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# The sensitivity of heparin-binding growth factor as a diagnostic marker for atherosclerosis

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**Abstract**

The study aimed to evaluate the level of heparin-binding growth factor (HBGF) as a sensitive ,arker for atherosclerosis. study included collecting 90 serum samples (60 samples for patients with atherosclerosis and 30 samples from healthy individuals as a control group) to evaluate the level of HBGF, calcium, and lipid profile in patients with atherosclerosis. The patients samples were collected from the Ibn Al-Bitar Cardiac Surgery Center in Baghdad Governorate for the period from 1/11/2023 to 1/1/2024. The levels of HBGF, calcium, and lipid profile'[total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)}. The results showed a significant increase in the levels of HBGF, TC, TG, LDL-C and calcium, with a significant decrease in HDL-C level in the patient s group as compared to the control.Receiver-operating characteristic curve analysis showed that the AUC for the HBGF is outstanding, with excellent sensitivity, in addition to the excellent accuracy for cholesterol LDL-C and HDL-C in the diagnosis of the disease. From the results, we can conclude that HBGF is a sensitive parameter for diagnosing atherosclerosis with a high sensitivity.

## Introduction

Atherosclerosis is a chronic inflammatory arteritis, and it is the main cause of cardiovascular disease (CVD). In atherosclerosis, the arteries gradually narrow and thicken, preventing blood flow to the tissues and organs because the arteries become stiff and inelastic [1]. Lipids and calcium accumulation in atherosclerosis. In addition to multiplying fibrous tissue and smooth muscle cells, phagocytic cells move from the tissue to the blood vessels and arteries. This causes inflammation. However, in some cases, macrophage deposition occurs, and in this case, the process becomes more complex, so these deposits and collections of cells and other materials are known as plaques [2,3]. These plaques impede the passage of blood, and thus, there is a weakness in tissue perfusion due to the narrowing of the arteries [4]. As soon as stress occurs in the vessel wall, it will affect the blood vessels, which will be more susceptible to atherosclerosis [5].They will lose their ability to maintain balance, so the vessel

walls become vulnerable to narrowing, increased permeability leading to fat infiltration, activation of platelets, and oxidative stress, and this contributes to stimulating the immune response, which leads us to inflammation, which plays a vital role in atherosclerosis [6,7]. It was found that endothelial dysfunction plays a vital role in the final stages of atherosclerosis, as it contributes to the plaque's development and the plaque's rupture, which causes devastating consequences [7].

Midkine (MK) is a heparin-binding growth factor (HBGF) act as cytokine [8,9]. HBGF is involved in many biological processes, such as initiating and directing the cellular differentiation of T cells and B cells during inflammatory processes, protecting cells from cell death (as seen in atherosclerosis), and managing oxidative stress [10]. It can also be expressed in many cells, perhaps the most prominent of which are megakaryocytes and cells lining blood vessels [11]. HBGF exerts a procoagulant effect through many changes in the pathophysiological processes involved in the process of atherosclerosis, including the accumulation of fats in macrophages, its effect on blood vessels, its role in insulin resistance, and many other factors contributing to the development of atherosclerosis [12]. It has also been shown that in patients with chronic heart failure, their HBGF levels increased twofold, which is an indication that high levels of HBGF are associated with functional dysfunction [13].

Dyslipidemia is one of the main risk factors for cardiovascular disease [14]. Researchers have found that low-density lipoprotein cholesterol (LDL-C) is a major cause of heart disease because it accumulates cholesterol in the artery walls. This buildup of cholesterol leads to a several of heart problems, including atherosclerosis [15]. Moreover, when LDL-C undergoes an oxidation process by free radicals due to oxidative stress, it affects the development of atherosclerosis [16]. Atherosclerosis represents a sequential event and interaction between high levels of LDL with both immune cells, differentiated mononuclear cells, and non-immune cells, which are smooth muscle cells. This process culminates in the secretion of growth factors and adhesion molecules, leading to foam cell formation and ultimately the development of an atherosclerotic plaque [17]. So, the study aimed to evaluate the level of HBGF as a sensitive marker for atherosclerosis .

**Subject And Methods**

Study design: A total of 90 blood samples were collected from male participants aged 35-70. The cohort comprised 60 patients diagnosed with atherosclerosis by a specialist and 30 healthy individuals serving as a control group. Blood samples were obtained from the Ibn Al-Bitar Cardiac Surgery Center in Baghdad Governorate between October 1 and December 1, 2023.

The study included estimating the concentration of HBGF using the sandwich method [enzyme-linked immunosorbent assay (ELISA) kit provided by the Chinese company SUNLONG]. The serum calcium concentration was also estimated using a colorimetric method kit[18] provided by the LiNEAR company/ Spanish. The concentration of the lipid profile(cholesterol, triglycerides-TG, high-density lipoproteins cholesterol-HDL-C) were determined using the enzymatic colorimetric methods kits provided by LiNEAR company / Spanishm while the LDL-C was calculated according to the following equation [19]:

*Conc of LDL-C (mg/dl) = Total cholesterol – HDL-C – VLDL*

**Statistical analysis**

The mean ± standard deviation (SD) was used to express the level of biochemical parameters under study between the two groups (patients and control) using the statistical analysis program SPSS. The difference between the two groups was also used based on the T-test at the probability level P ≥0.0001, and the receiver operating characteristic curve-ROC curve was calculated. For the parameters (HBGF, Ca, TC, TG, HDL, LDL) for the two groups. The ROC curve [ROC-MedCalc. V.20] was employed to estimate the accuracy, sensitivity, and specificity for parameters under investigation between patients and control at (p≤ 0.01) as statistical significance.

**Results and Discussion**

The level of HBGF and calcium were estimated in the sera of patients with atherosclerosis group and healthy controls, and the results are shown in Table 1.

**Table 1**: The levels of HBGF(mean±SD) in patients and the control groups

| Parameters | Mean±SD | | P≤ |
|---|---|---|---|
| | Control | Patients | |
| HBGF(pg/ml) | 28.665±4.649 | 105.493±29.227 | 0.01 |
| Calcium (mg/dl) | 9.401±1.571 | 10.542±1.117 | 0.01 |

Table 1 shows that the mean ± SD of HBGF level in the patient group was (105.493±29.227) pg/ml, while the control group had (28.665±4.649) pg/ml. The results of the current study showed that the level of HBGF significantly elevated (P≤0.05) in patients group. as compared to the control group, Figure 1.

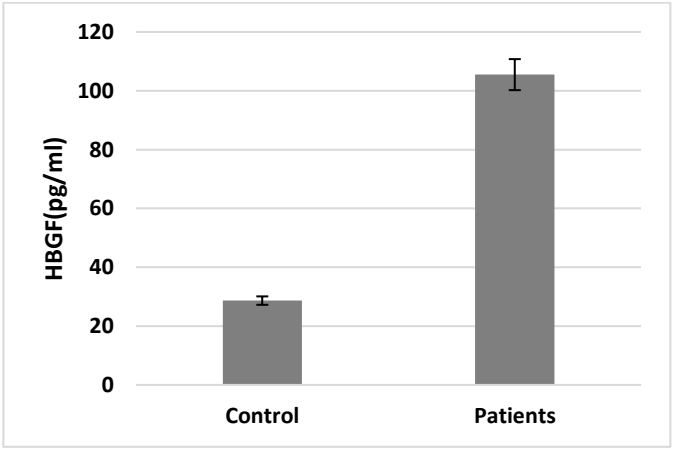



**Figure 1:** Mean of serum HBGF level in patients and control groups

The current study found that the level of HBGF is significantly higher in the sera of people who have atherosclerosis. This may be because HBGF plays a key role in supporting the growth and proliferation of the vascular smooth muscle. This migration of the smooth cells to the site of damage in the vessels, promotes plaque formation [20,10]. HBGF also promotes the

accumulation of lipids, which in turn represents a cause of injury, it is therefore closely correlated with the development of atherosclerotic plaques [21,22]. Alkado and Al-Helaly showed that the level of HBGF significantly increased in the sera of patients with myocardial infarction [23]. A study was found that proves HBGF relationship to the formation of new blood vessels from injured blood vessels in patients with cardiovascular disease [24]. Our study is consistent with a study conducted on 107 samples of patients with atherosclerosis, and the results showed that MK levels are high in patients compared to the control group, and that its levels are higher in males than females, so MK is considered a good indicator of atherosclerosis [25]. Another study also showed that high levels of MK were related to risk factors that cause atherosclerosis, such as high blood pressure, and this is due to it being linked to the proliferation of vascular smooth muscles, as well as the generation of blood vessels from blood vessels affected by atherosclerosis [26].

Table 1 shows the serum level ( mean ± SD) of calcium in patients was (10.542±1.117) mg/dL, while it was (9.401±1.571) in the control group. The results indicate that the level of calcium was significantly elevated in the patient's sera compared with the control group (Figure 2).

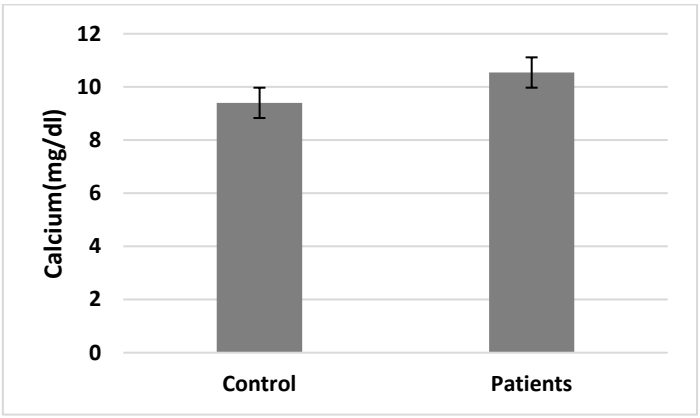



**Figure 2:** Mean serum calcium level in patients and control groups

Calcium is one of the most important minerals in the body, and it plays an important role in cellular physiological processes for the body such as blood clotting, nerve conduction, muscle contraction, and building bones and teeth [27]. The high level of calcium correlates with insulin resistance, metabolic syndrome, and dyslipidemia [28] .This elevation may be due to the continued use of calcium supplements, which may increase the risk of developing blood and vascular diseases [29]. The results of the present study agree with the results of the study of Park and Lee [30].The blood calcium is linked to cardiovascular disease and atherosclerosis where calcium accumulation occurs in the atherosclerotic plaque, which is a prominent feature of atherosclerotic plaque. The accumulation usually occurs in the plaque inside the necrotic core and later leads to the emergence of clinical complications such as blood clotting [31].

The levels of lipids profile, including (TC, TG, HDL-C, LDL-C,) were also estimated in the sera of males with atherosclerosis and healthy individuals as a control group, as in **Table 2.**

**Table 2**: The levels of lipid profile (mean±SD) in patients and the control groups

| Parameters | Mean±SD | | p≤ |
|---|---|---|---|
| | Control | Patients | |
| TC(mg/dl) | 201.136±6.432 | 206.072±3.568 | 0.01 |
| TG(mg/dl) | 98.861±6.298 | 130.509±24.210 | 0.01 |
| HDL-C(mg/dl) | 41.652±4.018 | 32.714±3.129 | 0.01 |
| LDL-C(mg/dl) | 139.711±8.535 | 147.256±6.145 | 0.01 |

Table 2 showed that the mean ± SD of cholesterol level was (206.072±3.568) mg/dL in the patient and (201.136±6.432) mg/dL in the control groups. The results shown that cholesterol level increased significantly (P≤0.01) in the patient group compared to the control group, Figure 3.

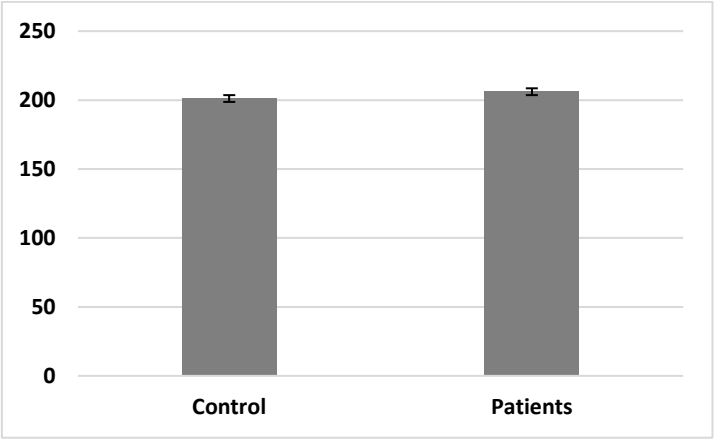



**Figure 3:** Mean of cholesterol level in patients and control groups

Many studies have indicated that abnormal levels of cholesterol that correlated with cardiovascular diseases, in which high level of cholesterol is associated with the risk of CVD, and that these high levels are often accompanied by an increase in the level of LDL-C, which increase motality rate between CVD patients [32].Numerous studies have shown that high levels of cholesterol increase the risk of developing cardiovascular diseases (CVD), and that these high levels frequently coincide with an increase in the level of LDL-C, which raises the motility rate in CVD patients [33]. Other studies have also clarified its role as a risk factor for coronary heart disease and how it has a strong effect on men compared to women based on its high levels [34], This correlation was confirmed by the study of John, *et al* [35], that was conducted on 500 people with coronary heart disease and measured their lipids levels. It was found that the cholesterol level showed a significant increase, with increase the level of TG, LDL-C, and with low level of HDL-C, that is indicates the role of cholesterol in the occurrence and development of the disease.

From Table 2 it is clear that the mean ± SD of the TG level was (130.509±24.210) mg/dL in the patient group, and (98.861±6.298) mg/dL in the control group. The results indicate that the triglyceride level showed a significant increase (P≤0.01) in patients group as compared to the control group, as shown in Figure 4.

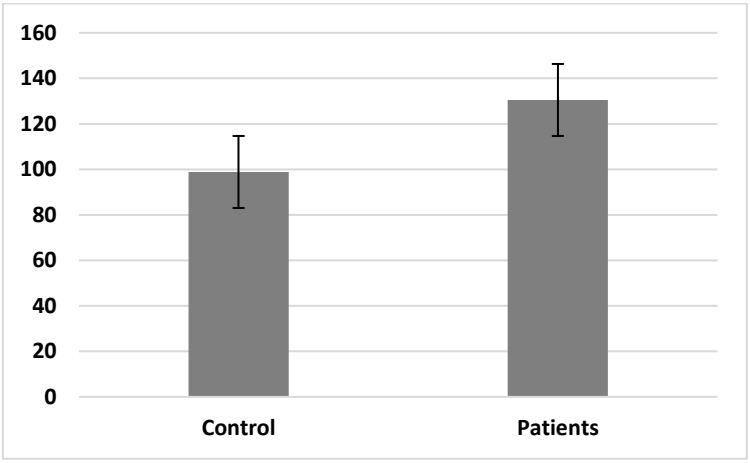



**Figure 4**: Mean level of TG in the sera of the patients and control groups.

The correlation between high TG level and atherosclerosis has been demonstrated in many studies, in which epidemiological evidence supports this correlation and most data indicate their role in causing CVD[36]. Hypertriglyceridemia is also considered a major contributor to the risk of developing Atherosclerotic Cardiovascular Disease (ASCVD) [37].

Table 2 showed that the mean ± SD of high-density lipoprotein cholesterol level was (32.714±3.129) mg/dL in the patient and (41.652±4.018) mg/dL in the control groups. The results showed a significant decrease (P≤0.01) in the level of HDL-C in sera of the patient group compared to the control group. Figure 5

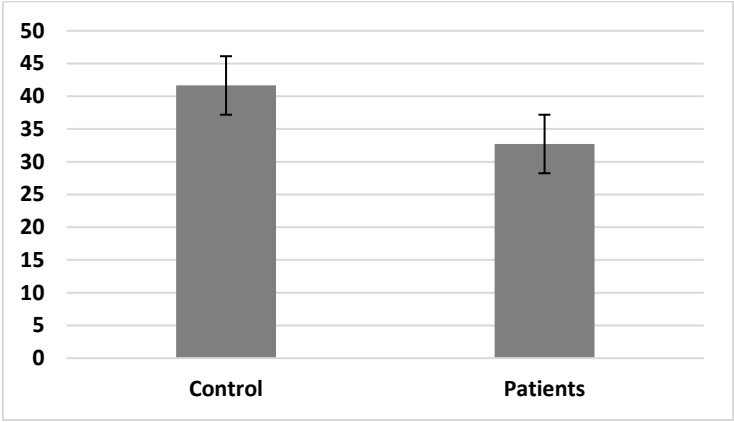



**Figure 5**: Mean level of HDL-C in the sera of the samples under study.

Researchers found that HDL-C is a natural antioxidant that prevents LDL oxidation. This means that they protect against atherosclerosis and its development [38]. In addition to the role of HDL-C in cholesterol removing from phagocytic foam cells and delivering it to the liver to be processed and secreted in the bile, epidemiological studies have indicated that a low level of HDL-C is considered a vital indicator for predicting atherosclerosis and cardiovascular diseases [39]. Epidemiological evidence suggests that there is an inverse relationship between HDL-C levels and ASCVD [40].

Table 2 showed that the mean ± SD of the level of LDL-C was (147.256±6.145) mg/dL in the patient and (139.711±8.535) mg/dL in the control groups. The results showed a significant increase (P≤0.01) in the level of LDL-C in the patient group compared to the control group. Figure 6

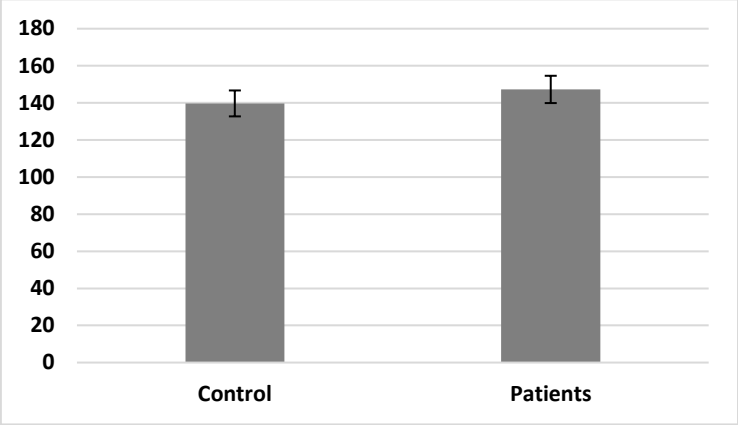



**Figure 6**: Mean level of LDL-C in the sera of the samples under study.

Most of the cholesterol in the body is transported by lipoproteins, which in turn transport it to different parts of the body to perform different roles depending on its functional need [41].Many studies have indicated the role of LDL-C in causing coronary artery disease, represented by atherosclerosis, as high levels of it indicate To the risk of developing atherosclerosis, because the disturbance of blood fats leads to accelerating the processes of atherosclerosis and is considered the main factor causing damage to vascular endothelial cells and vascular smooth muscle cells [42]. They also found that the subunits of LDL-C represented by Small dense LDL(sdLDL) have a major role in causing atherosclerosis and other diseases. Coronary arteries By collecting data from 21 studies that included 53% of them men and whose average age was 67 years, they found that high levels of sdLDL were an important risk factor for developing coronary artery disease [43].The results of recent studies also indicate that LDL has a role in the occurrence of ASCVD through follow-up conducted for a 3 to 9 years in a row, and it was found that high levels of it indicate a role in causing and promoting the disease[44].

ROC statistical analysis was used for the parameters under study, and the results are shown in Table 3.

**Table 3:** Sensitivity, specificity, and area under the curve values for the variables under study for both groups of patients and healthy people.

| Variables | Cut-off value | Sensitivity % | Specificity % | AUC | P-value |
|---|---|---|---|---|---|
| HBGF | >40.431 | 95.45 | 100.00 | 0.993 | <0.0001 |
| Ca | >9.201 | 87.93 | 47.83 | 0.705 | 0.0024 |
| Cholesterol | >201.504 | 87.88 | 62.50 | 0.722 | <0.0042 |
| TG | >104.29 | 87.88 | 87.50 | 0.917 | <0.0001 |
| HDL-C | ≤35.655 | 87.88 | 91.67 | 0.953 | <0.0001 |
| LDL-C | >141.7658 | 87.88 | 62.50 | 0.754 | <0.0001 |

Table 3 shows that the Cut-off value for HBGF was higher than 40.431 pg/ml, the sensitivity value was 95.45%, and the area under the curve(AUC) values were 0.993. It is clear from the results that the Cutt-of value indicates that values higher than >40.431 pg/ml have outstanding accuracy in diagnosing the disease, Figure 7

Table 3 shows that the Cut-off value for calcium was higher than >9.201 mg/dL, the sensitivity value was 87.93%, while the area under the curve values were 0.705.

The results indicate that the sensitivity of the calcium level to the disease was very good but the accuracy was good , Figure 8

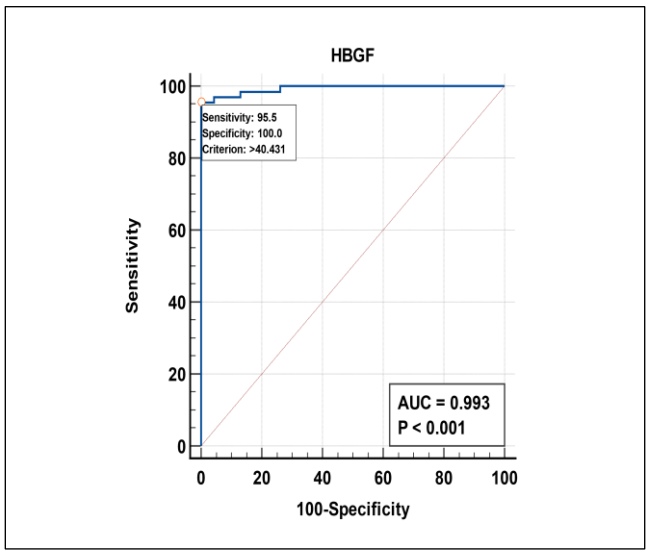



**Figure 7:** ROC curve for HBGF level

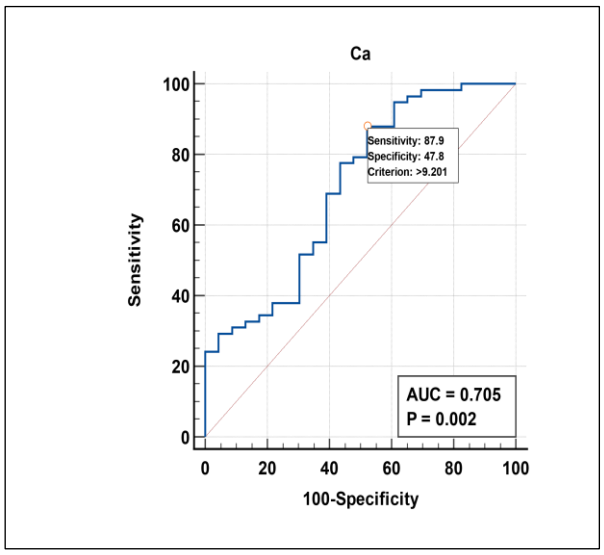
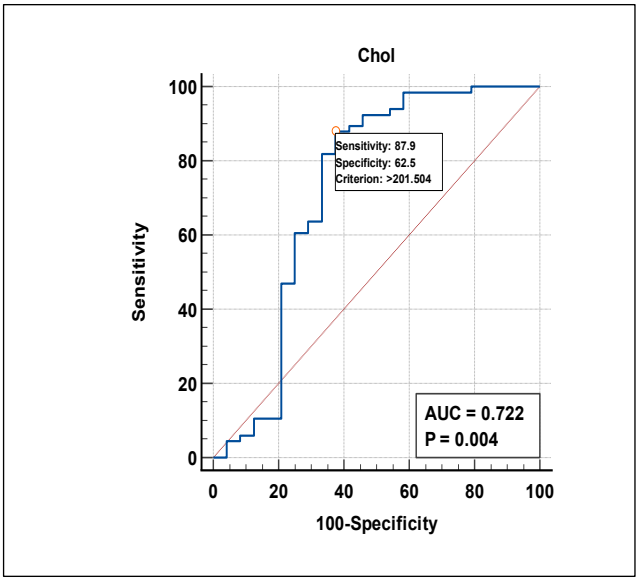



**Figure 8:** ROC curve for calcium level.

Table 3 shows that the Cutt-of value for cholesterol was higher than>201.504 mg/dL, the sensitivity value was 87.88 %, , while the area under the curve values were 0.917 .the results showed that the sensitivity of cholesterol for the disease was statistically high, and the accuracy of the area under the curve was excellent. Figure 9

Table 3 shows that the Cut-off value for TG was higher than >104.29 mg/dL, the sensitivity value was 87.88%, while the area under the curve values were 0.917. The results showed that the sensitivity of the parameter to the disease was high, and the accuracy of the area under the curve was acceptable. Figure 10

Table 3 shows that the Cut-off value for LDL-C was higher than >141.7658 mg/dL, the sensitivity value was 87.88%, while the area under the curve values were 0.754. The results showed that the sensitivity and specificity of the parameter for the disease were statistically significant, and it was found that the accuracy of the area under the curve was outstanding. Figure 11.



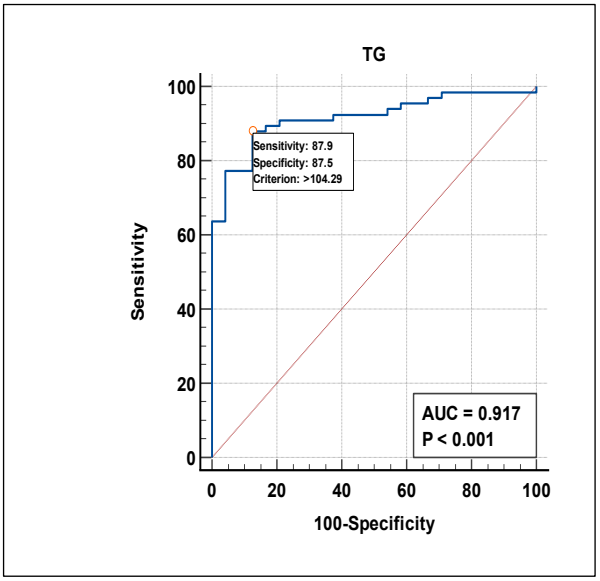




**Figure 9:** ROC curve for cholesterol level.

**Figure 10:** ROC curve for TG level

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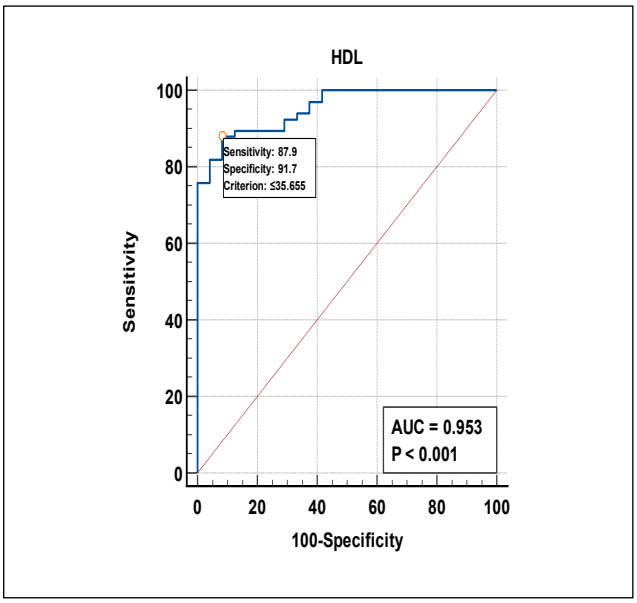
Table 3 shows that the Cutt-of HDL-C value was less than ≤ 35.655 mg/dL, the sensitivity value was 87.88 %, and the area under the curve values were 0.953.The results indicate that the sensitivity of the parameter for the disease was statistically high, and it was found that the accuracy of the area under the curve was outstanding. Figure 12.



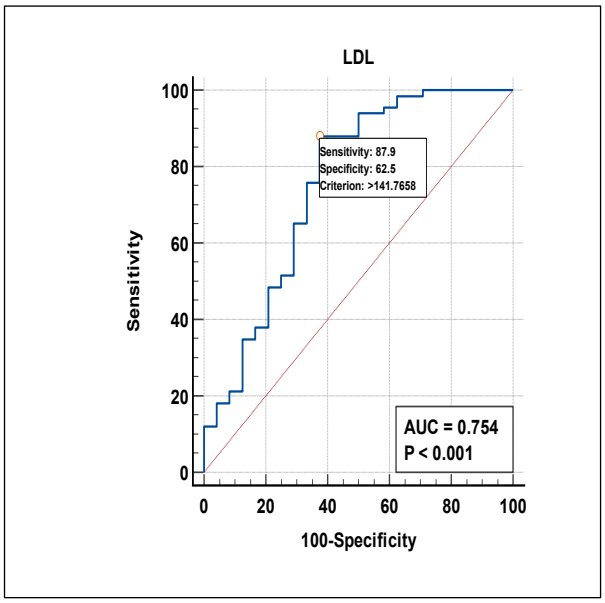




**Figure 11:** ROC curve for HDL-C level.

**Figure 12 :** ROC curve for LDL-C level.

## Conclusions

Heparin-binding growth factor showed a significant increase in sera of patients with atherosclerosis, and the results indicate that HBGF is a sensitive parameter for diagnosing the disease with high accuracy.

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# حساسية عامل النمو المرتبط بالهيبارين كمؤشر تشخيصي لمرض تصلب الشرايين

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**معلومات البحث:**
تأريخ الاستلام: 2024/05/04
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**الكلمات المفتاحية:**
*تصلب الشرايين، عامل النمو المرتبط بالهيبارين، الكالسيوم، الكوليسترول، الكليسريدات الثلاثية*

**معلومات المؤلف**
الايميل:
الموبايل:

**الخلاصة:**
هدفت الدراسة إلى تقييم مستوى عامل النمو المرتبط بالهيبارين (HBGF) باعتباره عامل حساس لتصلب الشرايين. شملت الدراسة جمع 90 عينة مصل (60 عينة للمرضى الذين يعانون من تصلب الشرايين و 30 عينة من الأفراد الأصحاء كمجموعة مراقبة) لتقييم مستوى HBGF والكالسيوم والدهون في المرضى الذين يعانون من تصلب الشرايين. تم جمع عينات المرضى من مركز ابن البيطار لجراحة القلب في محافظة بغداد للفترة من 2023/11/1 ولغاية 2024/1/1. مستويات HBGF والكالسيوم والدهون [الكوليسترول الكلي (TC)، والدهون الثلاثية (TG)، وكوليسترول البروتين الدهني عالي الكثافة (HDL-C)، وكوليسترول البروتين الدهني منخفض الكثافة (LDL-C)}. أظهرت النتائج زيادة معنوية في مستويات HBGF، TC، TG، LDL-C والكالسيوم، مع انخفاض معنوي في مستوى HDL-C في مجموعة المرضى مقارنة بمجموعة السيطرة. أظهر تحليل منحنى خاصية تشغيل المستقبل أن المساحة تحت المنحنى لـ HBGF متميزة، مع حساسية ممتازة، بالإضافة إلى الدقة الممتازة للكوليسترول LDL-C وHDL-C في تشخيص المرض. من النتائج، يمكننا أن نستنتج أن HBGF هو عامل حساس لتشخيص تصلب الشرايين بحساسية عالية.