = 0.019$ ).

Thirty-three of the obese cases had fatty liver (Grade 1; 11 cases, Grade 2; 13 cases, Grade 3; 9 cases) and two of them had SGOT-SGPT elevation. While fetuin-A levels of patients with fatty liver was  $446.4 \pm 185.3$  (239.3-1112.1) ng / ml, the fetuin-A levels of those without fatty liver was  $496.4 \pm 290.7$  (206.5–950) ng / ml and there was no statistical difference between them ( $p = 0.967$ ). There was no difference in terms of hs-CRP in cases with and without fatty liver ( $p = 0.733$ ).

Hypertension was determined in 15 of 40 obese patients with 24-hour blood pressure monitoring. While the fetuin-A levels of the hypertensive patients were  $480.0 \pm 230.0$  (239.3-1112.1) ng / ml, it was  $432.9 \pm 185.5$  (206.5–950.0) ng / ml in normotensive subjects and there was no significant difference ( $p = 0.643$ ). Also, there was no difference between the two groups in terms of hs-CRP ( $p = 0.376$ ).

## Discussion

The number of studies examining the relationship between obesity and fetuin-A in children is limited [14–18, 21]. In adult studies; a relationship between fetuin-A levels and obesity, insulin resistance, fatty liver has been shown and increased cardiovascular risk associated with fetuin-A has been emphasized [6, 11–13]. In our study, similar to the study of Pampanini et al., no difference was found in terms of fetuin-A levels in the obese and control groups [14]. Although there are studies revealing higher fetuin-A levels in obese children, there are studies in the literature with conflicting results. In another study evaluating 45 obese and 30 non-obese children, fetuin-A level was found to be higher in obese patients [15]. However, no relationship was found between fetuin-A and other parameters (glucose, insulin, HOMA-IR, lipid parameters, ALT, GGT) examined in this study. In a study comparing obese and normal weight patients, the relationship between glucose, insulin, lipid parameters, blood pressure, subcutaneous and cardiac fat accumulation and fetuin-A level was evaluated. Fetuin-A level was found to be significantly higher in the obese group. In addition, a correlation was found between fetuin-A level and insulin, HOMA-IR, subcutaneous and subepicardial fat accumulation in both groups [16]. In another study investigating cardiovascular disease risk in obese children, no difference was found in terms of fetuin-A, when obese children / adolescents with and without metabolic syndrome were compared [17].

Although 33 of the subjects in our study had fatty liver, no significant difference was found between the groups with and without fatty liver in terms of fetuin-A levels. Only two of the patients had elevated liver function tests and the diagnosis of fatty liver was made ultrasonographically. In a large cohort study of children comparing 160 obese and 23 non-obese children [14], higher fetuin-A levels were detected in obese patients with fatty liver on ultrasound, than those without. However, no difference was found in terms of fetuin-A level between obese patients diagnosed with non-alcoholic steatohepatitis (NASH) by liver biopsy and those who were diagnosed with simple steatosis (nonNASH) by biopsy. In this study, it was stated that unlike adults, the severity of liver damage and fetuin-A level were not correlated in children. In addition, no difference was found between fetuin-A levels of non-obese patients and those diagnosed with NAFLD by ultrasonography or biopsy. In some adult studies comparing fetuin-A levels in obese patients with and without fatty liver, no difference was found [12].

In a longitudinally designed study in which 36 obese and 14 normal-weight children were compared, there was no difference in terms of fetuin-A between both groups, while fetuin-A levels were found to be significantly higher in 12 obese children with fatty liver [18]. There was no difference in terms of fetuin-A between obese cases without fatty liver and normal weight cases. In this study, it was emphasized that especially fatty liver leads to an increase in the level of fetuin-A. In another study conducted with obese children, intra-group comparisons was made and fetuin-A levels were found to be higher in those with fatty liver [15]. In an adult study comparing obese and non-obese patients with type 2 DM and normal weight patients with type 2 DM and patients with normal glucose tolerance (NGT), fetuin-A was found to be highest in obese patients with type 2 DM [6]. In obese and NGT individuals, fetuin-A levels were found higher than non-obese individuals. In our study, since there was one case with Type 2 DM and four cases with impaired glucose tolerance, statistical analysis could not be made in this respect.

In a study evaluating the fetuin-A level in patients with type 1 DM, when obese cases were evaluated separately, a positive correlation was found between daily insulin dose and fetuin-A (fetuin-A levels were found to be higher in patients with insulin dose  $> 1$  / kg / day) [10]. In the same study, no relationship was found between lipid parameters and blood pressure and fetuin-A. In addition, it was found that fetuin-A levels were lower in both normal / underweight and overweight / obese type 1 DM patients compared to obese type 2 DM patients.

In our study, no relationship was found between lipid parameters and fetuin-A. Although there are studies in the literature that showed a relationship between low HDL as a metabolic syndrome component and fetuin-A level [21], there are also studies that have not found a relationship similar to our study [10, 15].

Although the factors affecting fetuin-A are not known exactly; it has been suggested that it is affected by diet, physical activity, genetic factors, acute infections and drug use [5]. In addition, although there are studies stating that it differs with age, there are also controversial studies [5, 14, 22, 23]. Among the possible reasons for the different results in the literature on fetuin-A, it has been emphasized that previous studies have a wide age range, lack of healthy control, use of different measurement methods (because the degree of post-translational modification of fetuin-A may affect the measurement accuracy) [5].

## Limitations Of The Study

Waist / hip ratios to evaluate the body fat composition of our patients were not measured. For the diagnosis of insulin resistance, HOMA-IR was used instead of the euglycemic clamp test, which has high specificity because it is difficult to apply in children. The cases were selected as pubertal but were not classified separately according to their puberty stages. Liver biopsy, which is the gold standard diagnostic method for fatty liver, was not applied to our pediatric patients, the diagnosis was made ultrasonographically.

## Conclusion

In our study, insulin resistance was 63%, dyslipidemia 76%, fatty liver 80% and hypertension 62% in obese patients. Although hs-CRP levels of obese cases were high, fetuin-A levels were found similar in all cases and in subgroup analyzes. This may suggest that although systemic inflammation starts in obese patients, fetuin-A is not involved in this process or that the negative effect of fetuin-A on inflammation with other factors is still balanced in the adolescent age group. Further studies are needed to evaluate at what stage and how fetuin-A participates in systemic inflammation physiopathologically.

## Declarations

**Funding:** There is no funding services.

**Conflict of interest:** The authors declare that they have no conflict of interest.

**Ethics approval:** The Ethics Review Board of Ankara Numune Training and Research Hospital approved the study protocol (approval number: E-16–1134).

**Consent to participate:** Informed consent was obtain from the all individual participants and their parents in the study.

**Consent for publication:** Not available.

**Availability of data and material:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Code availability:** Not applicable.

**Authors' contributions:** Conceptualization, patient recruitment: Kurnaz E., Özalkak Ş., Bayramoglu E., biochemical analysis: Demirci G., Öztürk HS., investigation, data collection and curation: Karacan Kucukali G., Kurnaz E.,Özalkak Ş., Bayramoglu E., statistical analyses, writing: Karacan Kucukali G., Cetinkaya S., original draft preparation, review and editing: Karacan Kucukali G., Cetinkaya S., Savas Erdeve Ş., Ayca Z. All authors read and approved the final manuscript.

**Informed consent:** Informed consent was obtained from all individual participants included in the study.

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## Table

**Table-1: Whole group and obese subgroups antropometric and laboratory datas**

| Whole Group                    |                                |                            |             | Obese Group        |              |             |               |              |             |               |             |             |              |
|--------------------------------|--------------------------------|----------------------------|-------------|--------------------|--------------|-------------|---------------|--------------|-------------|---------------|-------------|-------------|--------------|
|                                | Obese<br>(n:41)                | Normal-weight<br>(n:30)    | p<br>values | Insulin Resistance |              |             | Dyslipidemia  |              |             | Steatosis     |             |             | Ye:<br>(n:1) |
|                                |                                |                            |             | Yes<br>(n:26)      | No<br>(n:15) | p<br>values | Yes<br>(n:31) | No<br>(n:10) | p<br>values | Yes<br>(n:33) | No<br>(n:6) | p<br>values |              |
| Gender                         | 27F, 14M                       | 22F, 8M                    |             | 18F,8M             | 9F,6M        |             | 20F,11M       | 7F,3M        |             | 23F,10M       | 2F,4M       |             | 8F,7         |
| Age<br>(years)                 | 15,3±2,1<br>10,5-18            | 14,3±2,1<br>10,3-17,8      | 0,063       | 14,8±2,2           | 16,6±1,4     | 0,045       | 15,2±2,2      | 15,3±1,7     | 0,859       | 15,5±2,0      | 13,8±2,1    | 0,118       | 15,9±        |
| Height<br>sds                  | 0,33±1,4<br>-1,9-(+4,3)        | -0,145±0,7<br>-1,6-(1,1)   | 0,073       | 0,48±1,4           | 0,53±1,3     | 0,337       | 0,42±1,3      | 0,05±1,7     | 0,541       | 0,3±1,4       | 0,0±1,3     | 0,617       | 0,62±        |
| BMI<br>(kg/m <sup>2</sup> )    | 33,1±4,2<br>26,4-42,9          | 21,5± 2,2<br>17-25         | 0,000       | 33,6±3,8           | 32,3±4,8     | 0,386       | 33,6±4,3      | 31,8±3,5     | 0,204       | 33,8±4,2      | 30,3±3,2    | 0,076       | 36,0±        |
| BMI<br>SDS                     | 2,8±0,55<br>2-4,5              | 0,4±0,7<br>-1,3-(+1,4)     | 0,000       | 3,0±0,5            | 2,5±0,5      | 0,017       | 2,8±0,5       | 2,69±06      | 0,356       | 2,9±0,5       | 2,4±0,5     | 0,099       | 3,0±1        |
| Fasting<br>glucose<br>(mg/dl)  | 94,7± 8,8<br>76-115            | 91,2±7,9<br>71-106         | 0,087       | 94,8±7,7           | 94,5±10,7    | 0,912       | 94,9±8,2      | 94,2±10,8    | 0,847       | 94,2±8,4      | 98,0±10,1   | 0,258       | 95,9±        |
| Fasting<br>insulin<br>(µIU/ml) | 27,2± 15,4<br>8,7-81,5         | 13,4±7,2<br>4,6-30,8       | 0,000       | 35,0±14,0          | 13,6±4,4     | 0,000       | 30,8±15,9     | 16,1±6,0     | 0,002       | 26,5±15,2     | 25,7±15,7   | 0,985       | 27,3±        |
| HOMA-<br>IR                    | 6,3± 3,7<br>1,7-17,5           | 3,1±1,8<br>1,0-7,2         | 0,000       | 8,2±3,4            | 3,1±1,0      | 0,000       | 7,2±3,8       | 3,7±1,4      | 0,004       | 6,1±3,5       | 6,2±3,8     | 0,955       | 6,3±1        |
| Fetuin-A<br>(ng/ml)            | 453±200,2<br>206,6-<br>1112,12 | 484,2±160,7<br>114,1-923,9 | 0,481       | 419,3±159,8        | 513,3±250,8  | 0,231       | 430,5±177,5   | 525,6±255,9  | 0,296       | 446,4±185,3   | 496,4±290,7 | 0,967       | 480,0±1      |
| HSCRP<br>(mg/dl)               | 0,3±0,2<br>0,-0,5              | 0,16±0,16<br>0,-0,5        | 0,012       | 0,27±0,21          | 0,28±0,16    | 0,910       | 0,2±0,2       | 0,4±0,1      | 0,019       | 0,3±0,2       | 0,3±0,2     | 0,733       | 0,32±1       |

(F:female, M:male)