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ARAŞTIRMA / RESEARCH

A comparative evaluation of the angiopoietin-like protein 8 (ANGPTL8) and alarin levels in patients with type 2 diabetes mellitus

Tip 2 diyabetli hastalarda angiopoietin benzeri protein 8 (ANGPTL8) ve Alarin düzeylerinin karşılaştırmalı bir değerlendirmesi

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Abstract

Purpose: Type 2 Diabetes Mellitus (T2DM) is one of the most serious public health problems that affect millions of people worldwide. There are 537 million adults diagnosed with diabetes worldwide and approximately 90% of these adults have type 2 diabetes. The study examined angiopoietin-like protein 8 (ANGPTL8) and Alarin levels of the patients diagnosed with T2DM in comparison with each other and with the healthy control group.
Materials and Methods: The study was conducted with a diabetes group consisting of 67 patients who were newly diagnosed with T2DM and who did not use any medication, and the control group consisting of 55 healthy people. ANGPTL8 and Alarin levels were measured using the ELISA (enzyme-linked immunosorbent assay) method.
Results: We found a significant increase in alarin and ANGPTL8 levels in the diabetic group compared to the control group. Furthermore, a positive correlation between Alarin levels and ANGPTL8, triglyceride, and insulin levels was found in the patient group. In addition, while both adipokines were higher in males in the patient group, both adipokines levels were lower in males than females in the control group, and there was a significant difference in ANGPTL8 levels.
Conclusion: High levels of ANGPTL8 and Alarin may facilitate the development of diabetes through the insulin resistance pathway. If this mechanism is more clearly elucidated, there may be a significant improvement in diabetic treatment projection.
Keywords: ANGPTL8, alarin, diabetes mellitus, adipokines

Öz

Amaç: Tip 2 Diabetes Mellitus (T2DM), dünya çapında milyonlarca insanı etkileyen en ciddi halk sağlığı sorunlarından biridir. Dünyada diyabet teşhisi konan 537 milyon yetişkin mevcuttur ve bu yetişkinlerin yaklaşık %90'ı tip 2 diyabet hastasıdır. Çalışmamızda T2DM tanısı alan hastaların angiopoietin benzeri protein 8 (ANGPTL8) ve alarin düzeylerini kendi aralarında ve sağlıklı kontrol grubu ile karşılaştırmalı olarak inceledik.
Gereç ve Yöntem: Çalışmamız yeni T2DM tanısı almış ve herhangi bir ilaç kullanmayan 67 hastadan oluşan diyabet grubu ve 55 sağlıklı kişiden oluşan kontrol grubu ile yapıldı. ANGPTL8 ve Alarin seviyeleri ELISA (enzyme-linked immunosorbent assay) yöntemi kullanılarak ölçüldü.
Bulgular: Kontrol grubuna kıyasla diyabetik grupta Alarin ve ANGPTL8 düzeylerinde anlamlı bir artış bulduk. Hasta grubunda alarin düzeyleri ile ANGPTL8, trigliserit ve insülin düzeyleri arasında pozitif bir ilişki bulunmuştur. Ayrıca hasta grubunda erkeklerde her iki adipokin düzeyi daha yüksek iken, kontrol grubunda erkeklerde her iki adipokin düzeyinin kadınlara göre daha düşük olduğu ve ANGPTL8 düzeylerinde anlamlı farklılık olduğu sonucuna vardık.
Sonuç: Yüksek ANGPTL8 ve Alarin düzeylerinin insülin direnci yolu ile diyabet gelişimini kolaylaştırabileceği düşünülmüştür. Bu mekanizma daha net bir şekilde aydınlatılırsa diyabetik tedavi projeksiyonunda önemli bir iyileşme olabilir.

Anahtar kelimeler: ANGPTL8, alarin, diabetes mellitus, adipokinler

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic condition characterized by chronic hyperglycemia and caused by the interaction of genetic and environmental factors[1]. The International Diabetes Federation reported that there are 537 million adults diagnosed with diabetes worldwide and approximately 90% of these adults have type 2 diabetes[2]. Hyperglycemia, one of the main features of DM, is caused by the abnormal function of insulin as a hormone that regulates glucose metabolism. Insulin resistance is a pathological condition characterized by disruption of the insulin signaling pathway and changes in the insulin sensitivity of cells[3,4].

ANGPTL8 was recently identified and viewed as an atypical member of the angiopoietin-like protein (ANGPTL) family. It is also called RIFL (refeeding-induced fat and liver protein), lipacin, and betatrophin. This protein, weighing 22kDa, is produced mainly in the liver of human beings and in white and brown adipose tissue of mice. The early studies about functional characterization of ANGPTL8 showed that it has a physiological role in nutritional metabolism as an insulin and glucose-stimulated hormone. In the case of hunger, expression levels decrease, while circulating levels rise with the help of nutritional stimulation and insulin. This can lead to high blood sugar levels, usually combined with high lipids and insulin levels[4-8].

Alarin takes its name from the N-terminal alanine and C-terminal serine that occurs as a splice variant of the galanin-like peptide. It is a 25 amino acid cytokine which is a member of the galanin peptide family isolated from the gangliosides of human neuroblastic tumors[9]. Little is known about the physiological role or pharmacological properties of Alarin. Vasoconstriction and increased anti-edema activity in cutaneous microvascular in mice are the effects of Alarin reported to date[10].

Many studies have shown that galanin antagonists increase insulin resistance by reducing the effect of GLUT4 in rat adipocytes, while the galanin peptide family facilitates GLUT4 translocation[11-13].

Maintaining glucose homeostasis, preventing or improving diabetes mellitus has been the main purpose of many studies. Although ANGPTL8 is relatively well known, the number of studies on Alarin is very small and most studies have been conducted with rats. The number of studies related to risk factors or diagnostic biomarkers for T2DM in humans is rather limited. The aim of this study is to examine the levels of ANGPTL8 and Alarin in patients with T2DM in comparison with each other and with the healthy control group, and to indicate the possible effects of these adipokines on the pathophysiology of diabetes.

MATERIALS AND METHODS

Study design and paticipants

This study was conducted jointly by Elazig Fethi Sekin City Hospital Internal Medicine Clinic and Biochemistry Laboratory. The ethics approval was received from Fırat University Ethics Committee (Document No 2019 / 12-25). All patients were informed about the study and written informed consent was obtained.

GPower programme was used to calculate the sample size in the study. According to the criteria suggested by Cohen, the effect size was identified as small (d=0,2), medium (d=0,5) and large (d=0,8). The sample size was calculated using the sub-limit (0,8) of the large effect size noted by Cohen. In this respect, the minimum sample size for each group was determined to be 42.

Our study included 67 patients (Female: 34-Male: 33) who were newly diagnosed with T2DM according to the IDF Diabetes Atlas Tenth Edition 2021 diagnostic criteria and who did not use any medication, and a control group consisting of 55 healthy people (Female: 28-Male: 27). Patients with chronic systemic diseases (liver failure, chronic renal failure, congestive heart failure, cancer) were excluded from the study.

Biochemical analysis

In the study, samples were taken from the control and patient groups after 8-12 hours of fasting to the tube containing aprotinin (BD Vacutainer SST II Advance, BD, Plymouth, UK). The blood samples were centrifuged at 4000 rpm for 10 minutes and the plasma obtained by ANGPTL8 and Alarin were placed in small-volume tubes to be studied and stored at -20 ° C until the study day.

The measurements of glucose, cholesterol, HDL, LDL, Triglyceride measurements were made by the AU-5800 (Beckman Coulter, Inc., Miami, FL, USA) devices, insulin measurements were made by the

DXI-800 (Beckman Coulter, Inc., Miami, FL, USA) devices and HbA1c measurements were made by the Premier HB920 (Trinity Biotech, Ireland) devices.

Plasma ANGPTL8 and Alarin levels were studied using the Human ANGPTL8 ELISA kit (Sunred Biological Technology, catalog no: SRB-T-88039, Shanghai, China) and Human alarin ELISA kit (Sunred Biological Technology, catalog no: SRB-T-81290, Shanghai, China) in accordance with the study procedures specified in the kit catalog; and absorbance measurement was made by the Chromate 4300 Microplate Reader (Awareness Technology, Palm City, USA) devices. The absorbance of each was determined as 450nm. The standard curve was drawn as the mean absorbence of standards (y) and known as the concentration of standards (x). The results were reported as the ANGPTL8 and alarin concentration in the samples. The minimum detection limit of ANGPTL8 was 7.332 ng/L. The intra-assay and inter-assay coefficient of variation for plasma ANGPTL8 were <10% and <12%, respectively. The minimum detection limit of alarin was 0.214 ng/mL. The intra-assay and inter-assay coefficient of variation for plasma alarin were <10% and <12%, respectively.

Statistical analysis

The SPSS 21 package program was used for statistical analysis, data were calculated as mean ± standard deviation. Kolmogorov-Smirnov test was used to find out whether the variables showed normal distribution. For the analysis of parametric data (BMI, age, cholesterol, HDL, LDL, Triglyceride) Student's T-test was used and the Mann-Whitney U test was used for the analysis of non-parametric data (ANGPTL8, alarin, glucose, insulin, HbA1c). The Chi-square test in the evaluation of qualitative data. In addition, Pearson correlation analysis was performed to find out whether there is any relationship between the parameters examined. Statistical differences between averages were considered significant when p values were <0.05.

RESULTS

The Laboratory, clinical and demographic characteristics of our study are presented in Table 1. 33 of the 67 diabetic patients were males (49.3%) and 34 were females (50.7%). The healthy control group of 55 people, consisted of 27 men (49.1%) and 28 (50.9%) women.

There was no significant difference between the groups in terms of gender distribution and age. However, Body Mass Index (BMI), glucose, and HbA1c levels were significantly higher in the patient group compared to the control group (p <0.05). Also, cholesterol, low-density lipoprotein (LDL) and triglyceride levels were significantly higher in the diabetic group compared to the control group (p <0.05). High-density lipoprotein (HDL) was significantly lower in the diabetic group compared to the control group (p <0.05).

We determined that plasma ANGPTL8 and Alarin levels were significantly increased in the diabetic group compared to the control group (p <0.05) (Figure 1. a, b, c).

Table 1. Demographic, clinical and laboratory characteristics of T2DM and control group

	Control	**T2DM**	
	n=55	n=67	p value
	Mean± SD	Mean ± SD	
Age (years)	45.92±8.27	48.20±5.49	0.08
BMI (kg/m2) *	24.73±2.73	29.39±3.17	<0.001
Alarin (ng/mL)	12.36±4.94	16.79±9.83	<0.05
ANGPTL8 (ng/L)	414.27±150.04	531.40±287.68	<0.05
Glucose (mg/dL)	89.92±7.82	199.85±62.56	<0.001
Cholesterol (mg/dL)	193.09±31.02	210.26±35.34	<0.05
HDL (mg/dL) †	49.21±10.3	41.0±7.49	<0.001
LDL (mg/dL) ‡	120.06±26.59	135.26±28.92	**<0.05**
Triglyceride (mg/dL)	116.83±46.47	170.82±66.16	**<0.001**
Insulin (mIU/L)	9.09±6.83	10.54±6.23	0.208
HbA1C (%)	5.52±0.44	8.61±1.77	**<0.001**

*__BMI:__ Body Mass Index, †__HDL:__ High-density lipoprotein, ‡__LDL:__ Low-density lipoprotein

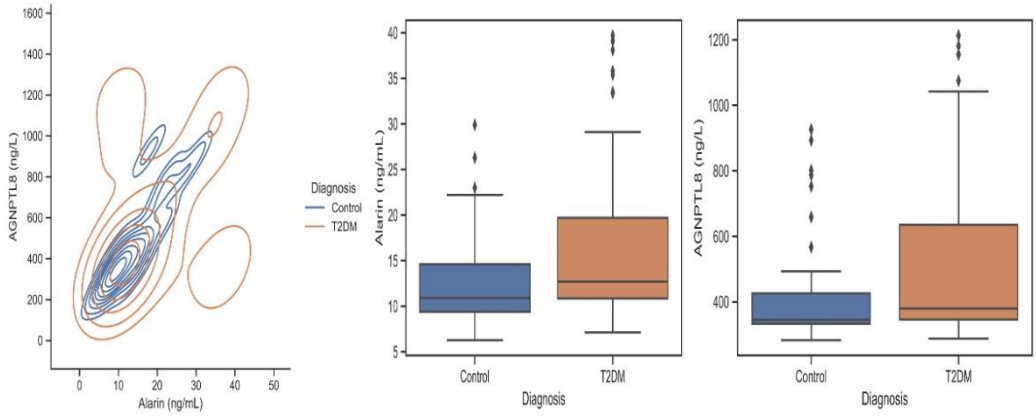

Figure1. a, b, c. Alarin and Angptl8 levels and diagnosis relationship

We found a positive correlation between Alarin levels and ANGPTL8 (r:0.395, p <0.01), Triglyceride (r: 0.334, p <0.05), Insulin (r: 0.322, p <0.05) levels in the patient group.

In addition, although ANGPTL8 and Alarin levels were both increased in the patient group in men and women; in the control group, both adipokine levels were lower in men than in women and there was a significant difference in ANGPTL8 levels (p = 0.018) (Figure 2. a, b)

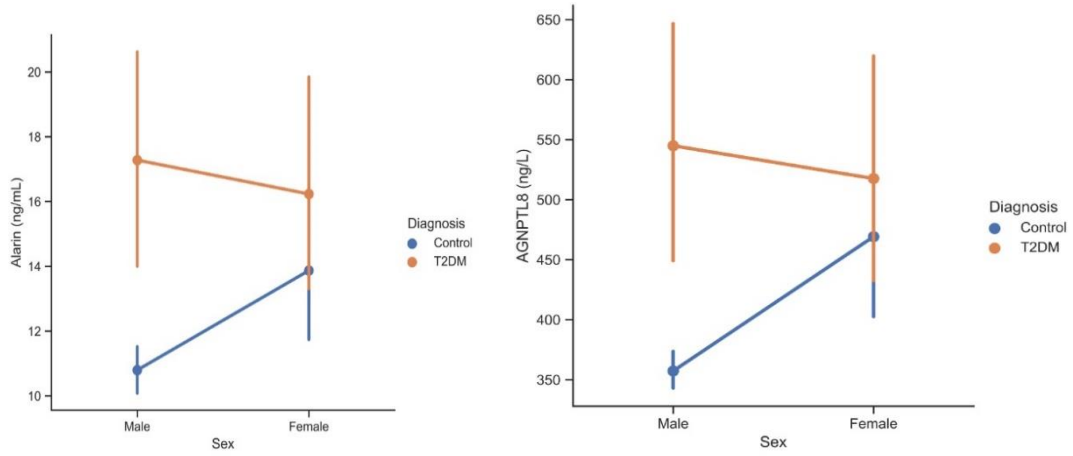

Figure2. a, b. Alarin and Angptl8 levels and relationship between gender and diagnosis

DISCUSSION

T2DM, is one of the most serious public health problems affecting more than 537 million people worldwide[2]. The pathophysiology mainly appears with the increase of insulin resistance in skeletal muscle, hepatic and adipose tissue[14]. Insulin resistance occurs as a disruption in the activation of the cellular insulin signal chain. The abnormal adipose tissue metabolism in T2DM directly contributes to insulin resistance in target tissues[15]. Adipose tissue is considered as one of the largest endocrine organs in the body due to its unlimited

growth potential and capacity to secrete various hormones and cytokines, as well as serving as an energy store. The number of adipokines known to be secreted by adipocytes increases in obesity and diabetes day by day[16].

While ANGPTL8 is mainly expressed in the liver of human beings, it has a much lower percentage of expression in adipose tissue, heart, rectum, and brain[17]. Yi et al showed a 17-fold increase in pancreatic cell proliferation due to overexpression of ANGPL8 in mouse liver via an unidentified receptor[8].

Years later, with the advent of other controversial reports, ANGPTL8's ability to stimulate beta-cell proliferation has been a topic of discussion for quite some time[18]. With the recent emergence of scientific hesitation, it has been concluded that ANGPTL8 does not affect beta-cell proliferation in humans[19].

Apart from the discussions on this subject, it has been reported that ANGPTL8 levels are increased in T2DM patients, in several studies[20-24]. It was reported that these levels did not change in two different studies[25,26] and that ANGPTL8 levels were measured low in the other two studies[27-29]. As seen in Table 1 and Figure 1, ANGPTL8 levels increased significantly in the diabetic group compared to the control group ($p < 0.05$), in our study.

Alarin, a member of the newly discovered galanin neuropeptides family, was first detected in the ganglion cells. Later, it has been found that Alarin is also present in skin and brain. More recent studies have shown that the administration of Alarin to the T2DM rats can reduce the blood glucose levels. Subsequently, it has been shown that it can increase glucose uptake and recover insulin resistance in rats. These studies suggest that Alarin is a metabolic regulatory molecule and closely related to the pathophysiology of diabetes mellitus[28-31].

Reports on the relationship between Alarin, insulin resistance, glucose, and lipid metabolism in diabetic patients as a potential regulator of metabolism are very few. One study showed that the Alarin level significantly increased in patients with impaired glucose tolerance and T2DM; so, they asserted that circulating Alarin gradually increased during the diabetic process[32]. Also, there are studies that reported higher Alarin levels in patients with T2DM compared to the control group[32,33], while in one study it was found to be higher in the control group[34]. As shown in Table 1 and Figure 1, in this study, the Alarin levels increased significantly in the diabetic group when compared to the control group ($p < 0.05$).

Fraley et al. concluded that Alarin levels were higher in men, and defended the thesis that this protein could be regulated by sex hormones[35]. In our study, as seen in Figure 2, we found that both adipokine levels were higher in T2DM in men than women, but lower in the control group.

Therefore, we think that this difference in ANGPTL8 and Alarin levels may be both related to sex hormones. Considering the hormonal differences between the sexes and the mean age of our patient group, premenopausal estrogen decrease in women comes to mind as a possible cause. Therefore, we think that gonadotropins have a possible regulatory role in this pathway. Broader studies on this subject may resolve question marks.

Taking into account all of these; the sample sizes of the studies, the lack of homogeneity in body mass indexes, possible sensitivity and specificity problems of different reagents, and gender-related events may be sources of contradiction in present studies.

In the literature, it is frequently hypothesized that both ANGPTL8 and Alarin play an important role in supporting the insulin signaling pathway during insulin resistance and its loss can rapidly lead to Diabetes Mellitus and aggravate the pathogenic process. We concluded that ANGPTL8 and Alarin levels in the diabetic group were significantly higher than in the control group, so our results are supported by the literature. Although we comment on the mechanism of ANGPTL8, which has not been clearly revealed yet, we conclude that it facilitates the development of diabetes through the insulin resistance pathway. We think that with a clear explanation of this mechanism, significant improvements will be achieved in diabetic treatment projection.

Our study has some limitations. The first of these is that this study is a cross-sectional study. Therefore, the causal relationship between circulating ANGPTL8, alarine, and T2DM has not been revealed. Further prospective studies are needed to show the exact relationship between them. The second is that this study has a small sample size and it was conducted in a single center. Larger samples and multi-center studies are needed to confirm the results of the study. Third, due to genetics and

dietetic factors the results of this study have their own inherent errors and biases.

In the literature review, we could not find any comparative studies on the relationship between T2DM, ANGPTL8, and Alarin levels in humans. For this reason, this study will be the first in which both adipokines are compared and correlated. ANGPTL8 and Alarin levels are higher in patients with T2DM than in healthy people.

This study shows that with a clearer understanding of the pathophysiology of adipokines, improvement can be enrolled in the treatment of DM. So, we advocate that gender-related variables should also be kept in mind. Thus, suggesting that possible future individual diagnosis and treatment modalities can be determined by gender-specific parameters.

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REFERENCES

1. Rosen ED, Kaestner KH, Natarajan R, Patti ME, Sallari R, Sander M et al. Epigenetics and epigenomics: Implications for diabetes and obesity. Diabetes. 2018;67:1923–31.
2. IDF Diabetes Atlas 2021. 10th Edition. https://www.idf.org/news/240:diabetes-now-affects-one-in-10-adults-worldwide.html (accessed Feb 2022).
3. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005; 26:19-39.
4. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest. 2016;126:12-22.
5. Ren G, Kim JY, Smas CM. Identification of RIFL, a novel adipocyte-enriched insulin target gene with a role in lipid metabolism. Am J Physiol Endocrinol Metab. 2012;303:334-51
6. Zhang R. Lipasin, a novel nutritionally-regulated liver-enriched factor that regulates serum triglyceride levels. Biochem Biophys Res Commun. 2012;424:786-92.
7. Quagliarini F, Wang Y, Kozlitina J, Grishin NV, Hyde R, Boerwinkle E et al. Atypical angiopoietin-like protein that regulates ANGPTL3. Proc Natl Acad Sci U S A. 2012;109:19751-6.
8. Yi P, Park JS, Melton DA. Betatrophin: a hormone that controls pancreatic beta cell proliferation. Cell. 2013;153:747–58.
9. Santic R, Fenninger K, Graf K, Schneider R, Hauser KC, Schilling FH et al. Gangliocytes in neuroblastic tumors express alarin, a novel peptide derived by differential splicing of the galanin-like peptide gene. J Mol Neurosci. 2006;29:145-52.
10. Santic R, Schmidhuber SM, Lang R, Rauch I, Voglas E, Eberhard N et al. Alarin is a vasoactive peptide. Proc Natl Acad Sci U S A. 2007;104,10217–22.
11. Guo L, Shi M, Zhang L, Shao H, Fang P, Ma Y et al. Galanin antagonist increases insulin resistance by reducing glucose transporter 4 effect in adipocytes of rats. Gen Comp Endocrinol. 2012;173:159–63.
12. Liang Y, Sheng S, Fang P, Ma Y, Li J, Shi Q et al. Exercise-induced galanin release facilitated GLUT4 translocation in adipocytes of type 2 diabetic rats. Pharmacol Biochem Behav. 2012;100:554–9.
13. Zhang Z, Sheng S, Guo L, Li G, Zhang L, Zhang L et al. Intracerebroventricular administration of galanin antagonist sustains insulin resistance in adipocytes of type 2 diabetic trained rats. Mol Cell Endocrinol. 2012;361:213–8.
14. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:773–95.
15. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444:860–867.
16. MacDougald OA, Burant CF. The rapidly expanding family of adipokines. Cell Metab. 2007;6:159–61.
17. Abu-Farha M, Al-Khairi I, Cherian P, Chandy B, Sriraman D, Alhubail A et al. Increased ANGPTL3, 4 and ANGPTL8/betatrophin expression levels in obesity and T2D. Lipids Health Dis. 2016;15:181.
18. Gusarova V, Alexa CA, Na E, Stevis PE, Xin Y, Bonner-Weir S et al. ANGPTL8/betatrophin does not control pancreatic beta cell expansion. Cell. 2014;159:691–6.
19. Cox AR, Lam CJ, Bonnyman CW, Chavez J, Rios JS, Kushner JA. Angiopoietin-like protein 8 (ANGPTL8) /betatrophin overexpression does not increase beta cell proliferation in mice. Diabetologia. 2015;58:1523–1531.
20. Yi M, Chen RP, Yang R, Guo XF, Zhang JC, Chen H. Betatrophin Acts as a Diagnostic biomarker in type 2 diabetes mellitus and is negatively associated with HDL-Cholesterol. Int J Endocrinol. 2015;2015:479157.

21. Yamada H, Saito T, Aoki A, Asano T, Yoshida M, Ikoma A et al. Circulating betatrophin is elevated in patients with type 1 and type 2 diabetes. Endocr J. 2015;62:417–21.
22. Chen X, Lu P, He W, Zhang J, Liu L, Yang Y et al. Circulating betatrophin levels are increased in patients with type 2 diabetes and associated with insulin resistance. J Clin Endocrinol Metab. 2015;100:96-100.
23. Gao T, Jin K, Chen P, Jin H, Yang L, Xie X et al. Circulating betatrophin correlates with triglycerides and postprandial glucose among different glucose tolerance statuses – a case-control study. PLoS One. 2015;10:0133640.
24. Abu-Farha M, Abubaker J, Noronha F, Al-Khairi I, Cherian P, Alarouj M et al. Lack of associations between betatrophin/ANGPTL8 level and C-peptide in type 2 diabetic subjects. Cardiovasc Diabetol. 2015;14:112.
25. Fenzl A, Itariu BK, Kosi L, Fritzer-Szekeres M, Kautzky-Willer A, Stulnig TM et al. Circulating betatrophin correlates with atherogenic lipid profiles but not with glucose and insulin levels in insulin-resistant individuals. Diabetologia. 2014;57:1204-8.
26. Guo K, Lu J, Yu H, Zhao F, Pan P, Zhang L et al. Serum betatrophin concentrations are significantly increased in overweight but not in obese or type 2 diabetic individuals. Obesity. 2015;23:793-7.
27. Gomez-Ambrosi J, Pascual E, Catalan V, Rodriguez A, Ramirez B, Silva C et al. Circulating betatrophin concentrations are decreased in human obesity and type 2 diabetes. J Clin Endocrinol Metab. 2014;99:2004–9.
28. Fu Z, Berhane F, Fite A, Seyoum B, Abou-Samra AB, Zhang R. Elevated circulating lipasin/betatrophin in human type 2 diabetes and obesity. Sci Rep. 2014;4:5013.
29. Zhang Z, Wu Y, Sheng S, Guo L, He B, Fang P et al. Intracerebroventricular injection of alarin increased glucose uptake in skeletal muscle of diabetic rats. PLoS One. 2015;10:0139327
30. Guo L, Fang P, Yu M, Shi M, Bo P, Zhang Z. Central alarin ameliorated insulin resistance of adipocytes in type 2 diabetic rats. J Endocrinol. 2014;223:217-25.
31. Mikó A, Füredi N, Tenk J, Rostás I, Soós S, Solymár M et al. Acute central effects of alarin on the regulation on energy homeostasis. Neuropeptides. 2017;64:117-122.
32. Hu W, Fan X, Zhou B, Li L, Tian B, Fang X et al. Circulating alarin concentrations are high in patients with type 2 diabetes and increased by glucagon-like peptide-1 receptor agonist treatment. Medicine. 2019;98:16428.
33. Zhou X, Luo M, Zhou S, Cheng Z, Chen Z, Yu X. Plasma alarin level and its influencing factors in obese newly diagnosed type 2 diabetes patients. Diabetes Metab Syndr Obes. 2021;14:379.
34. Kilinc F, Demircan F, Gozel N, Onalan E, Karatas A, Pekkolay Z et al. Assessment of serum alarin levels in patients with type 2 diabetes mellitus. Acta Endocrinol (Buchar). 2020;16:165.
35. Fraley GS, Leathley E, Lundy N, Chheng E, King I, Kofler B. Effects of alarin on food intake, body weight and luteinizing hormone secretion in male mice. Neuropeptides. 2012;46:99–104.