ARTÍCULO ORIGINAL

Gac Méd Caracas 2024;132(3):647-655
DOI: 10.47307/GMC.2024.132.3.7

Relation between serum levels of advanced glycation end products and omentin in type 2 diabetes mellitus subjects

Relación entre los niveles séricos de los productos finales de glicación avanzada y la omentina en sujetos con diabetes mellitus tipo 2

Vifriana [1], Liong Boy Kurniawan[2]*, Nurahmi[2], Andi Alfian Zainuddin[3], Husaini Umar [4], Andi Ariyandy [5]

SUMMARY

Diabetes mellitus Type 2 (DMT2) is a chronic disease characterized by high levels of sugar in the blood (hyperglycemia) that can cause serious, potentially life-threatening complications. Chronic hyperglycemia, combined with oxidative stress, is known to enhance the formation of advanced glycation end products (AGEs) as a normal consequence of metabolism. Continued elevation of AGEs is known to contribute to the complications of diabetes by raising intracellular oxidative stress. It has been suggested that Omentin is negatively correlated with oxidative stress. Omentin is an adipokine with anti-inflammatory and anti-insulin resistance properties synthesized abundantly in the visceral adipose tissue. The current study aims to determine the association between serum AGEs and Omentin levels in type 2 DM subjects. This study utilized a cross-sectional design and involved 62 subjects with type 2 DM, comprising 23 males and 39 females. The findings demonstrated no significant relation between the serum AGE and Omentin level in overall type 2 DM patients (p=0.054, r=0.246). Furthermore, no notable relationship was observed between serum level of AGEs and Omentin in male subjects with type 2 DM (p=0.485, r=0.153). Similarly, no significant relationship was found between AGEs and Omentin serum levels in female subjects with type 2 DM (p=0.478, r=0.117).

Keywords: *Type 2 diabetes mellitus, serum AGEs, serum Omentin*

DOI: https://doi.org/10.47307/GMC.2024.132.3.7

ORCID: 0000-0002-2633-0441[2]
ORCID: 0000-0003-4436-3906[3]
ORCID: 0000-0002-6529-2986[4]
ORCID: 0000-0002-6492-5235[5]

[1]Master of Biomedical Science, Postgraduate Program, Hasanuddin University, Makassar, South Sulawesi, Indonesia
[2]Department of Clinical Pathology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia
[3]Department of Public Health, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia
[4]Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia / Dr. Wahidin Sudirohusodo General Hospital, Makassar, South Sulawesi, Indonesia

Recibido: 21 de junio 2024
Aceptado: 5 de julio 2024

RESUMEN

La diabetes mellitus tipo 2 (DMT2) es una enfermedad crónica caracterizada por niveles elevados de azúcar en la sangre (hiperglucemia) que pueden causar complicaciones graves y potencialmente mortales. Se sabe que la hiperglucemia crónica, en combinación con el estrés oxidativo, incrementa la formación de productos finales de glicación avanzada (AGE), que se

[5]Department of Physiology, Hasanuddin University, Makassar, South Sulawesi, Indonesia.

Corresponding Author: Liong Boy Kurniawan, E-mail: liongboykurniawan84@gmail.com
Phone: +6281241738007, Address: Jln Perintis Kemerdekaan KM 10 Makassar

forman como consecuencia normal del metabolismo. Se sabe que la elevación continua de los AGE contribuye a las complicaciones de la diabetes al aumentar el estrés oxidativo intracelular. Se ha sugerido que la Omentina se correlaciona negativamente con el estrés oxidativo. La Omentina es una adipocina con propiedades antiinflamatorias y antirresistencia a la insulina que se sintetiza abundantemente en el tejido adiposo visceral. El estudio actual tiene como objetivo determinar la asociación entre los AGE séricos y los niveles de Omentina en sujetos con DM tipo 2. Este estudio utilizó un diseño transversal e involucró a 62 sujetos con DM tipo 2, 23 hombres y 39 mujeres. Los hallazgos demostraron que no existe una relación significativa entre los niveles séricos de AGE y de Omentina en pacientes con DM tipo 2 en general (p = 0,054, r = 0,246). Además, no se observó una relación notable entre el nivel sérico de AGE y Omentina en sujetos masculinos con DM tipo 2 (p=0,485, r=0,153). De manera similar, no se encontró una relación significativa entre los AGE y el nivel sérico de Omentina en mujeres con DM tipo 2 (p = 0,478, r = 0,117).

Palabras clave: *Diabetes mellitus tipo 2, AGE séricos, omentina sérica.*

INTRODUCTION

Diabetes mellitus is a disease of metabolic dysregulation, most notably abnormal glucose metabolism, accompanied by characteristic long-term complications. Complications from diabetes can be classified as microvascular or macrovascular. Microvascular complications include nervous system damage (neuropathy), renal system damage (nephropathy), and eye damage (retinopathy). Macrovascular complications include cardiovascular disease, stroke, and peripheral vascular disease (1). Furthermore, diabetes mellitus is among the immunocompromised conditions, signifying a weakened immune system that heightens susceptibility to complications and increases vulnerability to infections in individuals (2). During the current COVID-19 pandemic, individuals diagnosed with DMT2 also tend to be more vulnerable to diseases and worsening inflammatory reactions. Advanced glycation end-products are a complex and heterogeneous group of compounds implicated in diabetes-related complications. It is unknown if they are the cause or the consequence of the complications observed. An increase in the levels of Advanced Glycation End Products (AGEs) in the body is one of the factors that can exacerbate complications in type 2 diabetes mellitus, and measuring serum AGE levels is considered a highly accurate method for evaluating the true impact of chronic hyperglycemia (3).

Advanced glycation end products (AGEs) are proteins or lipids that become glycated due to exposure to the carbamyl group of reducing sugars. When blood glucose levels remain consistently high, glycation reactions increase, ultimately leading to an elevated formation of AGEs. The increased accumulation of AGEs can play a part in the onset of complications which is associated with diabetes, including eye diseases, nerve damage, kidney diseases, and cardiovascular problems. AGEs are pro-inflammatory compounds that affect the normal function of proteins and trigger inflammatory responses and oxidative stress, all of which are risk factors associated with type 2 diabetes (4).

Omentin is a protein classified as an adipokine, possessing anti-inflammatory properties. Numerous studies have indicated that serum Omentin levels were significantly lower in diabetic patients compared with the control and also during insulin resistance and obesity. A meta-analysis revealed a significant reduction in serum Omentin levels among patients diagnosed with type 2 diabetes mellitus (DMT2), suggesting that omentin-1 is important for glucose metabolism (5). This implies that with increasing insulin resistance, the body tends to produce less Omentin, leading to reduced responsiveness of body cells to insulin. This condition can impact the production and function of Omentin. Inflammation caused by adiposity can disrupt the production and release of omentin by adipose tissues, affecting the ability of adipose tissues to function properly (6).

Earlier investigations have primarily explored the correlation between AGEs and DMT2 and Omentin and obesity. Currently, there are no studies assessing the relationship between the level of serum AGEs and the reduction in the level of serum Omentin among individuals suffering from type 2 diabetes mellitus (DMT2). Therefore, the current study aims to investigate a potential association between the elevation of

serum AGE levels and the reduction of serum Omentin levels in type 2 DMT2 subjects, which could exacerbate type 2 DMT2 complications.

METHOD

Study Design and Population

The current research employed an analytical observational method and a cross-sectional study design. Type 2 diabetes mellitus (DMT2) patients visiting Dr. Wahidin Sudirohusodo General Hospital, Makassar, for treatment, were determined as the study population. The study was conducted from October to November 2023. The inclusion criteria were male and female patients with type 2 DMT2 aged >18 years who received information and willingly to participate in the research by providing informed consent. The exclusion criteria included patients taking corticosteroids, those with genetic polymorphisms, those experiencing infections or malignancies, and those exhibiting serum jaundice, lipemia, or hemolysis. There were 62 samples involved in the study, comprising 23 males and 39 females. This study was carried out at the Laboratory of Hasanuddin University Medical Research Center (HUM-RC), Makassar. Ethical approval for the study was obtained from the Health Research Ethics Committee (KEPK), Faculty of Medicine, Hasanuddin University, RSPTN-UH, with Ethical Approval Number 826/UN4.6.4.5.31/PP36/2023.

Level Measurement

Patient identities were recorded. Before blood collection, patients underwent fasting and anthropometric examinations. Complete blood samples were collected in red-capped tubes without anticoagulants to examine AGEs and Omentin serum levels. Subsequently, the blood samples were allowed to stand for 15-30 minutes inside the vacuum tubes and then left to clot. The samples were centrifuged at 3 000 rpm for 10 minutes. After centrifugation, serum was transferred to sample cups using a disposable pipette, with a volume of 150 μl for each serum cup. The serum was stored in a calibrated freezer at -20°C to ensure sample stability. The Enzyme-Linked Immunosorbent Assay (ELISA) kit from MyBioSource was utilized on the Thermo ELISA Reader instrument to examine AGE and Omentin serum levels.

Data Analysis

The data were analyzed using the Statistic package SPSS software, Version 22. The analysis involved entering all variables, including gender, age, and laboratory test results. Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted to determine the normality of the data distribution, utilizing a significance level (α) of 0.05. Spearman and Pearson correlation tests were performed in this study.

RESULTS

Table 1 shows that the current research involved 62 individuals with type 2 diabetes mellitus, 23 male and 39 female subjects.

Table 1. Frequency Distribution of Gender Variables in Research Subjects

Characteristic	Category	Type 2 DM	
		N	%
Gender	Male	23	37.1
	Female	39	62.9

Individuals suffering from type 2 diabetes mellitus ranged in age from 22 to 83 years, with an average Body Mass Index (BMI) of 24.95 kg/m^2, an average HbA1c of 8.56 %, an average Fasting Blood Glucose (FBG) of 149.74 mg/dL, an average serum Omentin level of 5.05 ng/mL, and an average serum AGEs level of 22.37 ng/m (Table 2).

Table 3 shows that the Kolmogorov-Smirnov and Shapiro-Wilk tests revealed that the serum Omentin levels in individuals diagnosed with type 2 diabetes mellitus exhibited a p-value of 0.009<0.05, implying that the data does not follow a normal distribution. Conversely, the

Table 2. Descriptive Analysis of Age, Serum AGE Levels, and Serum Omentin Levels in Subjects of the Research

Characteristics	n	Mean±SD	Median	Min-Max
Age (Years)	62	58.00±11.07	58	22-83
BMI (kg/m^2)	62	24.95±4.01	24.14	17.78-36.89
HbA1c (%)	62	8.56±1.88	8.5	5.7-14.1
FBS (mg/dL)	62	149.74±49.18	143	75-291
Serum Omentin level (ng/mL)	62	5.05±0.93	4.97	3.3076-8.9457
Serum AGEs level (ng/mL)	62	22.37±4.58	22.10	12.2075-36.9892

Source: Primary Data
BMI= Body Mass Index, HbA1c= Hemaglobin A1c, FBS= Fasting Blood Sugar, AGEs= Advanced Glycation end products

distribution of serum AGE levels in overall type 2 diabetes mellitus subjects was revealed to be normal, as indicated by a p-value of 0.200>0.05. Table 3 further illustrates that the serum Omentin levels in individuals with type 2 diabetes mellitus demonstrated a p-value of 0.132>0.05, suggesting a normal data distribution. Similarly, serum AGE levels in males suffering from type 2 diabetes mellitus showed a p-value of 0.134>0.05, indicating normal data distribution. Moreover, the level of serum Omentin in individuals suffering from type 2 diabetes mellitus revealed a p-value of 0.115>0.05, implying normal data distribution, and serum AGE levels in male individuals suffering from type 2 diabetes mellitus presented a p-value of 0.090>0.05, implying normal data distribution as well.

Table 3. Normality Test of Serum AGE Levels and Serum Omentin Levels in Research Subjects

	Normality Test		Distribution	
	Statistic	n	p	
Serum Omentin Levels (Overall)	0.13	62	0.009*	Not normal
Serum AGE Levels (Overall)	0.08	62	0.200*	Normal
Serum Omentin Levels (Male)	0.93	23	0.132**	Normal
Serum AGE Levels (Male)	0.93	23	0.134**	Normal
Serum Omentin Levels (Female)	0.95	39	0.115**	Normal
Serum AGE Levels (Female)	0.95	39	0.090**	Normal

Source: Primary Data
* Kolmogorov-Smirnov Test, ** Shappiro-Wilk Test, BMI= Body Mass Index, AGEs= Advanced Glycation end products

Correlation Test

According to the Spearman correlation test conducted to compare the relationship between serum levels of AGE and serum Omentin in individuals diagnosed with type 2 diabetes mellitus, a p-value of 0.054 was obtained. As $0.054 > \alpha\,(0.05)$, this data indicates that there was a tendency to the correlation between variables; however, the correlation between serum levels of AGE and Omentin in patients diagnosed with DMT2 was not statistically significant (Table 4).

Table 4. Correlation Test of Serum AGE Levels and Serum Omentin Levels in Overall Research Subjects

Variable	Serum AGEs Level	
Serum Omentin Level	r =	0.246
	p=	0.054
	n=	62

Source: Primary Data, Notes: *p = Spearman Correlation Test

The scatterplot in Figure 1 shows that the data distribution forms a random pattern. This observation suggests the absence of a significant correlation or relationship between the variables of serum AGE levels and serum Omentin levels.

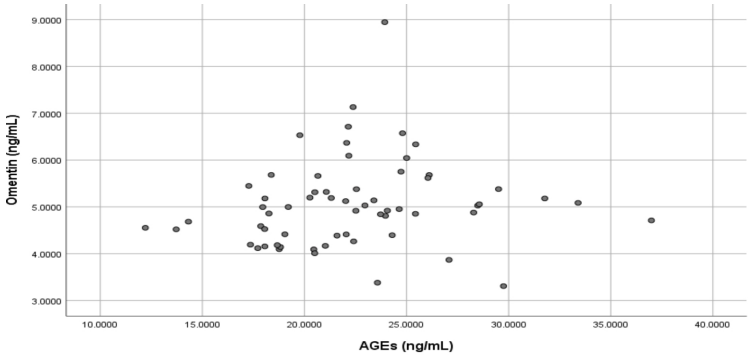

Figure 1. Scatterplot of Serum AGE levels and Serum Omentin Levels in Overall Research Subjects.

Correlation between Serum Levels of AGEs and Omentin in Male Type 2 Diabetes Mellitus Subjects

The Pearson correlation test between serum levels of AGEs and Omentin in males suffering from type 2 diabetes mellitus yielded a p-value of 0.485. Given that $0.485 > \alpha$ (0.05), this indicates that there was no significant association between serum levels of these two variables in male individuals diagnosed with DMT2 (Table 5).

Table 5. Correlation Test of Serum Levels of AGE and Omentin in Male Subjects Suffering from Type 2 Diabetes Mellitus

Variable	Serum AGEs Level	
Serum Omentin Level	r =	0.153
	p=	0.485
	n=	23

Source: Primary Data, *p = Pearson Correlation Test

The scatterplot in Figure 2 shows that the data distribution forms a random pattern. This implies that there is no correlation between the variables of serum levels of AGE and Omentin in male subjects diagnosed with type 2 diabetes mellitus.

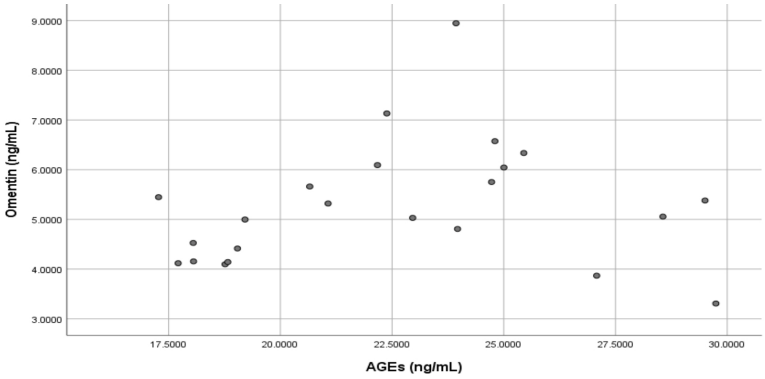

Figure 2. Scatterplot of Serum levels of AGE and Omentin in Male Subjects.

Correlation between Serum Level of AGEs and Omentin in Female Subjects with Type 2 Diabetes Mellitus

The Pearson correlation test between serum levels of AGE and Omentin in female subjects with type 2 diabetes mellitus yielded a p-value of 0.478. As 0.478 > α (0.05), no significant association was detected between these two variables in female subjects with type 2 diabetes mellitus (Table 6).

Table 6. Correlation Test Between Serum Level of AGEs and Omentin in Female Subjects with Type 2 Diabetes Mellitus

Variable	Serum AGEs Level	
Serum Omentin Level	r =	0.117
	p=	0.478
	n=	39

Source: Primary Data, *p=Pearson Correlation Test

The scatterplot in Figure 3 shows that the data distribution forms a random pattern. This suggests no significant correlation or relationship between the variables of serum levels of AGE and Omentin in female subjects suffering from type 2 diabetes mellitus.

DISCUSSION

The serum AGEs and Omentin levels were measured in samples from individuals with type 2 diabetes mellitus. Multiple studies have pointed out a rise in serum AGE levels in diabetes complications, a significant factor contributing to mortality in patients with DMT2. Uncontrolled continued exposure to a hyperglycemic state is a precursor to AGE formation and accumulation in diabetes mellitus. This non-enzymatic glycation and cross-linking of protein, lipids, and nucleic acid modifications alter these macromolecules' structural integrity and function. The deleterious effects of AGEs are underpinned by their ability to trigger the release of pro-inflammatory molecules, impair mitochondrial oxidative stress, activate AGEs/RAGE signaling cascade, and trigger transcription factors that upregulate the

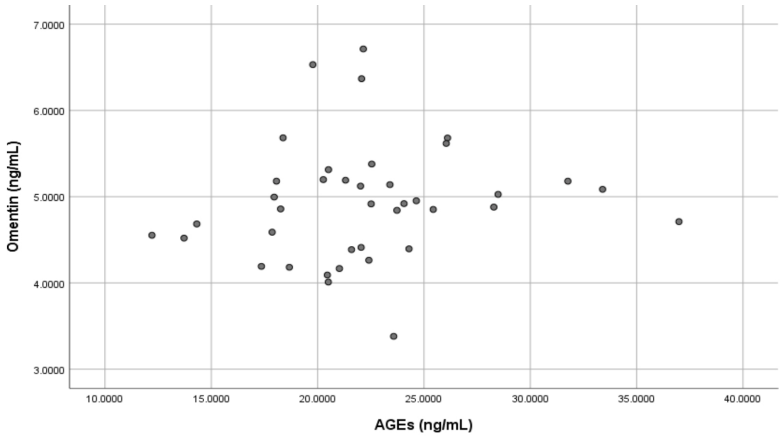

Figure 3. Scatterplot of Serum AGE levels and Serum Omentin Levels in Female Subjects

expression of genes that have potential roles in the pathogenesis of diabetic complications.

Ying et al. (7) detailed the association between AGEs and the prevalence of diabetic retinopathy severity, one of the microvascular complications of DMT2. They stated that AGEs are reported to be correlated with diabetic vascular complications and they examined the association between AGEs and carotid atherosclerosis as a surrogate marker of cardiovascular disease (CVD) in a total of 1 006 patients with T2DM. The authors concluded that AGEage, the non-invasive measurement of AGEs combined with age, is a promising approach for triaging patients at high risk of CVD. Other research has also highlighted the increased accumulation of AGEs in tissues among individuals with type 2 diabetes mellitus (3,4). The detection of circulating AGEs may indicate the risk of future diabetes (4).

Omentin, originating from visceral fat tissue, is an anti-inflammatory protein biomarker for metabolic risk (8). Omentin is associated with glucose metabolism and insulin sensitivity, with a relationship between increased serum Omentin levels and enhanced insulin sensitivity. Moreover, Omentin also functions as a biomarker for metabolic risk and can be involved in proinflammatory conditions in various contexts, such as obesity, insulin resistance, or imbalanced metabolic conditions. The levels of Omentin serum in the body often decrease in these situations, and this decrease can then become a contributing factor to higher inflammation, which, in turn, may contribute to various health conditions, such as cardiovascular diseases, diabetes, or autoimmune diseases. Mustafa et al. (9) reported a noteworthy reduction in the level of serum Omentin among diabetic patients in comparison to the control group. This study also suggests that serum Omentin significantly decreases in diabetic patients diagnosed with retinopathy compared to those without retinopathy.

Our findings using the Spearman correlation test conducted on subjects with DMT2 show no significant correlation between serum levels of AGE and Omentin ($p=0.054$, $r=0.246$). Similarly, these variables had no significant association in male subjects with type 2 diabetes mellitus ($p=0.485$, $r=0.153$) or female subjects with DMT2 ($p=0.478$, $r=0.117$). This finding contradicts the ones reported by Liang et al. (10), who studied the relationship between Omentin-1 levels and coronary artery disease (CAD) and reported an association between low levels of Omentin-1 and CAD and elevated levels of AGEs in CAD individuals. Other research also indicates a decrease in Omentin-1 among individuals suffering from type 2 diabetes mellitus and peripheral artery disease, with Omentin-1 levels being linked with the gravity of the disease (11,12). On the other hand, contrasting results were presented by Yilmaz et al. (13),

stating that serum Omentin levels increase in Non-alcoholic fatty liver disease (NAFLD), a disease related to obesity, even though obesity is associated with lower levels of Omentin (13).

The absence of a correlation between serum levels of AGE and Omentin in the present study may be influenced by several factors, with the duration of suffering from diabetes mellitus (DMT2) being one potential factor. Before a significant decrease in Omentin levels occurs, the Omentin levels might still be relatively high. According to Abdelraour Korany et al. (14), serum Omentin, diabetes duration, and IMT (Intima Media Thickness) exhibit a negative correlation. Various medications can also affect Omentin levels; medications such as metformin may increase Omentin levels (15). Recent studies have demonstrated that atorvastatin enhances serum Omentin levels in individuals diagnosed with coronary artery disease, indicating that there may be medications that respondents consume without the researcher's knowledge (16).

Moreover, smoking is also associatd with various hormonal and chemical changes in the body, including those related to lipid metabolism and the inflammatory system. Several studies have found a relationship between smoking and the level of serum Omentin. For instance, by Ansari et al. (17) found an increase in serum Omentin levels among smokers when compared to non-smokers. Smoking is regarded as one of the primary contributors to oxidative stress. When someone smokes, various chemical compounds in cigarette smoke can stimulate the production of Reactive Oxygen Species (ROS) within cells. These reactive oxygen species are highly reactive molecules capable of causing cellular damage and triggering responses to oxidative stress. This oxidative stress can alter gene expression and the production of adipokines, including Omentin.

CONCLUSION

No significant association was found between serum levels of AGEs and Omentin in subjects suffering from type 2 diabetes mellitus (DM), including both male and female subjects.

REFERENCES

1. Decroli E. Diabetes Melitus Tipe 2. Pusat Penerbitan Bagian Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Andalas Padang; 2019.
2. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol. 2020;16(7):377-390.
3. Simó-Servat O, Planas A, Ciudin A, Simó R, Hernández C. Assessment of advanced glycation end-products as a biomarker of diabetic outcomes. Endocrinol Diabetes Nutr. 2018; 65(9):540-545.
4. Jiang T, Zhang Y, Dai F, Liu C, Hu H, Zhang Q. Advanced glycation end products and diabetes and other metabolic indicators. Diabetol Metab Syndr. 2022;14(1):1-15.
5. As'habi A, Sadeghi M, Arab A, Hajianfar H. The association between omentin and diabetes: A systematic review and meta-analysis of observational studies. Diabetes Metab Syndr Obes. 2019;12:1277-1286.
6. Halabis M, Dziedzic M, Warchulinska J, Kaznowska. Bystryk I, Solski J. Omentin - A new adipokine with many roles to play. Curr Issues Pharm Med Sci. 2015;28(3):176-180.
7. Ying L, Shen Y, Zhang Y, Wang Y, Liu Y, Yin J, et al.. Association of advanced glycation end products with diabetic retinopathy in type 2 diabetes mellitus. Diabetes Res Clin Pract. 2021;177:108880.
8. Moreno-Navarrete JM, Ortega F, Castro A, Sabater M, Ricart W, Fernández-Real JM. Circulating omentin as a novel biomarker of endothelial dysfunction. Obesity. 2011;19(8):1552-1559.
9. Mustafa HI, Zbaar SA, Salman MS. Study the Role Serum Omentin-1 in Occurrence and Development of Diabetic Retinopathy. Medico-Legal Update. 2020;20(4):1949-1955.
10. Liang W, Ye D Dong. The potential of adipokines as biomarkers and therapeutic agents for vascular complications in type 2 diabetes mellitus. Cytokine Growth Factor Rev. 2019;48(June):32-39.
11. Biscetti F, Nardella E, Rando MM, Cecchini AL, Angelini F, Cina A, et al. Association between plasma omentin-1 levels in type 2 diabetic patients and peripheral artery disease. Cardiovasc Diabetol. 2019;18(1):1-7.
12. Hayashi M, Morioka T, Hatamori M, Kakutani Y, Yamazaki Y, Kurajoh M, et al. Plasma omentin levels are associated with vascular endothelial function in patients with type 2 diabetes at elevated cardiovascular risk. Diabetes Res Clin Pract. 2019;148:160-168.

13. Yilmaz Y, Yonal O, Kurt R, Alahdab YO, Eren F, Ozdogan O, et al. Serum levels of omentin, chemerin, and adipsin in patients with biopsy-proven nonalcoholic fatty liver disease. Scand J Gastroenterol. 2011;46(1):91-97.
14. Abdelraouf Korany M, Sonbol A, Mohamed Elgouhary S. Omentin-1 and diabetic retinopathy in type 2 diabetic patients. Alexandria J Med. 2018;54(4):323-326.
15. Tan BK, Adya R, Farhatullah S, Chen J, Lehnert H, Randeva HS. Metformin treatment may increase omentin-1 levels in women with polycystic ovary syndrome. Diabetes. 2010;59(12):3023-3031.
16. Watanabe T, Watanabe-Kominato K, Takahashi Y, Kojima M, Watanabe R. Adipose tissue-derived omentin-1 function and regulation. Compr Physiol. 2017;7(3):765-781.
17. Ansari MHK, Gholamnejad M, Meghrazi K, Khalkhali HR. Association of circulating omentin-1 level with lung cancer in smokers. Med J Islam Repub Iran. 2018;32(1):1-5.