The Relationship of Growth Differentiation Factor 15 with Some Biochemical Parameters in Cardiovascular Disease Patients in Babylon City

Hiba Resheed Behayaa, Zinah Abbass Ali, Seenaa Badr Mohammed, Suhayr A. Alqaysi
Department of Clinical Biochemistry, College of Medicine, University of Babylon, Babylon, Iraq

Abstract

Background: Cardiovascular disease (CVD) is one of the reasons of mortality in the world. In the developing world, deaths from CVD have been increasing. Growth differentiation factor 15 (GDF15) is about cachexia, CVD, and a lot of inflammatory diseases. GDF15 is very low in most tissues, except the placenta (in healthy conditions), which expresses GDF15 in high levels. Though in cardiovascular damage, the level of GDF15 may rise, the natural effects of GDF15 may vary according to the stage of the disease. **Objective:** The objective of the study was the valuation of GDF15 level in the serum of patients with CVD in Babylon City and to check whether there was a link between age, body mass index, lipid profile, insulin resistance, adiponectin and C-reactive protein with GDF15. **Materials and Methods:** GDF15 was assessed in 80 Iraqi subjects; 40 were diagnosed with CVD and 40 subjects who appear healthy were considered for this study. The age ranged between 41 and 73 years for patients and control was considered for this study. Enzyme-linked immunosorbent assay technique was used for GDF15 estimation. **Results:** The results suggested that the serum levels of GDF15 and homeostatic model assessment for insulin resistance displayed a non-significant difference among studied groups ($P > 0.05$), whereas total cholesterol, high-density lipoprotein, triglyceride, adiponectin, and C-reactive protein appeared to have a significant difference among studied groups ($P < 0.05$). In contrast, the current study observed a non-significant ($P > 0.05$) association for GDF15 with all the clinical and biochemical parameters measured in this study. **Conclusion:** The study concluded that among the patients with CVD, the level of GDF15 revealed a non-significant relationship with the disease.

Keywords: Adiponectin, cardiovascular disease, C-reactive protein, growth differentiation factor 15

Introduction

Heart failure, stroke, ischemic heart disease, arterial disease, and other cardiac and vascular conditions comprising cardiovascular diseases (CVDs) remain the chief reasons for death in the world.[1]

Aging, gender, smoking habits, physical inactivity, extreme alcohol ingesting, fast food, higher body mass index (BMI), inherited tendency of CVD, hyperglycemia, hypertension, high blood cholesterol, air pollution, low educational status, and poor sleep are considered risk factors for heart disease.[2]

Usually, deaths by CVD are common and elevated in the developing world, whereas rates of death have come down in the developing world since the 1970s.[3]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_371_23

In 2015, 17.9 million subjects (32.1%) died because of CVDs.[4] Stroke and coronary artery disease are the reasons for 75% of CVD deaths in women and 80% of CVD deaths in men.[5]

Older adults represent the most affected subjects by CVD.[6] About 80 years is the usual age of death by coronary artery disease around the world, but it is about 68 years in the developing world.[7]

Address for correspondence: Dr. Hiba Resheed Behayaa, Department of Clinical Biochemistry, College of Medicine, University of Babylon, Babylon, Iraq.
E-mail: hibbarashed@gmail.com

Submission: 29-Mar-2023 **Accepted:** 20-Apr-2023 **Published:** 09-May-2024

How to cite this article: Behayaa HR, Ali ZA, Mohammed SB, Alqaysi SA. The relationship of growth differentiation factor 15 with some biochemical parameters in cardiovascular disease patients in Babylon City. Med J Babylon 2024;21:112-7.

Beforehand, macrophage inhibitory cytokine 1 is another name for growth differentiation factor 15 (GDF15), and represents the member of the transforming growth factor β family with similarity in amino acids from 15% to 29% compared with other members, proposing that it shows an exclusive living role.[8]

GDF15 is related to cachexia, CVD, and a lot of inflammatory diseases. GDF15 is very low in most tissues, except the placenta (in healthy conditions), which expresses GDF15 in high levels.[9]

The chief membrane of adipocytokines is adiponectin, with a normal value between 5 and 30 μg/mL. Adiponectin is secreted from adipocytes in three forms: trimer, hexamer, and a molecule of 18 monomers.[10]

Adipocyte size, adiposity, and insulin sensitivity are inversely associated with adiponectin.[11]

Skeletal muscle and liver are examples of insulin target tissues, so adiponectin stimulated the addition of phosphate group to adenosine monophosphate-activated protein kinase to activate the sensitivity of insulin.[12]

In all tissues of the body and before a reduction in the sensitivity of insulin, plasma adiponectin is decreased leading to independent diabetes, though adiponectin elevation acts as protective from type 2 diabetes mellitus (T2DM).[13]

For the risk of developing CVD, C-reactive protein (CRP) level might be used as a marker. This is because the progression of atherosclerosis is connected with inflammation within the vessel walls, which causes higher levels of CRP in atherosclerosis patients than in those without atherosclerosis.[14]

Yet, GDF15 may be distinctly elevated in the items of cardiovascular injury, like myocardial infarction, higher blood pressure, heart failure, and atherosclerosis.[9]

The expected effects of GDF15 might be dependent on the period of the illness.[15]

Materials and Methods

Study design

A case–control study is the design of revision.

Patients and control

Daniel's sample size formula was employed to determine the required sample size. A total of 80 Iraqi subjects took part in this study, with 40 of them having CVDs. Detailed clinical histories were obtained from all participants, including information on age, residence, tobacco use, and family history. Additionally, 40 healthy subjects were included as a control group. The age range of the participants in both groups was between 41 and 73 years.

Statistical analysis

Statistical analysis was conducted utilizing the Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS, IBM Company, Chicago, IL, USA). The results were expressed as mean ± SD, with significance determined for *P* values below 0.05.

Methods

1- The concentrations of GDF15, insulin, adiponectin, and high-sensitivity CRP in serum were measured using an enzyme-linked immunosorbent assay (ELISA) kit. This kit contains pre-coated monoclonal antibodies specific to GDF15, insulin, adiponectin, and CRP on the micro-ELISA plate.[16]
2- The glucose levels were determined using the enzymatic hexokinase method, whereas triglyceride and total cholesterol levels were assessed through enzymatic colorimetric methods. Additionally, the estimation of high-density lipoprotein cholesterol levels was conducted using the enzymatic method following phosphotungsten/magnesium precipitation.
3- The Tjokroprawiro method is used for homeostatic model assessment for insulin resistance (HOMA-IR) calculation.[17]

$$\text{HOMA-IR (mmol/l)} = \frac{G0 \times I0}{22.5},$$

where G0 and I0 are the fasting glucose and insulin levels, respectively.

4- BMI was estimated by weight (in kg) divided by the square of height (in m).[18]

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Square Height (m}^2\text{)}}.$$

Ethical approval

This study was dependent on the ethical principles that originated in the Declaration of Helsinki. Verbal and analytical approval of patients were taken before sample collection. The protocol and information of the study were reviewed and accepted by a local ethics committee according to document number 3 on May 4, 2022, to get this approval.

Results

The sample of the study groups was 80 adults designated into two categories.

1- adults with CVDs (n = 40); and
2- adults represent the control group (n = 40).

Age

The age discrepancy (as mean) verified significant diversity between control and patients with CVD is shown in Figure 1.

Gender

The prevalence of CVD based on sexual characteristics is shown in Figure 2. This study recognized that the CVD in males (80%) was larger than in females (20%).

Body mass index

The mean ± standard deviation [SD] of BMI for the control and CVD group was 26.24 ± 1.67 and 26.14 ± 2.64, respectively. No significant differences in BMI in patients and control group ($P > 0.05$) appeared in the studied groups as shown in Table 1.

Table 1 demonstrated the mean ± SD of clinical and biochemical parameters in the CVD group compared with the control group.

Table 2 shows the correlation coefficients between GDF15 and clinical and biochemical parameters in the patient group.

The linear regression analysis shows a non-significant link between GDF15 with all the clinical and biochemical parameters studied in the patients group as shown in Figures 3 and 4.

Discussion

Some risk factors of CVD, such as family history, age, or sex, are unchallengeable; however, changes in lifestyle, drug treatment, and social change represent modifiable risk factors of CVD.[19]

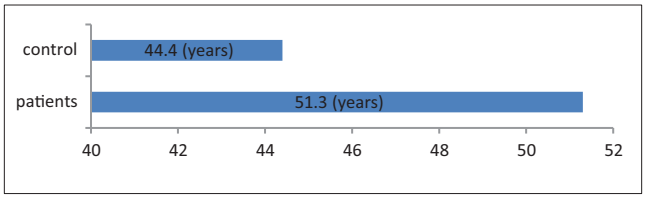

Figure 1: Age of studied groups as mean

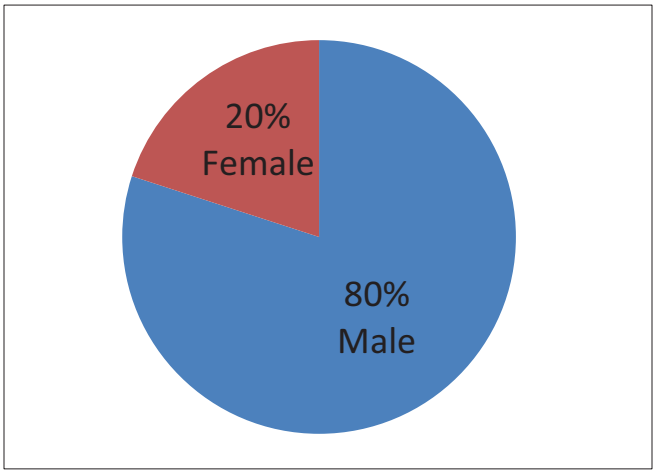

Figure 2: Distribution of groups studied according to gender

This study's findings align with the research outcomes. The average age of CVD patients and control subjects was 51.3 and 44.4 years, respectively. Additionally, there was a slight male predominance of 80% in this review, which was consistent with previous study.[20] "Man's problem" is the traditional name of CVD, because they found that in men. Age-standardized degrees of CVD were greater compared with women.

The links between GDF15 and coronary artery disease were described in other studies. Brown *et al.*[21] published the first paper in this field.

GDF15 was assessed in patients with CVD and the control group with non-significant variability between them ($P > 0.05$) [Table 1]. This result was in contrast with Li *et al.*[9] and Taddei and Virdis[22] they found an opposite result.

In individuals with good health, GDF15 is typically found at low levels throughout all organs. However, in times of

Table 1: Study sample characteristics

Parameters	Patients group $n = 20$ Mean± SD	Control group $n = 20$ Mean± SD	*P* value
Weight (kg)	76.75±9.04	78.0±3.49	$P = 0.568$
Height (cm)	1.7±0.05	1.71±0.04	$P = 0.364$
BMI (kg/m^2)	26.14±2.64	26.24±1.67	$P = 0.889$
Total cholesterol (mmol/L)	4.02±1.1	2.34±0.9	0.041
HDL-C (mmol/L)	1.08±0.59	2.3±0.47	0.05
Triglyceride (mmol/L)	1.63±1.2	0.91±1.3	0.01
Glucose (mmol/L)	6.7±2.2	4.4±1.9	0.063
Insulin (mIU/mL)	8.9±2.5	6.8±2.1	0.073
HOMA-IR	2.7±1.01	1.7±0.91	0.08
Adiponectin (µg/mL)	10.5±1.05	11.2±1.1	0.047
C-reactive protein (mg/L)	3.47±1.85	2.49±1.74	0.038
GDF15 (ng/L)	354.92±107.47	370.23±122.61	$P = 0.676$

SD: standard deviation, BMI: body mass index; HDL: high-density lipoprotein, HOMA-IR: homeostatic model assessment for insulin resistance; GDF15: growth differentiation factor 15

Table 2: Correlation coefficients between the studied parameters

Parameters	Correlation coefficients (r)	P value
BMI (kg/m2)	0.391	0.088
Age (years)	0.365	0.113
Total cholesterol (mmol/L)	0.018	0.325
HDL-C (mmol/L)	−0.009	0.651
Triglyceride (mmol/L)	−0.021	0.183
HOMA-IR	0.052	0.288
Adiponectin (µg/mL)	0.043	0.41
C-reactive protein (mg/L)	0.012	0.873

SD: standard deviation, BMI: body mass index; HDL: high-density lipoprotein, HOMA-IR: homeostatic model assessment for insulin resistance; GDF15: growth differentiation factor 15

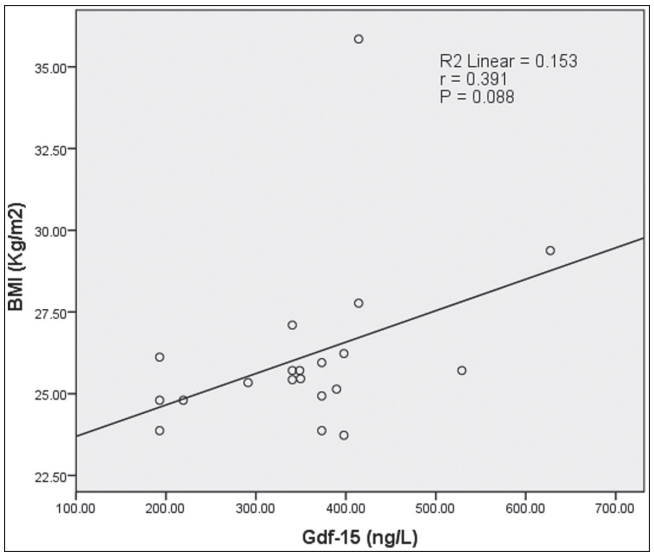

Figure 3: Correlation of GDF15 with BMI in patients group

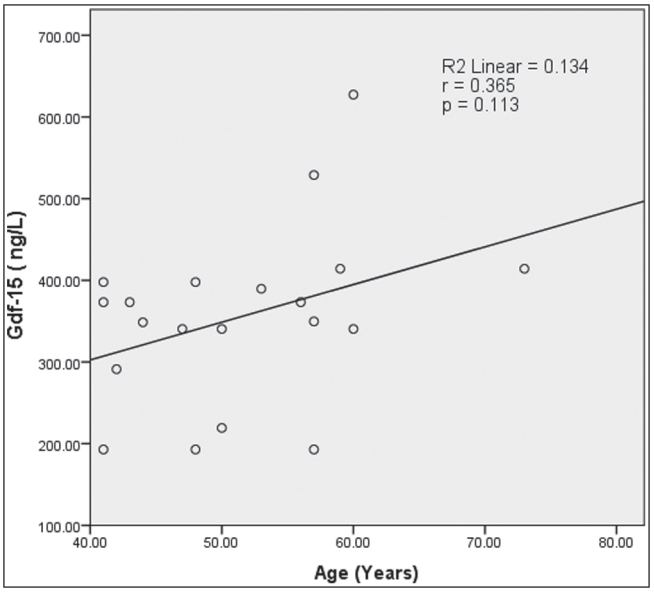

Figure 4: Correlation of GDF15 with age in patients group

stress during adulthood, elevated levels of GDF15 are notably present in the liver, kidney, heart, and lungs. At a cellular level, macrophages, endothelial cells, cardiac myocytes, and smooth muscle cells respond to stress signals like ischemia, pro-inflammatory cytokine stimulation, or oxidative stress by producing and releasing GDF15.[23]

Mature GDF15 (after secretion) quickly spreads into the circulation. The circulating levels of GDF15 are used to determine the progression of CVD, cancer, heart failure, and chronic renal and pulmonary embolism.[24] In addition, GDF15 was a strong analysis of cardiovascular, non-cardiovascular, and all-reason for death in healthy subjects and subjects with diseases.[25]

The result of the present study revealed significant differences in lipid profile between patients and control groups, which is inconsistent with some revisions that stated significantly decreased total cholesterol and low-density lipoprotein levels with increased GDF15 levels, may patients of these revisions have more physical activity than patients participated in our study.[26,27]

Fasting serum glucose and fasting insulin level are controlled by HOMA-IR, which is used for insulin resistance estimation, where insulin release is constant at some time, HOMA-IR normally as an analysis parameter in epidemiological studies.[28]

Insulin resistance in cardiovascular patients and healthy controls showed non-significant variation ($P > 0.05$) [Table 1]. This result was incompatible with Vila *et al*.[29] they stated elevated insulin resistance with elevated GDF15 levels.

The main characteristics of obesity are decreased levels of systematic inflammation, higher inflammatory cytokines levels, elevated adipokines, and acute phase proteins.[30]

The metabolic disorders progressed by obesity, CVD, and chronic disease.[31]

Adipose tissue expressed GDF15 both in humans and in mice, which produce fat cells both in pre and in differentiated forms.[32]

In addition, plasma levels of adiponectin in patients with obesity, T2DM, and heart disease institute low levels (in a previous study).[33]

In our research, the decrease in adiponectin levels surpassed the impact on insulin sensitivity in the human body. This suggests that adiponectin plays a crucial role in enhancing insulin sensitivity.[34]

Ding, *et al*.[32] revealed a positive correlation between GDF15 mRNA levels with adiponectin mRNA, and GDF15 elevated adiponectin secretion by differentiated human adipocytes.

CVDDespite the correlation between elevated CRP levels and future cardiovascular events, the routine measurement of CRP for assessing cardiovascular risk is not recommended due to its low accuracy, the absence of a definitive cut-off point for elevated CRP levels, and the lack of an absolute prognostic value. As a result, CRP's significance as a risk marker for CVD remains uncertain.[14] This explains the result of the present study that observed a significant elevation of CRP in cardiovascular patients.

In the current study, the interrelationships among plasma level of GDF15, age, and BMI in patients with CVD were found to be non-significant ($P > 0.05$) correlation, as in Figures 3 and 4, respectively.

Wang *et al*.[35] found that aging patients have a higher concentration of GDF15, due to aging accompanied by chronic inflammatory events. In addition, Pence *et al*.[36]

found that older adults have a higher concentration of GDF15 in plasma (about threefold) when compared with younger adults.

He *et al*.[37] revealed that high serum GDF15 levels were independent of BMI.

Behind the correlation of GDF15 plasma level with lipid profile, HOMA-IR, adiponectin, and CRP in patients with CVD was found to be a non-significant ($P > 0.05$) correlation, as in Table 2.

However, another previous study has shown that the relationship between the GDF15 level and cardiovascular actions might be explained by numerous mechanisms. In inflammation and oxidative stress, GDF15 is produced by several cells and plays a role in apoptosis, cellular repair, and proliferation. These living activities are crucial mechanisms of cardiovascular pathobiology.[38]

Conclusion

The study concluded that among cardiovascular patients, the level of GDF15 indicates a non-significant link between all the clinical and biochemical parameters measured in the present study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. J Am Coll Cardiol 2019;74:2529-32.
2. Zainal IG. Study the profile of some antioxidant markers in diabetic mellitus and non-diabetic mellitus patients with cardiovascular disease. Med J Babylon 2022;19:196-222.
3. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Murray CJ, *et al*. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: The Global Burden of Disease 2010 study. Circulation 2014;129:1483-92.
4. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459-544.
5. Shanthi M, Pekka P, Norrving B. Global Atlas on Cardiovascular Disease Prevention and Control. Vol. 1. World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization; 2011. p. 3-18.
6. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB. Heart disease and stroke statistics--2013 update: A report from the American Heart Association. Circulation 2013;127:6-245.
7. In Fuster V, Kelly BB. Epidemiology of Cardiovascular Disease. Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health. Vol. 2. Washington, DC: Institute of Medicine of the National Academies National Academies Press; 2010. p. 12-23.
8. Hsu LA, Wu S, Ming Jimmy Juang J, Chiang FT, Sheng Teng M, Feng Lin J. Growth differentiation factor 15 may predict mortality of peripheral and coronary artery diseases and correlate with their risk factors. Mediators Inflamm 2017;1:1-13.
9. Li M, Duan L, Lun Cai1 Y, Ying Li H, Chuan Hao B, Qiao Chen J, *et al*. Growth differentiation factor-15 is associated with cardiovascular outcomes in patients with coronary artery disease. Cardiovasc Diabetol 2020;19:1-12.
10. Hui X, Lam KS, Vanhoutte PM, Xu A. Adiponectin and cardiovascular health: An update. Br J Pharmacol 2012;165: 574-90.
11. Lara-Castro WT. Adiponectin and the metabolic syndrome: Mechanisms mediating risk for metabolic and cardiovascular disease. Curr Opin Lipidol 2007;18:263-70.
12. Buff PR, Dodds AC, Morrison CD, Whitley NC, McFadin EL, Daniel JA, *et al*. Leptin in horses: Tissue localization and relationship between peripheral concentrations of leptin and body condition. J Anim Sci 2002;80:2942-8.
13. Christine W. Plasma adiponectin, insulin sensitivity, and subclinical inflammation in women with prior gestational diabetes mellitus. Diabetes Care 2004;27:1721-7.
14. Sellmayer A, Limmert T, Hoffmann U. High sensitivity C-reactive protein in cardiovascular risk assessment. CRP mania or useful screening? Int Angiol 2003;22:15-23.
15. Wollert KC, Kempf T, Wallentin L. Growth differentiation factor 15 as a biomarker in cardiovascular disease. Clin Chem 2017;63:140-51.
16. Shanghai Yehua Biological Technology Co. Ltd. Human Growth Differentiation Factor 15 (GDF15), Insulin, Adiponectin and C-Reactive ELIZA Kits User Manual. 2020 Shanghai, China.
17. Elena P, Annunziata L, Maria GD. Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. Hypertension 2006;47:449-53.
18. Sturm R. Increases in morbid obesity in the USA: 2000–2005. Public Health 2007;121:492-6.
19. Azeez DM, Habeeb MA. Clinical characteristics and spectrum of cyanotic congenital heart diseases diagnosed in pediatric age group. Med J Babylon 2022;19:115-22
20. Woodward M. Cardiovascular disease and the female disadvantage. Int J Environ Res Public Health 1175;2019:1165.
21. Brown DA, Breit SN, Buring J. Concentration in plasma of macrophage inhibitory cytokine-1 and risk of cardiovascular events in women: A nested case-control study. Lancet 2002;359:2159-63.
22. Taddei S, Virdis A. Growth differentiation factor-15 and cardiovascular dysfunction and disease: Malefactor or innocent bystander? Eur Heart J 2010;31:1168-71.
23. Xu X, Li Z, Gao W. Growth differentiation factor 15 in cardiovascular diseases: From bench to bedside. Biomarkers 2011;16:466-75.
24. Wiklund FE, Bennet AM, Magnusson PK, Eriksson UK, Lindmark F, Wu L, *et al*. Macrophage inhibitory cytokine-1 (MIC-1/GDF15): A new marker of all-cause mortality. Aging Cell 2010;9:1057-64.
25. Lin JF, Wu S, Hsu SY. Growth-differentiation factor- 15 and major cardiac events. Am J Med Sci 2014;347:305-11.
26. Ho JE, Mahajan A, Chen MH. Clinical and genetic correlates of growth differentiation factor 15 in the community. Clin Chem 2012;58:1582-91.
27. Daniels LB, Clopton P, Laughlin GA, Maisel AS, Barrett-Connor E. Growth-differentiation factor-15 is a robust, independent predictor of 11-year mortality risk in community-dwelling older adults: The Rancho Bernardo study. Circulation 2011;123: 2101-10.
28. Ahsan S, Ahmed S, Mamji M, Ahmed S, Nauman K, Haque M. Role of adiponectin as a biomarker of prediabetes. Med Channel 2012;18:72-5
29. Vila G, Riedl M, Anderwald C, Resl M, Handisurya A, Clodi M, *et al*. The relationship between insulin resistance and the cardiovascular biomarker growth differentiation factor-15 in obese patients. Clin Chem 2011;57:309-16.

30. Al Mamoori AN, Ewadh MJ, Alqaysi SE. Leptin and adiponectin levels of asthmatic Iraqi children in Hilla province. Asian J Pharm Clin Res 2017;10:431-4.
31. Bollapragada MK, Shantaram M, Kumar RS. Obesity: Development, epidemiology, factors affecting, quantity, health hazards, management and natural treatment-A review. Int J Pharm Sci 2017;9:12-26.
32. Ding Q, Mracek T, Gonzalez-Muniesa P. Identification of macrophage inhibitory cytokine-1 in adipose tissue and it secretion as an adipokine by human adipocytes. Endocrinology 2009;150:1688-96.
33. Arita Y, Kihara S, Ouchi N. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 2000;257:79-83.
34. Aleidi S, Issa A, Bustanji H, Khalil M, Bustanji Y. Adiponectin serum levels correlate with insulin resistance in type 2 diabetic patients. Saudi Pharm J 2015;23:250-6.
35. Wang W, Tao Song X, Dai Chen Y, Yuan F, Xu F, Zhang M. Growth differentiation factor-15 is a prognostic marker in patients with intermediate coronary artery disease. J Geriatr Cardiol 2020;17: 210-6.
36. Pence BD, Yarbro JR, Emmons RS. Growth differentiation factor-15 is associated with age-related monocyte dysfunction. Aging Med (Milton) 2020;4:47-52.
37. He X, Su J, Ma X, Lu W, Zhu W, Wang Y, *et al*. The association between serum growth differentiation factor 15 levels and lower extremity atherosclerotic disease is independent of body mass index in type 2 diabetes. Cardiovasc Diabetol 2020;19:40-55.
38. Liu BH, Li YG, Liu JX, Zhao XJ, Jia Q, Liu CL, *et al*. Assessing inflammation in Chinese subjects with subtypes of heart failure: An observational study of the Chinese PLA Hospital Heart Failure Registry. J Geriatr Cardiol 2019;16:313-9.