Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2022;11(1):394-8

Does Ramadan fasting affect glicemic control in patients with diabetes mellitus? effects of fasting on betatrophin and insulin resistance

Mustafa Timurkaan[1], Esra Suay Timurkaan[1], Yilmaz Aslan[1], Mehmet Kalayci[2], Hakan Ayyildiz[2]

[1]Fethi Sekin City Hospital, Department of Internal Medicine, Elazig, Turkey
[2]Fethi Sekin City Hospital, Department of Biochemistry, Elazig, Turkey

Received 23 September 2021; Accepted 26 October 2021
Available online 30.12.2021 with doi: 10.5455/medscience.2021.09.303

Abstract

Insulin resistance, which is involved in the pathogenesis of Type 2 Diabetes (T2DM), is considered to be associated with betatrophin. Moreover, it is known that betatrophin levels may be affected by environmental factors. In this study, the changes in pre-Ramadan and post-Ramadan betatrophin levels, HOMA-IR levels, and metabolic parameters were evaluated in patients with T2DM, using oral antidiabetic (OAD) and wanting to fast during Ramadan. 50 patients with T2DM receiving OAD treatment and 40 healthy volunteers were included in the study. Glucose, cholesterol, HDL, LDL, triglyceride measurements were performed with AU-5800 autoanalyzer. Insulin levels were measured with DXI-800 and HbA1c levels with the Premier HB920 device. Furthermore, betatrophin levels were measured using the enzyme-linked immunosorbent assay method. At the beginning and the end of Ramadan, betatrophin levels were detected to be higher in the diabetic group compared to the control group. It was revealed that the post-Ramadan insulin and HOMA-IR levels were lower than the pre-Ramadan values in both of the groups. A positive correlation was found between betatrophin levels and triglyceride (r: 0.289, p= 0.042), and insulin (r: 0.276, p= 0.053) levels in the diabetic group. The study indicated that Ramadan fasting reduced the body mass index and average glucose. Thus, insulin resistance decreased. Betatrophin levels, which may be affected by environmental factors, displayed no changes. Ramadan fasting of diabetic patients in the low and moderate risk group did not disrupt metabolic order and glucose regulation.

Keywords: Ramadan, fasting, diabetes mellitus, betatrophin, HOMA-IR

Introduction

The global prevalence of diabetes in adults is approximately 463 million as of 2019. It is predicted that this number will reach 700 million by 2045. Type 2 diabetes is the most common type of diabetes, accounting for about 90% of all diabetes cases [1].

Fasting during the holy month of Ramadan is an obligation for all healthy Muslims and it has been clearly expressed in the holy book, Quran. However, in cases of illness, Muslims have also been granted exemption from fasting [2]. Nevertheless, the majority of Muslims with diabetes do not consider themselves exempted and prefer to fast.

Muslims do not have any drinks, including water, and eat anything between dawn and sunset for 29-30 days in Ramadan, which concurs with the ninth month of the lunar calendar. Although it changes depending on the country and financial power, it is a traditional practice to eat two meals in 24 hours. One of these two meals is the meal eaten before dawn in preparation for fasting (sahur meal) and the other one is the sunset meal eaten at the end of fasting (iftar meal) [3, 4].

It is estimated that there are more than 150 million Muslims with diabetes worldwide. Therefore, the month of Ramadan is so significant in terms of diabetes management in the Muslim population. Due to the effects of fasting on metabolism, people with diabetes are at risk of complications based on the specific alteration in food and drink intake [5].

Insulin resistance and beta-cell dysfunction, which are widely acclaimed in T2DM, play a significant role in the pathogenesis.

***Corresponding Author:** Mehmet Kalayci, Fethi Sekin City Hospital, Department of Internal Medicine, Elazig, Turkey E-mail: dr_mehmetkalayci@msn.com

Betatrophin is a hormone that weighs 22kDa. It is produced mainly in the liver in humans and white and brown adipose tissue in mice [6]. The determination that betatrophin increases glucose tolerance has led to the investigation of this subject matter. Betatrophin levels increase in the circulation system of T2DM patients and this increase reduces insulin resistance [7]. There are studies indicating that betatrophin is associated with lipid metabolism and significantly correlated with atherogenic lipid profiles, particularly in cardiovascular diseases. It has also been shown to be closely related to insulin resistance based on clinical study results [8, 9].

All this information brings to mind the question of "Does the change in eating and drinking habits, eating at night, and disrupting sleep patterns for about 1 month in Ramadan cause a deterioration in the glucose homeostasis of diabetic patients?". The aim of this study is to shed light on whether fasting disrupts the regulation of diabetes by comparing the betatrophin, HOMA-IR, Hba1C, body mass index, and lipid profile of T2DM patients receiving OAD treatment.

Materials and Methods

This study was carried out in partnership with Elazig Fethi Sekin City Hospital Internal Medicine Clinic and Biochemistry Laboratory. The study was approved by the Ethics Committee of Fırat University. Initially, 59 patients diagnosed with T2DM, who received OAD treatment and were determined as low and moderate risk according to the International Diabetes Federation (IDF) Ramadan Guidelines [5], and 40 healthy fasting individuals were included in the study. Those with diabetes duration over 10 years and those receiving insulin therapy were not included in the study. The current medications of patients, who want to fast and use OAD, were arranged according to the guidelines outlined in the IDF Ramadan Guidelines. According to these guidelines, 6 patients were found to be at high risk and they were excluded from the study. 2 patients left the study at their request and 1 patient was excluded from the study because s/he interrupted the fast. Thus, the study was maintained with 50 patients with T2DM and receiving OAD treatment (Female:28-Male:22) and 40 healthy and voluntary individuals (Female:22-Male:18). Participants who voluntarily participated in the study signed a voluntary consent form at the beginning of the study.

Venous blood samples were taken from the individuals participating in the study between the first and third days of Ramadan and the last three days of Ramadan. Blood samples were taken into 3 tubes. One of them was a serum separator tube (SST), one contained K2-EDTA, and the other contained aprotinin. The blood samples, which were taken into SSTs, were centrifuged at 4000 rpm for 10 minutes. The fasting blood glucose and lipid panel (Cholesterol, HDL, LDL, triglyceride) were studied in a biochemistry autoanalyzer. Insulin levels of these samples were studied in the DXI-800 hormone device and HbA1C levels obtained from the tube with K2-EDTA were studied by the HPLC method. The blood samples, which were taken into tubes with Aprotinin, were centrifuged at 4000 rpm for 10 minutes. The obtained serum was put into small volume tubes to study betatrophin and stored at -20°C until the study day. The plasma betatrophin levels were studied by using the Human Betatrophin ELISA kit (Sunred Biological Technology, catalog no: SRB-T-88039, Shanghai, China) in accordance with the operating procedures specified in the kit catalogs. The washing-incubating of the plates was done in the CombiWash (Human Diagnostics, Wiesbaden, Germany) device and the absorbance measurement was done with the Chromate Microplate Reader (Awareness Technology, Palm City, USA) device. The minimum detection limit of betatrophin was 7.33 ng/L. The intraassay and inter-assay coefficient of variation for plasma betatrophin were <10% and <12%, respectively.

The study data were given as mean ± and standard deviation. Before comparing the groups, it was checked whether the data distribution was normal with the Kolmogorov-Smirnov test. Chi-square test was used for non-dimensional parameters. Student's t-test or Mann Whitney U test was used to compare the parameters between the groups. Pearson correlation test was used to examine the relationships between parameters in groups with each other. For the analysis of parameters during and after Ramadan, Paired T test or Wilcoxon test was used. P values <0.05 were accepted as the lowest level of significance

Results

The patient group consisted of 22 (44%) men and 28 (56%) women. The control group consisted of 18 (45%) men and 22 (55%) women. There was no statistically significant difference between the groups in terms of age and gender.

Demographic and biochemical data of the groups are shown in Table 1. Comparative data for the beginning and end of Ramadan are given in Table 2. When the data of the beginning and end of Ramadan were compared, it was determined that there was no difference between the groups. It was found out that the betatrophin level in the diabetic group was higher than the control group both at the beginning and at the end of Ramadan ($p<0.05$). When the groups were compared within themselves, no significant difference between betatrophin levels at the beginning and end of Ramadan was not detected. The bodyweight of the T2DM group was determined to be significantly lower at the end of Ramadan ($p<0.05$).

Body mass index (BMI) values also decreased and the result was statistically significant ($p<0.05$). It was concluded that the average control glucose values at the end of Ramadan in both groups were significantly lower than at the beginning of Ramadan ($p<0.05$ and $p<0.001$, respectively). The insulin levels at the end of Ramadan were lower in both groups compared to their initial values. This difference was statistically significant in the control group ($p<0.001$). It was also indicated that HOMA-IR levels at the end of Ramadan in both groups were significantly lower than their initial levels ($p<0.05$ in the diabetic group; $p<0.001$ in the control group).

There was a positive correlation between betatropin levels and triglyceride (r: 0.289, p= 0.042) and insulin (r: 0.276, p= 0.053) levels in the diabetic group.

Table 1. Demographic and biochemical data of the groups

	Control group n=40	T2DM n=50	p value
Age (years)	49.67±7.58	52.40±6.42	0.056
Female/Male	22/18	28/22	0.547
Fasting period (day)	25.10±2.54	24.92±2.58	0.725
BMI (kg/m2)	25.16±1.51	29.75±3.67	0.000
Glucose (mg/dl)	88.13±7.3	163.5±52.4	0.000
HbA1C (%)	5.38±0.35	7.86±1.09	0.000
Cholesterol (mg/dl)	179.8±25.1	198.6±32.1	0.003
HDL (mg/dl)	47.8±7.2	44.6±7.6	0.046
LDL (mg/dl)	107.7±19.2	118.6±28.6	0.034
Tryglicerides (mg/dl)	139.3±56.9	177.4±80.5	0.013
Insulin (mIU/L)	8.55±3.16	11.32±5.57	0.006
HOMA-IR	1.86±0.72	4.5±3.0	0.000
Betatrophin (ng/L)	243.11±92.33	338.32±239.53	0.020

BMI: Body mass index, HDL: High density lipoprotein, LDL: Low density lipoprotein,
HOMA-IR: Homeostatic Model Assessment for Insulin Resistance

Table 2. Comparative data for the beginning and end of Ramadan

	Control group n=40		T2DM n=50	
	Beginning of Ramadan	**End of Ramadan**	**Beginning of Ramadan**	**End of Ramadan**
Weight (kg)	70.4±7.8	69.9±6.86	81.9±10.5	81.5±10.2c
BMI (kg/m2)	25.16±1.51	25.02±1.55	29.75±3.67	29.6±3.64c
Glucose (mg/dl)	88.1±7.3	85.4±6.3b	160.5±52.4	153.6±41.5c
HbA1C (%)	5.38±0.35	5.37±0.29	7.86±1.09	7.82±1.10
Cholesterol (mg/dl)	179.8±25.1	177.4±20.4	198.6±32.1	201.7±28.4
HDL-C (mg/dl)	47.8±7.2	48.6±6.9	44.6±7.6	46.3±7.2
LDL-C (mg/dl)	107.7±19.2	110.7±19.8	118.6±28.6	120.7±24.5
Tryglicerides (mg/dl)	139.3±56.9	126.1±46.1	177.4±80.5	172.3±65.7
Insulin (mIU/L)	8.55±3.16	6.98±2.87a	11.32±5.57	10.5±4.68
HOMA-IR	1.86±0.72	1.48±0.63a	4.5±3.0	4.02±2.31c
Betatrophin (ng/L)	243.11±92.33	240.65±112.04	338.32±239.53	317.63±221.9

a: p<0.001; Compared with control group RB c: p<0.05; T2DM compared with RB group
b: p<0.01; Compared with control group RB

BMI: Body mass index, HDL-C: High density lipoprotein Cholestreol, LDL-C: Low density lipoprotein Choleterol,
HOMA-IR: Homeostatic Model Assessment for Insulin Resistance

Discussion

It is estimated that the total Muslim population, which constitutes approximately 24.4% of the world population, has approached 1.9 billion as of 2019 [10]. According to the International Diabetes Federation 2021 Ramadan Guideline, it is predicted that more than 150 million Muslims with diabetes will fast worldwide [5].

Fasting in Ramadan, which is practiced by more than 1.5 billion Muslims every year, is a time-limited form of nutrition. There is no break between fasting days that last for 29 or 30 days. People who fast from dawn to sunset stay completely away from food, drinks, and even water [11, 12].

The main flaw in T2DM is insulin resistance. Along with this, the disease may progress in the form of beta-cell failure and more insulin deficiency may occur [13]. At the beginning level of T2DM, a controlled diet or fasting may have positive effects on

insulin resistance. It is considered that as secondary to moderate weight loss these effects are related to the normalization of blood sugar, decrease in body adiposity, and prevention of increase in body fatness [14, 15]. Moreover, a reduction in caloric intake without malnutrition has been shown to have health benefits in several species, including primates [16,17].

The necessity to meet the needs and desires of the world's Muslim population, particularly the diabetic population, has arisen due to their questions about fasting during Ramadan. In this regard, various guidelines were developed by scientific authorities to instruct physicians and patients. The American Diabetes Association (ADA) published its first Ramadan notice in 2005 and then it was revised. In a consensus report, most recently published in 2020, the ADA/European Association for the Study of Diabetes (EASD) applied Type 2 diabetes management guidelines to Ramadan. The International Diabetes Federation (IDF) published a Ramadan-specific Guideline in 2016 and made it available for physicians. The last update of this highly detailed guideline was in April 2021 [5]. According to the "EPIDIAR" study conducted with the simultaneous participation of 13 Muslim countries, it was reported that approximately 86% of patients with Type 2 diabetes fast and 78.7% of these patients fast for at least 15 days in Ramadan [18]. The results of the "CREED" study, which was organized according to the ADA criteria and carried out with the simultaneous participation of 13 different countries, were similar. In this study, it was stated that 94.2% of T2DM patients fasted for at least 15 days, and 63.6% of the patients fasted every day [19].

There is a general view that fasting is beneficial for health and is a potential non-pharmacological intervention to increase healthy life expectancy [20]. Fasting in Ramadan means rearranging many daily routines such as eating and drinking habits, sleep duration, drug frequency, and dose in T2DM patients, as in all fasting patients. All of these may be beneficial to the individual, as well as suggesting the possibility of disrupting the metabolic control of diabetic patients. On the other hand, intermittent fasting, which is used to lose weight and control chronic diseases, is a diet that increases its popularity day by day [21]. Intermittent fasting can also be done for non-religious reasons, such as losing weight. Based on available evidence, intermittent fasting under medical supervision is safe. It reduces body weight and central adiposity thus causes a positive decrease in HbA1c levels. There are also studies showing that intermittent fasting improves insulin sensitivity [22]. In addition, there are some studies indicating that Ramadan fasting, in which the drugs of the patients are regulated according to the guideline at the beginning, risk scoring is determined and kept under the control of a physician, has a positive effect on T2DM and does not disrupt diabetic regulation [23, 24]. However, it should be noted that Ramadan fasting, unlike all other types of intermittent fasting, does not include water/fluid intake [25]. When Ramadan fasting is categorized, it may be defined as an intermittent rigid diet period with certain boundaries (the beginning and the end) that may be used.

Many metabolic benefits of fasting have been described in the literature. Intermittent fasting helps to maintain lean muscle mass, improving body composition, optimizing physiological function, and decelerating aging and disease processes [16]. Fasting also has a significant impact on metabolic hormone concentration and function, including insulin, Insulin-like growth factor 1 (IGF-I), adiponectin, and ghrelin. It also has an efficient role in tissue homeostasis by suppressing cell growth and increasing apoptosis of damaged cells [26]. There is increasing evidence that short-term fasting can improve patient response to cancer chemotherapy while protecting from toxicity [27].

Betatrophin is a protein consisting of 198 amino acids. Its concentration has been shown to vary in many metabolic diseases, including diabetes, obesity, and metabolic syndrome. The association between betatrophin and other biomarkers of these diseases has also been reported. Although the results obtained from these studies are not consistent, the results show that betatrophin may play a role in the onset and progression of diabetes. There are studies on the alteration of nutrition-related betatrophin expression in humans. Betatrophin levels have been shown to be inversely proportional to animal protein intake in obese individuals with metabolic syndrome fed low-calorie diets. Thus, it has been concluded that diet is an important modulator of betatrophin expression. In addition, it has been reported that Betatrophin change is affected by many factors such as age, gender, duration of diabetes, and BMI, as well as environmental and genetic factors [28-30].

Although the study and survey results vary by country, the general attitude of the Muslim population with T2DM about Ramadan fasting is similar. Therefore, it is an interesting and alternative model to investigate the benefits, harms, and potential effects on T2DM of Ramadan fasting or intermittent fasting. Because of the limited duration of Ramadan fasting (29-30 days), it is not possible to make a chronic diabetic assessment. It may not be a suitable parameter for the evaluation of Ramadan alone due to the need for an average of 3 months of value calculation to determine HbA1C levels and the possibility of mixing the pre- and post-Ramadan periods. Therefore, we designed our study with HOMA-IR, which we can make a shorter-term evaluation, and betatrophin, which has been proven to be associated with insulin resistance in previous literature.

In the study, it was found that the Homa-IR values of both groups at the end of Ramadan significantly decreased compared to the values at the beginning of Ramadan. However, the decrease in insulin was not significant in the diabetic group. This result showed that the main reason for the current HOMA-IR decrease was secondary to the decrease in the glucose mean of the groups. It was determined that there was a significant decrease in the diabetic group's post-Ramadan and pre-Ramadan glucose averages. The fact that the current weight and therefore BMI values of both groups decreased significantly after Ramadan probably contributed to the breaking of insulin resistance. As a result of this, there was a decrease in insulin levels. Although betatrophin levels also decreased compared to the first table, it was not statistically significant. We consider that this may be due to some reasons such as the lack of uninterrupted hunger, the duration of Ramadan fasting, high-calorie and unbalanced nutrition between iftar and sahur. Already based on the evidence that betatrophin levels are also affected by environmental factors, it is not difficult to guess that this may be a normal variation. In all aspects, the current findings clearly show that Ramadan fasting does not impair metabolic regulation and glucose homeostasis in the population of patients in the low and

moderate risk group.

Conclusion

OFasting is recommended in almost all religions. As a type of intermittent fasting, Ramadan fasting is a non-pharmacological intervention that improves overall health. It reduces the body mass index, and the body mass index and glucose average decrease thanks to the diet made with fasting. As a result, insulin resistance decreases. Betatrophin levels, which may be affected by environmental factors, did not changed. Ramadan fasting of diabetic patients in the low and moderate risk group does not impair metabolic order and glucose regulation.

Limitations of the study

The main limitations of the study are the inability to measure sleep duration and timing, the exact calorie intake and expenditure during the day, and the inability to control some interfering factors that may have affected serum parameters such as the working duration of the individuals. Furthermore, the volunteer subjects in the study did not agree to come to weekly controls and donate blood every week. Therefore, two samples, the beginning of Ramadan and the end of Ramadan, were necessarily collected to measure the available parameters. Another limitation is that patients with the type 2 DM did not continue the study for one more month and no comparison was made outside of Ramadan. In subsequent studies, weekly controls, starting from the beginning of Ramadan, in the first, second, third, and last weeks of the study design, may provide access to a wider data level.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethics committee approval was received from the Ethics Committee of Fırat University for the study (May 17, 2018; No: 09/18)

References

1. International Diabetes Federation. IDF diabetes atlas, ninth edition 2019. https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html. access date 20.09.2021.
2. The Holy Qur'an Sura 2:v.183-185.
3. Ghouri N, Gatrad R, Sattar N, et al. Summer-winter switching of the Ramadan fasts in people with diabetes living in temperate regions. Diabet Med. 2012;29:696-7.
4. Aadil N, Houti IE, Moussamih S. Drug intake during Ramadan. Br Med J. 2004;329:778-82.
5. Diabetes and Ramadan. IDF-DAR Practical Guidelines 2021. Accessed September 20, 2021. https://www.idf.org/our-activities/education/diabetes-and-ramadan.html. access date 20.09.2021
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. Rong Guo X, Li Wang X, Chen Y, et al. ANGPTL8/betatrophin alleviates insulin resistance via the Akt-GSK3β or Akt-FoxO1 pathway in HepG2 cells. Experimental Cell Research. 2016;345:158-67.
8. Fenzl A, Itariu BK, Kosi L, et al. Circulating betatrophin correlates with atherogenic lipid profilesbut not with glucose and insulin levels in insulin-resistant individuals. Diabetologia. 2014;57:1204-8.
9. Wang S, Hong X, Tu Z, et al. Angiopoietin-like protein 8: An attractive biomarker for the evaluation of subjects with insulin resistance and related disorders. Diabetes Res Clin Pract. 2017;133:168-77.
10. Ibrahim M, Davies MJ, Ahmad E, et al. Recommendations for management of diabetes during Ramadan: update 2020, applying the principles of the ADA/EASD consensus. BMJ Open Diabetes Res Care. 2020;8:e001248.
11. BaHammam AS, Almeneessier AS. Recent Evidence on the impact of ramadan diurnal intermittent fasting, mealtime, and circadian rhythm on cardiometabolic risk: a review. Front Nutr. 2020;7.
12. Faris MeA-I, Jahrami H, BaHammam A, et al. A systematic review, meta-analysis, and meta-regression of the impact of diurnal intermittent fasting during Ramadan on glucometabolic markers in healthy subjects. Diabetes Res Clin Pract. 2020;165:108226.
13. Ramlo-Halsted BA, Edelman SV. The natural history of type 2 diabetes. Implications for clinical practice. Prim Care. 1999;26:771-89.
14. Taylor R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. Diabetologia. 2008; 51:1781-89.
15. Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. Diabetes Care. 2016;39:808-15.
16. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: Understanding and applying the health benefits of fasting. Obesity (Silver Spring). 2018;26:254-68.
17. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science. 2009;325:201-4.
18. Salti I, Benard E, Detournay B, et al. A Population-based study of diabetes and its characteristics during the fasting month of ramadan in 13 countries: results of the epidemiology of diabetes and ramadan 1422/2001 (EPIDIAR) study. Diabetes Care. 2004;27:2306-11
19. Jabbar A, Hassanein M, Beshyah SA, et al. CREED study: Hypoglycaemia during Ramadan in individuals with Type 2 diabetes mellitus from three continents. Diabetes Res Clin Pract. 2017;132:19-26.
20. Trepanowski JF, Bloomer RJ. The impact of religious fasting on human health. Nutr J. 2010;9:57.
21. Grajower MM, Horne BD. Clinical management of intermittent fasting in patients with diabetes mellitus. Nutrients. 2019;11:873.
22. Shubrook J, Katuna J. A physician's introduction to therapeutic fasting. Intermittent fasting and type 2 diabetes | diabetes.medicinematters.com access date 20.09.2021
23. Sahin SB, Ayaz T, Ozyurt N, et al. The impact of fasting during Ramadan on the glycemic control of patients with type 2 diabetes mellitus. Exp Clin Endocr Diab. 2013;121:531-4.
24. Bener A, al-Hamaq AOAA, Öztürk M, et al. Effect of Ramadan fasting on glycemic control and other essential variables in diabetic patients. Ann Afr Med. 2018;17:196-202.
25. Chaudhury A, Duvoor C, Reddy Dendi VS, et al. Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Front Endocrinol. 2017;8:6.
26. Longo VD, Mattson MP. Fasting: Molecular mechanisms and clinical applications. Cell Metab. 2014;19:181-92.
27. de Groot S, Pijl H, van der Hoeven JJM, et al. Effects of short-term fasting on cancer treatment. J Exp Clin Cancer Res. 2019;38:209.
28. Zhang R, Abou-Samra AB. A dual role of lipasin (betatrophin) in lipid metabolism and glucose homeostasis consensus and controversy. Cardiovasc Diabetol. 2014;13:133.
29. Crujeiras AB, Zulet MA, Abete I, et al. Interplay of atherogenic factors, protein intake and betatrophin levels in obese-metabolic syndrome patients treated with hypocaloric diets. Int J Obes (Lond). 2016;40:403-10.
30. Ebert T, Kralisch S, Hoffmann A, et al. Circulating angiopoietin-like protein 8 is independently associated with fasting plasma glucose and type 2 diabetes mellitus. J Clin Endocrinol Metab. 2014;99:E2510-7.