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Fabkin Hormone As A Marker For Early Diagnosis Of Atherosclerosis And Its Relationship With Some Clinical Biochemical Variables

Raghad A. M. Hamoo[1]; Zena A. M. Al-Jawadi[2]
[1,2]University of Mosul, College of Science, Department of Chemistry, Iraq.
zena_aljawadi@uomosul.edu.iq[2]

abstract
Given that atherosclerosis is a very widespread disease worldwide and often leads to an increase in the number of deaths worldwide, this has provided an incentive to study its influencing factors with the aim of developing early diagnostic parameters for treatment and prevention. The study included measuring fabkin hormone (FABP4) concentrations and examining their effect on patients with atherosclerosis by collecting samples from two groups (the first included patients with atherosclerosis and the second included apparently healthy individuals who served as a control group). Its relationship with clinical biochemical variables was also investigated by measuring leptin hormone, in resistin hormone, proprotein convertase subtilisin/kexin type 9, high-sensitivity C-reactive protein (hs-CRP), creatine kinase CK-MB, and hormone-sensitive lipase (HSL). The antioxidant effect of vitamin E, calcium, and glucose was also measured. In addition, lipid profiles and the atherogenic index (AI) were measured. The effect of body mass index (BMI) was also studied for both groups, and the study found a significant relationship between FABP4 and other hormonal and biochemical variables in atherosclerosis. Finally, it was found that FABP4 levels were higher in patients compared to the control group, which may serve as a biomarker in the early stages of atherosclerosis.
Keywords: *Atherosclerosis, Fabkin hormone, C-reactive protein, Lipid profiles, Resistin hormone.*

INTRODUCTION

Atherosclerosis it is a process mean hardening, narrowing and loss of flexibility of arteries, in which the gradual buildup of plaque in the walls of arteries [1]. Plaque (atheroma) is a sticky material it consists of fat, cholesterol, calcium and other substances this make the artery wall thicker and more rigid, this thickening of the arteries" is usually a quite process in the early stages, you may not visible symptoms for a long time leading to artery narrows, this process gradually restricts the blood flow, it means the least amount of blood that nourishes the organs and tissues [2,3]. Atherosclerosis linked with Fabkin hormone (FABP4) it is a family of proteins hormone newly discovered, intracellular lipid-binding proteins of molecular weight (14-15) kilo dalton, known as intracellular small molecular lipid chaperones, that regulate lipid trafficking and responses in cells is, consist of 132 amino acids encoded by the human known as fatty acid binding proteins 4 (FABP4) gene is located at chromosome 8q21 [4]. hormone mainly expressed in adipose cells or macrophages, is related with arterial stiffness, dysmetabolic syndrome act as marker of atherosclerosis [5,6]. Also known as Adipocyte Fatty Acid Binding Proteins (AFABP4), this protein has also been termed adipocyte protein 2 (aP2), is an adipokine with a role in glucose metabolism [7]. The concentration of its circulating is higher compared with other Adipokines, AFABP increases lipolysis, circulating and impairs cardiomyocyte contractility [8]. Fatty acid binding protein-4 have the ability to bind to diverse hydrophobic molecules such as saturated, unsaturated long-chain fatty acids, eicosanoids, and other lipids, release from fat cells during lipid degradation [9]. This study aimed to determine the possibility of considering FABP4 as a marker for the early diagnosis of atherosclerosis.

MATERIALS AND METHODS:

Samples

Blood serum samples for both sexes and of different ages were collected from individuals with atherosclerosis. Serum samples were also collected from healthy individuals. The total number of samples was 90 for the patients and 90 for the control group. The samples were obtained from the Ministry of Health in Mosul/ Iraq, and the patient's condition was diagnosed by specialist doctors. After collecting samples, the clinical biochemical variables of both groups were measured using special kit for each variable of ELISA technology the variables are: Fabkin (FABP4), Leptin Hormone, Resistin Hormone, creatine kinase (CK-MB), high-sensitivity C-reactive protein (hs-CRP), Hormone-sensitive lipase (HSL), and Vit. E. Also the spectrophotometry technic was used for variables:

Calcium (Ca^{+2}), Glucose, and Lipid profile**.** Both the atherogenic index (AI) was calculated according to special mathematical equation by dividing triglycerides/ HDL-C. Also, the BMI (kg/ m^2) = Weight / $Height^2$

Ethical approval:

The study was conducted under all applicable national legislation, institutional policy, and the Helsinki Declaration ideals, and was approved by the author's institutional review board No. 59675 at 15-12-2024.

Statistical analysis:

The results were statistically analyzed using SPSS version (27), the * mean: *Significant difference at $p<0.05$, **Significant difference at $p<0.01$, ***Significant difference at $p<0.001$, and N.S. = No statistically significant difference

During this study, the normal range of FABP4 hormone was determined for the first time for healthy males and females, as shown in Table (1).

RESULTS:

The normal range of the FABP4 hormone was determined for the first time through this study by measuring its concentration in healthy people, as shown in Table (1). The range was different for males than it is for females as seen in the Table (1).

Table (1): Determination of the normal level of FABP4 hormone in healthy

Normal Concentration of FABP4 Hormone in Human	
Male Normal Range (pg/ml)	435.2 – 541.6
Female Normal Range (pg/ml)	412.64 – 556.72

Table (2): Level of clinical variables for males' atherosclerosis disease compared to the control group:

Biochemical Variables	**Male Control Group (Mean±SD)**	**Male Atherosclerosis Disease (Mean±SD)**	**p-value**
FABP4 (pg /ml)	488.4 ± 53.2	2596.5 ± 84.2	>0.001
LEP (pg/ml)	910.8 ± 35.6	2387± 39.7	>0.001***
Resistin Hormone (ng/ml)	3.8 ± 0.36	6.4 ± 0.5	0.02
PCSK9 (ng/ml)	519 ± 90	1860 ± 86	>0.001***
CK-MB (pg/ml)	43.8 ± 6.7	43.2 ± 7.7	0.1(n.s)
hs-CRP (mg/L)	1.1 ± 0.3	3.4 ± 0.7	0.04
HSL (pg/ml)	2066 ± 31.2	2353 ± 79.33	0.003**
Vit.E (µg/ml)	18.7 ± 3.7	4.6 ± 0.6	>0.001***
Ca+2 (mg/dl)	8.6 ± 0.13	8.79 ± 0.36	0.1(n.s)
Glu (mg/dl)	90.86 ± 5.46	94.43 ± 7.08	0.09 (n.s)

Table (3): Level of lipid profile for males' atherosclerosis disease compared to the control group:

Clinical Variables	**Male Control Group (Mean±SD)**	**Male Atherosclerosis Disease (Mean±SD)**	**p-value**
CHO (mg/dl)	130.8 ± 25.4	233.04 ± 18.5	>0.001***

TG (mg/dl)	143.4 ± 7.5	254.33 ± 13.7	>0.001***
HDL-C (mg/dl)	41.5 ± 1.01	39.26 ± 5.3	0.09 (n.s)
LDL-C (mg/dl)	58.93 ± 6.36	154.3 ± 16.6	>0.001***
VLDL (mg/dl)	28.72 ± 1.5	49.40 ± 9.5	0.004**
AI	3.45 ± 0.16	5.75 ± 0.45	>0.001***
BMI (Kg/m2)	23.63 ± 0.92	24.6 ± 1.36	0.04

Table (4): Level of clinical variables for females' atherosclerosis disease compared to the control group:

Clinical Variables	**Female Control Group (Mean±SD)**	**Female Atherosclerosis Disease (Mean±SD)**	**p-value**
FABP4 (pg/ml)	484.68 ± 72.04	2734.22 ±74.8	>0.001***
LEP (pg/ml)	947.23 ± 65.4	2613.5 ± 84.7	>0.001***
Resistin Hormone (ng/ml)	4.9 ± 0.4	8.2± 0.8	0.01
PCSK9 (ng/ml)	596.4 ± 65.37	1507.12± 71.8	>0.001***
CK-MB (pg/ml)	40.66 ± 6.8	43.9 ± 4.3	0.06(n.s)
hs-CRP (mg/L)	1.3 ± 0.4	3.9 ± 1.0	0.03
HSL (pg/ml)	1953.2 ± 77.25	2364.4 ± 52.9	0.002**
Vit.E (µg/ml)	21.42 ± 3.6	4.6 ± 0.77	>0.001***
Ca^{+2} (mg/dl)	8.65 ± 0.16	8.58 ± 0.38	0.4 (n.s)
Glu (mg/dl)	92.9 ± 4.7	92.1 ± 3.9	0.4 (n.s)

Table (5): Level of lipid profile for females' atherosclerosis disease compared to the control group:

Clinical Variables	**Female Control Group (Mean±SD)**	**Female Atherosclerosis Disease (Mean±SD)**	**p-value**
CHO (mg/dl)	131.6 ± 29.2	234.2 ± 25.3	>0.001***
TG (mg/dl)	145.0 ± 6.2	220.9 ± 9.8	>0.001***
HDL-C (mg/dl)	41.75 ± 1.06	41.3 ± 3.4	0.5 (n.s)
LDL-C (mg/dl)	58.95 ± 14.36	153.5 ± 17.3	>0.001***
VLDL (mg/dl)	28.88 ± 1.36	45.5 ± 8.0	>0.001***
AI	3.45 ± 0.20	5.7 ± 0.7	>0.001***
BMI (Kg/m^2)	23.0 ± 1.5	25.3 + 1.23	0.002**

Table (6): Correlation of FABP4 hormone with other clinical variables in atherosclerosis disease

Clinical Variables	Pearson Correlation	P-value
LEP (pg/ml)	0.741	<0.001***
Resistin Hormone (ng/ml)	0.32	0.02
PCSK9 (ng/ml)	0.654	<0.001***
CK-MB (pg/ml)	0.09	0.4
hs-CRP (mg/L)	0.827	<0.001***
HSL (pg/ml)	0.842	<0.001***
Vit.E (µg/ml)	-0.827	<0.001***
Ca^{+2} (mg/dl)	0.242	0.08(n.s)
Glu (mg/dl)	0.125	0.38(n.s)

Table (7): Correlation of FABP4 hormone with lipid profile in atherosclerosis disease:

Clinical Variables	Pearson Correlation	P-value
CHO (mg/dl)	0.774	<0.001***
TG (mg/dl)	0.636	<0.001***
HDL-C (mg/dl)	-0.226	0.10 (n.s)
LDL-C (mg/dl)	0.766	<0.001***
VLDL (mg/dl)	0.732	<0.001***
AI	0.821	<0.001***
BMI (Kg/m^2)	0.504	<0.001***

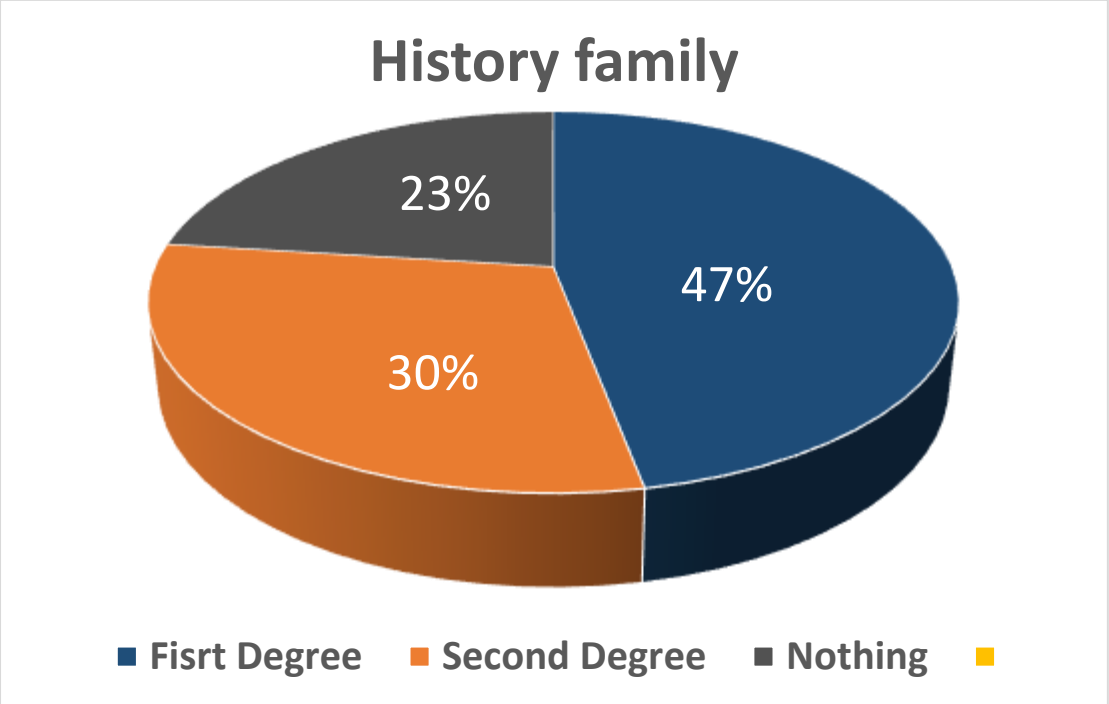

Figure (1): Family history of atherosclerosis patients.

DISCUSSION:

The results showed in Table (2) a significant increase in the levels of the hormone FABP4 for male patients with atherosclerosis compared to the control group at $p<0.001$, the high level of FABP4 in men with atherosclerosis linked with dyslipidemia, oxidative stress, inflammation and endothelial dysfunction, theses may contribute to atherosclerosis development [10,11].

Also, there was a significant increase in leptin levels in patients for male with atherosclerosis at $p<0.001$ compared to the control group, this is due to the role of the leptin hormone regulate lipid metabolism and hyperleptinemia have the ability to stimulate smooth muscle cell proliferation, platelet activation and induce inflammation and developed arterial stiffness [12,13].

A slight increase in Resistin hormone level was observed in male patients compared to the control group, but this slight increase was found to be within the normal range, is due to Resistin hormone can induce a major inflammatory response in vascular promotes inflammation by activating the production of pro-inflammatory cytokines to aggravation of atherosclerosis by increasing LDL-C uptake in macrophages [14]. The results in the same Table showed a significant increase in the level of PCSK9 in male patients at $p<0.001$ compared to the control group, PCSK9 levels were found a significant difference to be higher in males patients showed in Table (2) than females patients that showed in Table (4), according to the findings of the current study LDL-C levels were found to be higher in males than in females as shown in Tables (3, and 5), serum LDL-C levels are linked to PCSK-9 levels, as this protein is linked to its effect on LDL-C receptors, thus causing higher PCSK9 levels in males compared to females, high LDL-C may be due to genetic effects as well as lifestyle factors [15,16].

Samples were taken from patients with atherosclerosis in the early stages before the occurrence of a heart attack or infarction in skeletal muscle heart, so the results showed the appearance of normal levels of CK MB for male with atherosclerosis, and the appearance of a slight increase in CK MB levels at p 0.1 but within the normal range compared with control group, shown in Tables (2), this is consistent with other study [17,18,19]. Also, in Tables (2) showed that the hs-CRP level was higher in male patients with atherosclerosis at $p<0.001$ compared with control group, hsCRP is a widely used marker of systemic low-grade inflammation and is associated with the occurrence of ASCVD events [20,21].

A significant increase in the HSL level was observed in patients for male compared to the control group indicated in Table (2) at $p<0.003$, the reason for the increase in the HSL level with atherosclerosis is due to the increase in the basic substance triglycerides on which the enzyme works and the increase in the production of free fatty acids that contribute to the development of the disease, the overexpression of HSL in the liver is associated with over production of lipids and cholesterols in circulation [3,22].

When studying the effect of low levels of vitamin E for males of atherosclerosis was a significant decrease at $p<0.001$compared with control , It was found that the vitamin E level in males was lower than in females with patients as shown in Tables (2, and 4), the reason may be attributed to the presence of free radicals in males at a higher rate and it leads to increased availability of oxidized LDL-C due to smoking and metabolic activity that causes the consumption of vitamin E at a higher rate in males to neutralize the free radicals present in the body compared to females [23,24]. Table (3) showed total cholesterol, TG, and LDL-C increases levels in male for atherosclerosis patients compared with control at $p>0.001$ respectively, their elevation leads to the accumulation of lipids in the arteries, which narrows them and restricts blood flow [25,26]. In addition, dysregulation of triglycerides important lead to the development of atherosclerosis and pass through the artery endothelium and kept in the artery with suffer oxidative modification [27]. There is a significant increase in the level of TG in males compared to women, these are patients with atherosclerosis as shown in Tables (3, and 5) due to genetic effect and life style of male that causes these cases it was found that [28,29], while increases of VLDL-C level in male of atherosclerosis compared with control group as shown in Table (3) this is identical to other study [30].

The atherosclerosis index (AI) was found to be higher in male atherosclerosis patients compared to the control group as shown in Tables (3) This may be due to increased levels of triglycerides, which lead to a higher risk of atherosclerosis in males compared to the control group. Second reason may be due the smoking also plays a role in the disease in male [31]. In the same table BMI was found in male patients was relatively higher compared to control group, may be because the relationship between arterial stiffness and BMI is influenced by variations in the distribution of fat across the sexes due to increased visceral fat as well as metabolic dysfunction in males [32,33].

Table (4) illustrated that there is a significant increase in FABP4 levels in patients for female with atherosclerosis at p<0.001 compared to the control group, there are significant difference the higher FABP-4 levels in women than in men due to sex hormones might possibly play a role ,after menopause, women experience a notable rise in cardiovascular risk due to lower estrogen levels lead stiffness of the arteries by causes linked to increased visceral fat accumulation and chronic inflammation, both of which result in a greater occurrence of central obesity and dyslipidemia in women and women's with larger levels of adipose tissue, or body fat, which is the primary source of plasma FABP-4 moreover ,in addition [34]. There are significant difference increases in level of leptin in female of patients compared with control group, the higher leptin levels in women than in men may be explained by the conclusion of the current study due to the fact that leptin is a protein hormone secreted from adipose tissue and the presence of a greater amount of adipose tissue in women than in men, in addition female sex hormones affect many factors that regulate the elasticity of the blood vessel wall.

In Table (4) showed a higher significant difference in resistin hormone level in women patients than the control at p 0.01but within normal range of resistin, because hs-CRP in this study in female more than in male, and increased inflammatory responses contributing to endothelial dysfunction as a result of an imbalance in the distribution and level of fats by increasing BMI in female compared with male as shown in Tables (5).

CK-MB levels were found to be higher but not significant within the normal range in women patients than control group, in the early stages of atherosclerosis, as shown in Tables (4). may be due to the influence of hormonal factors in women compared to men. Also, the hs-CRP level was higher in female patients with atherosclerosis compared with control group, also, the hs-CRP level of females was higher compared to males in patients with atherosclerosis, these results indicate a significant difference in sex that there are higher inflammatory factors in females than in males, due to estrogen suppresses pro-inflammatory cytokine production and the decreases estrogen levels may be contributed to this case [35].

The HSL a significant increase in female compared to the control group, elevated HSL levels related to metabolic disorders and dyslipidemia may contribute to increased risk of atherosclerosis indicated in Table (4). Also, the level of the HSL was found to be higher in women than in men as Tables (2, and 4), according to the conclusions of the current study it was observed that the level of triglycerides increased in women to a relatively lower level compared to men due to the increased effectiveness and level of the HSL enzyme, which contributed to the initiation and decomposition of triglycerides, which are considered basic materials for the HSL enzyme. Finally: Table (4) showed a significant decrease in the level of the antioxidant vitamin E in female with atherosclerosis at p<0.001 compared to the control group due to the vitamin E has a very important role in protecting fats from oxidation by inhibiting the oxidized LDL-C and reducing its absorption in the walls of blood vessels oxidized LDL-C when the level of the vitamin in the blood serum decreases, it causes an increase in the oxidation of bad fats LDL-C is rapidly absorbed by macrophages, stimulating the inflammatory response of blood vessels, and accumulation of oxidized fats in the vessel walls and their deposition the formation of foam cells, and the development of atherosclerotic plaques, so vitamin E protects the arteries from atherosclerosis by interrupting the oxidative chain of the arterial lining [36].

There was a significant increase in total cholesterol levels in females of patients compared to control at p<0.001, as Tables (5) this is due to BMI of female higher than male in patients with atherosclerosis [37]. A significant increase in the level of triglycerides was observed in patients for female with atherosclerosis compared to the control group at p<0.001, as shown in Tables (5). The reason for the increase in the level of triglycerides is due to the high level of TG linked to pathogenesis via vascular endothelium dysfunction association with atherosclerotic cardiovascular disease (ASCVD) [35]. The LDL-C, VLDL-C levels increase in female patients compared with control at p<0.001, the AI% for female of atherosclerosis patients higher than control group shown in Table (5) It was found that there was an increase in the (AI) in patients compared to the control group [39], which indicates the extent of the risk of atherosclerosis and taking the necessary precautions to treat the disease. Atherogenic index (AI) a marker of atherosclerosis of plasma Atherogenicity because of its strong and positive relationship with cholesterol esterification rates, lipoprotein particle size, and remnant lipoproteinemia [40]. It was found in Table (5) that there was an increase in the BMI in patients for female compared to the control group. This indicates the role of excess weight in the development of atherosclerosis, which requires taking the necessary precautions and reducing the intake of fatty foods containing saturated fats and long-chain unsaturated fats, which contribute to the development of the disease. obesity can exacerbate the progression of AS through various mechanisms, including the secretion of pro-inflammatory adipokines and the accumulation of visceral fat,

which is closely associated with cardiovascular risk [41]. For the general population, body mass index (BMI) ≥25 kg/m2 is considered overweight; BMI ≥30 kg/m2 is considered obesity [42]. It was found that the BMI of females was relatively higher compared to males in patients with atherosclerosis [43], as shown in Tables (3, 5). research indicates that the relationship between arterial stiffness and BMI is influenced by variations in the distribution of fat across the sexes, the strongest correlations between arterial stiffness and male waist size and waist-to-height ratio were found. Conversely, BMI was more closely linked to elevated arterial stiffness in women [44].

Table (6) shows a direct correlation between FABP4 and all hormonal and enzyme variables, and its correlation with leptin was found at a p-value <0.001, given their important role in regulating lipid metabolism. FABP4 and leptin are positively correlated, especially with obesity, suggesting that they may share a pathway regulating inflammation and energy balance. Both resistin, hs-CRP and HSL affect endothelial cell function and play a role in the pathogenesis of atherosclerosis by causing oxidative stress and inflammation.

Its correlation with PCSK9 is also direct, as PCSK9 contributes to the degradation of LDL-C receptors, leading to increased lipid profile, which promotes increased FABP4 secretion, which in turn increases lipolysis, CK-MB not correlate with FABP4 levels in early stage of atherosclerosis while rise when blood vessels stiffen and lose elasticity throw progress of atherosclerosis. There for CK-MB levels gradually increase, reaching high levels during vascular and myocardial injury as atherosclerosis progresses.

The negative correlation between levels of vitamin E and FABP4, in atherosclerosis patients at p<0.001 due to the role of vitamin E as anti-inflammatory by reducing neutrophil chemotaxis, antioxidant effects and anti-coagulant activities and inhibiting platelet aggregation, while FABP4 is pro-inflammatory and expression is upregulated by oxidative stress that linked to cardiovascular disease.

Table (7) showed a strong positive correlation between FABP4 and cholesterol, TG, LDL-C, VLDL, AI%, and BMI. This is due to FABP4 being overexpressed and secreted into the bloodstream, which is typically associated with elevated total cholesterol and lipid disorders. This is also due to elevated triglycerides, which increase the risk of atherosclerosis through lipolysis and the free fatty acids produced by triglyceride breakdown. These free fatty acids bind to the free fatty acids transported by FABP4 and accumulate in the arteries, triggering inflammatory reactions that accelerate atherosclerosis. Since FABP4 is pro-inflammatory and is often elevated in obesity and metabolic syndrome, HDL-C has an anti-inflammatory role, helping to remove cholesterol from macrophages. There is a direct relationship between LDL-C and FABP4 levels. LDL-C transports cholesterol from the liver to peripheral tissues. Since FABP4 is primarily found in adipocytes and macrophages, it plays an important role in lipid metabolism, binding to fatty acids and transporting them within the cells. High levels of FABP4 lead to atherosclerosis. The VLDL-C is also a key player in lipid metabolism and is predominantly released by adipocytes. Increased levels of circulating triglycerides, an important component of VLDL particles, have been independently linked to elevated FABP4 concentrations. Based on this association, elevated VLDL-C levels may be a result of elevated FABP4 levels, which may affect lipid levels and increase the risk of atherosclerosis. Finally, a direct correlation has been found between AI% and obesity with FABP4, given that both are associated with dyslipidemia. These indices may be useful in assessing cardiovascular disease risk.

Figure (1) shows the incidence rates in terms of their occurrence among first- and second-degree relatives, indicating the role of genetic factors in the development of atherosclerosis [45].

CONCLUSION

The study showed that Fabp4 is an indication of the early stages of atherosclerosis, and that this indicator can be used to take the necessary precautions to prevent the development of atherosclerosis. And providing a healthier life for individuals and society and thus achieve one of the sustainable development goals and is the third goal related to good health.

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