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ORIGINAL ARTICLE

# Evaluation of β-Arrestin1 and Total Protein in Patients with Metabolic Disorders

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**ABSTRACT**

Metabolic disorders are serious and complex syndromes characterized by a group of diseases, such as abdominal obesity, dyslipidemia, blood pressure, hyperglycemia, vascular disease, type 2 diabetes, chronic kidney disease, stroke, and cancer. The aim of the study is to evaluate both the biomarker β-arrestin 1and total protein in patients with metabolic disorders and to find the relationship between them. Samples were collected from Al-Yarmouk Teaching Hospital; with a total of 135 samples selected for the study. The groups were divided according to body mass index (BMI) and metabolic diseases into three groups: G1 includes 46 healthy subjects that represent the control group, patients group with metabolic disorders (G2, n=45), and patients with T2DM who have obesity (G3, n= 44). The age range of the participants was (30 -55) years. The β-arrestin 1, and insulin were evaluated using ELISA, Al-Kit and technology from Huma Reader HS made in (USA). The results indicate that there was a significant difference between the three groups Total Protein(g\dL) [G1(5.48±0.12), G2 (6.02±0.07), G3 (6.93±0.14)], and β-arrestin 1 (pg\mL) [ G1(273.98±21.30) G2 (311.16± 20.23) G3(520.75±27.25 )]. The results showed a negative correlation between total Protein and β-arrestin 1in G3 (r=-0.385) but no correlation G1and G2. β-arrestin 1gave a very good result area under the curve (AUC) is a biomarker for predicting metabolic disorders, and total protein is also a biomarker for predicting metabolic disorders.

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## 1- INTRODUCTION

Metabolic disorders are serious and complex syndromes characterized by a group of diseases, such as abdominal obesity, dyslipidemia, blood pressure, hyperglycemia, vascular disease, type 2 diabetes, chronic kidney disease, stroke, and cancer. Disruption of normal metabolic processes, resulting in energy and redox imbalances, leads to the development of many physiological diseases in the body, called metabolic disorders [1]. The most important causes of metabolic disorders are dyslipidemia and diabetes, and obesity is currently a global problem and an international health concern. It is a collection of fats resulting from overnutrition, stored in various organs, leading to high levels of reactive oxygen species (ROS) and autoimmune diseases, with chronic inflammation resulting from obesity playing a major role in the development of insulin resistance [2]. The development of insulin resistance leads to type2 diabetes, the most common form of diabetes, and occurs as a result of cells becoming resistant to the effects of insulin or a progressive decline in insulin secretion from the pancreas. Type 2 diabetes mellitus (T2DM) accounts for approximately 90–95% of diabetes cases. It typically appears after the age of 40, but

its prevalence is increasing among young adults and adolescents due to obesity and physical medication [3] inactivity. It can often be controlled without insulin in the early stages through diet and β-arrestin 1proteins are a family of small cytoplasmic proteins. In their basic structure, arrestins are stable molecules with two domains, commonly designated carbon and nitrogen. The structures of the four arrestins are highly similar. Furthermore, arrestin only binds to other proteins, often multiple proteins simultaneously, and lacks any enzymatic action [4]. Total protein studies have revealed the presence of at least 4,826 proteins in human serum, underscoring its importance as a source of biomarkers. Among the abundant proteins, albumin is the most abundant, accounting for 55% of the total serum protein mass by weight. The second most abundant group is immunoglobulins, which represent the largest proportion (35% of total protein) [5]. Serum proteins and other blood components interact with all organs in the body to regulate overall homeostasis, meaning they play a role in controlling complex processes such as aging and the onset of common chronic diseases. Numerous studies have confirmed an important biological link between proteins and the molecular mechanisms that malfunction before and after their regulation, leading to disease [6]. The aim of the study is to evaluate both the biomarker β-arrestin 1and total protein in patients with metabolic disorders and to find the relationship between them.

## 2- MATERIALS AND METHODS

Samples were collected from Al-Yarmouk Teaching Hospital; with a total of 135 samples selected for the study. The groups were divided according to body mass index(BMI) and metabolic diseases into three groups: G1 includes 46 healthy subjects that represent the control group, patients group with metabolic disorders (G2, n=45), and patients with T2DM who have obesity (G3, n= 44). The age range of the participants was (30 -55) years. The BMI and waist-to-hip ratio (WHR) was calculated using the following equations: BMI=: weight in kg / height m² [7], and WHR= waist cm/hip cm [8]. The study population consisted of healthy individuals as well as patients diagnosed with metabolic disorders including dyslipidemia, hyperglycemia, and obesity, and those with T2DM of 1 to 10 years duration who were receiving treatment with metformin and Diamicron. Exclusion Criteria in this study included individuals who use insulin injections and suffer from T1DM, thyroid diseases, heart disease, kidney disease, pregnant women, liver diseases, and hypertension.

Six mL of venous blood was drawn from each individual using a 10 mL syringe. The blood was subsequently transferred into a gel tube and allowed to clot. After coagulation, the samples were centrifuged at 3000 rpm for 10 min to separate and collect the serum. Afterwards, the serum was frozen at -20 ℃. The arrestinβ-1, and insulin were evaluated using ELISA, Al-Kit and technology from Huma Reader HS made in (USA). The lipid profile including (serum cholesterol, triglycerides (TG), low-density lipoprotein (LDL-C), very low-density lipoprotein (VLDL) and fasting blood glucose (FBG) were also measured with a UV-visible spectrophotometer from Huma Reader HS (USA). The (AIP) was derived through mathematical calculations utilizing a logarithm of (TG/HDL-C) [9]. Homeostasis Model Assessment (HOMA) for IRusing HOMA IR = (FBG x Insulin / 405) [10].

### 2.1 Statistical Analysis

The analysis was conducted utilizing version 26 of the Statistical Packages for Social Sciences (SPSS Inc., Chicago, U.S.A.). The data was presented as (mean ± SE). This study involved several tests, including the ANOVA test to assess the correlation coefficient (r) between parameters, the Tukey test, the ROC curve, and the analysis of differences among three independent variables. The expected value, identified as significant at $p \leq 0.05$ and non-significant at $p > 0.05$, was utilized to determine the statistical significance.

## 3- RESULTS AND DISCUSSION

**Table (1): Clinical and biochemical parameters among studied groups**

| Parameters / Groups | Control G1 No. (46) | Metabolic disorders G2 No. (45) | T2DM with Obesity G3 No. (44) | P-value |
|---|---|---|---|---|
| **Age (year)** | 40.82±1.28[a] | 40.84±1.10[a] | 44.45±1.04[a] | 0.071 |
| **BMI (kg/m$^2$)** | 22.85±0.17 [a] | 36.51±0.74 [c] | 34.01±0.65[b] | 0.001** |
| **WHR** | 0.87±0.01[a] | 1.12±0.02[c] | 1.04±.0.02[b] | 0.001** |
| **FBG (mg/dL)** | 97.79±1.96 [a] | 131.58±2.34 [b] | 212.67±6.71 [c] | 0.001** |
| **Insulin ( IU/ mL )** | 3.36±0.11 [a] | 6.05±0.12 [b] | 7.66±0.17 [c] | 0.001** |

| | | | | |
|---|---|---|---|---|
| **IR** | 0.79±0.02 [a] | 1.91±0.06[c] | 4.05±0.19 [b] | 0.001** |
| **Cholesterol (mg/dL)** | 173.91±1.11 [a] | 209.17±2.30 [b] | 213.56±2.45[b] | 0.001** |
| **TG (mg/dL)** | 156.49±1.16[a] | 204.38±2.97 [b] | 217.87±1.91 [c] | 0.001** |
| **HDL-C (mg/dL)** | 38.67±0.69 [b] | 18.05± 0.48[a] | 21.46±1.71[a] | 0.001** |
| **LDL-C (mg/dL)** | 103.39±1.58 [a] | 150.06±2.58 [b] | 148.59±1.80[b] | 0.001** |
| **VLDL-C (mg/dL)** | 31.00±0.22[a] | 40.80±0.59[b] | 43.46±0.38[c] | 0.001** |
| **AIP** | 0.609 ±0.008 [a] | 1.059± 0.013 [b] | 1.051± 0.028 [b] | 0.001** |
| **β-arrestin1 (pg\mL)** | 273.98±21.30 [a] | 311.16± 20.23 [a] | 520.75±27.25 [b] | 0.001** |
| **Total Protein (g\dL)** | 5.48±0.12 [a] | 6.02±0.07 [b] | 6.93±0.14 [c] | 0.001** |

**Significant difference between means using ANOVA -test at 0.05 level.**
****Significant difference between means using ANOVA -test at 0.01 level.**
**a : Indicate significant difference between G1and G3**
**b: Indicate significant difference between G2and G3**
**c: Indicate significant difference between G1and G2**

The results indicate that there was no significant difference in the ages of the three groups, However, a significant difference in WHR and BMI (kg/m²), ($p<0.001$) as indicated in Table 1. Additionally, the lipid profile showed significant differences, with mean values ± SE for cholesterol, TG, LDL-C and VLDL as indicated in Table 1, while, HDL-C demonstrated a significant decrease HDL demonstrated significant differences among the groups Atherogenic index plasma AIP showed a significant difference between the three groups. in insulin, insulin resistance (IR), and fasting blood glucose (FBG) levels in both G2 and G3 groups compared to G1. Insulin resistance was assessed using the HOMA-IR equation, , total protein in G3 = 6.93 g/dL, significantly higher than in G1 = 5.48 g/dL and G2 = 6.02 g/dL and a significant difference between the three groups β-arrestin 1 (pg\mL) G1(273.98±21.30 ) G2 (311.16± 20.23) G3( 520.75±27.25 ) and the results showed a statistically significant increase ($P<0.05$), as presented in Table 1.

In Table 1, based on the results shown above, it appears that body mass index (BMI) is the most commonly used indicator to determine obesity. In our study, the average age was (44) years. With age, failure to follow a healthy diet, lifestyle, and regular exercise leads to an increase in BMI. On the other hand, the advantage of being overweight can be explained by the fact that fat stores energy that can be used positively, leading to a negative energy balance. A high BMI has been associated with an increased risk of death. Some studies have confirmed that a stable BMI with age is a sign of good health and a sign that the body is able to maintain internal balance. Therefore, BMI increases with age. Longevity leads to many diseases, most notably dyslipidemia, diabetes, and heart disease, most notably atherosclerosis, which are positively associated with age. Overall, BMI reflects a complex relationship with age, as the risk of obesity and underweight may increase with age, consistent with Anna [11]. On the other hand, the relationship between BMI and waist-to-hip ratio is distinct. Both are used to measure different aspects of body fat distribution, but they differ in how they reflect health status and fat distribution. Waist-to-hip ratio is positively associated with metabolic disease, and excess weight contributes to many metabolic-related diseases such as dyslipidemia, obesity, and diabetes, concurring with Li [12]. As previously mentioned, β-arrestin 1 is a multifunctional protein that plays a key role in signaling. β-arrestin 1is known for its important role in regulating metabolic pathways, including diabetes. It also plays a role in dyslipidemia, a cause of heart disease and heart failure, as β-arrestin 1attenuates signaling. β-arrestin 1interacts with beta-adrenergic receptors and angiotensin II receptors to reduce the harmful response to excessive sympathetic stimulation, simultaneously activating protective cardiac signaling cascades that maintain cardiac structure and function in response to injury agreement with Bussey and Frischmann [13]. Understanding insulin's wide-ranging physiological processes and its effects on its synthesis and secretion, as well as its functions, extends from the molecular level to the whole body level. Some have shown that metabolic disorders and type2 diabetes are the most common syndromes associated with impaired insulin secretion. The causes of the nonlinear progression of diabetes over time are environmental factors, obesity, and glycemic disturbances, all of which contribute to the development of type 2 diabetes, which is characterized by multiple cellular mechanisms, the most important of which are alterations in insulin signaling, which in turn lead to

beta cell dysfunction and dysregulation of key genes involved in oxidative stress and inflammation [14]. Intracellular glucose transport into adipose cells after a meal is insulin-dependent via GLUT4, with adipose tissue estimated to account for approximately 10% of total glucose uptake and entirely stimulated by insulin. This leads to enhanced metabolic effects of insulin and increased glucose production through gluconeogenesis, consistent with Smith [15]. Excess body fat, particularly visceral fat, can trigger the release of chemicals known as inflammatory cytokines. These promote chronic inflammation in the body, which increases HOMA-IR. Fat cells themselves contribute to insulin resistance by secreting hormones such as adiponectin, which normally helps improve the cells' response to insulin, thus increasing HOMA-IR. Lipid abnormalities associated with insulin resistance resulting from impaired insulin secretion affect all fasting lipid profiles, such as high TG-rich lipoproteins, low HDL, and high VLDL. This pattern is closely associated with cardiovascular risk, consistent with [16]. The results showed an association between AIP and lipid profile, particularly TC and HDL, in obese type 2 diabetic patients. Furthermore, patients with a higher BMI and WHR had higher AIP levels, a finding consistent with Kearn *et al.* Several studies have shown that chronic diseases, such as dyslipidemia and diabetes, are more prevalent in obese individuals, and are a cause of metabolic disorders [17]. The results indicate differences in total protein levels between the studied groups. Patients with metabolic disorders and type2 diabetes were found to have higher total protein levels than healthy individuals. Total blood protein is an important indicator of nutritional status, as it consists mainly of albumin and globulin. In the context of metabolic disorders such as metabolic syndrome, as well as in type 2 diabetes, high total blood protein often does not mean that patients have consumed large amounts of dietary protein; rather, it often reflects an increase in circulating proteins such as globulin, or an increase in proteins associated with inflammation or the immune system (such as antibodies and acute inflammatory proteins). To explain why total protein is higher in patients with type2 diabetes and obesity compared to patients with metabolic disorders, type 2 diabetes is often associated with a chronic, low-grade inflammation that is more pronounced than that found in uncomplicated metabolic disorders. This inflammation stimulates the liver to produce acute phase proteins, such as globulins, leading to an increase in total protein. Chronic inflammation in type2 diabetes and hyperactive immune system in diabetes cause oxidative stress and microvascular damage, which activates the immune system more than in metabolic disorders. The body produces immune proteins that are included in globulins, which increases the percentage of total protein. This also affects the effect of medications and blood sugar regulation. Some diabetes medications (such as metformin) may improve liver performance or reduce protein consumption, which may maintain blood protein levels. However, some patients with metabolic disorders may not receive regular treatment or suffer from greater nutritional imbalance, leading to a decrease in total protein due to differences in muscle mass and nutrition. On the other hand, type 2 diabetes patients are often more prone to overweight with a high-protein diet than some patients with metabolic disorders who may suffer from relative malnutrition, which is reflected in total protein. This is consistent with Speelman, [18].

**Table (2): Correlation Coefficients between Different Parameters and Total Protein**

| Parameters / Groups | Total Protein (g\dL) | | |
|---|---|---|---|
| | **Control Group No. (46)** | **Metabolic disorders Group G2 No. (45)** | **T2DM with Obesity Group G3 No. (44)** |
| **Age (years)** | -0.231 | 0.177 | -0.056 |
| | 0.123 | 0.244 | 0.718 |
| **BMI (kg/m$^2$)** | -0.169 | 0.104 | -0.035 |
| | 0.261 | 0.498 | 0.824 |
| **W/H ratio** | -0.291* | -0.024 | 0.206 |
| | 0.049 | 0.874 | 0.179 |
| **FBG (mg/dL)** | 0.207 | -0.311* | -0.616** |
| | 0.168 | 0.038 | 0.000 |
| **Cholesterol (mg/dL)** | -0.191 | -0.292 | -0.270 |
| | 0.203 | 0.052 | 0.077 |
| **Triglyceride (mg/dL)** | 0.341* | 0.111 | -0.184 |
| | 0.021 | 0.466 | 0.231 |
| **HDL-C (mg/dL)** | -0.053 | -0.007 | -0.591** |
| | 0.725 | 0.964 | 0.000 |

| | | | |
|---|---|---|---|
| **LDL-C (mg/dL)** | -0.203 | -0.285 | 0.232 |
| | 0.177 | 0.058 | 0.130 |
| **VLDL-C (mg/dL)** | 0.244 | 0.155 | -0.177 |
| | 0.102 | 0.310 | 0.251 |
| **Insulin(μU/mL)** | -0.069 | 0.074 | -0.356* |
| | 0.648 | 0.629 | 0.018 |
| **HOMAIR** | 0.005 | -0.139 | -0.560** |
| | 0.973 | 0.364 | 0.000 |
| **β-arrestin 1 (pg\mL)** | -0.033 | -0.146 | -0.385* |
| | 0.825 | 0.337 | 0.010 |
| ***Correlation is significant at the 0.05 level.** ****Correlation is significant at the 0.01 level.** | | | |

In Table 2, the results showed a negative correlation between Total Protein and WHR in G1 (r= -0.291*) but no correlation G2 and G3 and a negative correlation between Total Protein and FBG inG3(r=-0.616**) and a negative correlation in G2 (r=-0.311*) but no correlation in G1.

A positive correlation between total protein and TG in G1 (r=-0.341*) but no correlation G2 and G3and a negative correlation between Total Protein and HDL in G3(r=-0.591**) but no correlation G2 and G1, the results showed a negative correlation between Total Protein and insulin inG3 (r= -0.356 *) but no correlation G1and G2, a negative correlation between β-arrestin 1and Total protein in G3 (r=-0.385*) but no correlation G1and G2. Total protein and WHR, here depend on the quality of protein intake, as it increases the quality of protein based on the quantity. Essential amino acids in food work to improve glycemic and metabolic indicators in general a negative correlation between total protein and the WHR. Here we rely on the quality of protein intake, as it leads to an increase in the quality of protein based on the quantity. Essential amino acids in food work to improve glycemic and metabolic indicators in a general sense. Here we confirm that a healthy diet rich in proteins improves blood sugar indicators.
People with a high WHR often suffer from chronic, low grade inflammation. This inflammation affects protein metabolism and may lead to increased protein consumption in the body low albumin (especially in chronic diseases) and this is consistent with Yu [19] Negative correlation between Total Protein and FBG suggests that higher total protein levels may be associated with better glucose metabolism and lower fasting blood glucose levels. This may indicate that an improved protein status reflects better hepatic and metabolic function, which could enhance glucose utilization and reduce hyperglycemia. The stronger negative correlation observed in G3 indicates a more pronounced inverse relationship between Total Protein and FBG, possibly reflecting a greater physiological or therapeutic effect in this group. In G2, the negative correlation was weaker but still followed the same trend. On the other hand, an Although previous studies reported a positive correlation between insulin resistance and total protein, the negative correlation observed in the current study may be attributed to differences in sample characteristics, nutritional status, liver function, and severity of metabolic disturbances. Chronic insulin resistance may also promote protein catabolism or reduce hepatic protein synthesis, leading to lower total protein levels. In addition, methodological differences and sample size may explain the discrepancy with previous findings [20]. This agrees with Sandra obesity also affects insulin sensitivity to the process of protein metabolism, and poor control of blood sugar levels in patients with T2DM leads to an acceleration of the process of protein turnover in fasting states. According to results, T2DM had higher HOMA-IR compared to control and metabolic disorder and this It indicates greater resistance to insulin in the process of protein metabolism Studies agree with the current findings. The relationship between total protein and lipids (especially triglycerides and cholesterol) in patients with T2DM is indirect but very important because it is linked to liver function, chronic inflammation, and metabolic status [21].

Also, from the results, note the important role of β-arrestin 1, which is necessary for the complete stimulation of protein synthesis, although it is known to transmit receptor signals to biochemical pathways, thus consolidating the appreciation of β-arrestin 1 as a positive modulator of receptor signals, as well as in regulating protein synthesis and regulation [22]. Although there are no direct studies linking β-arrestin 1levels to total serum protein, there are some points that may suggest an indirect relationship. Given the role of β-arrestin 1in regulating the immune response, changes in this protein's levels may affect serum globulin concentrations, which in turn affect total serum protein. Also, becauseβ-arrestin 1 interacts with multiple proteins, these interactions may affect the levels of different proteins in the serum, and thus affect the total protein in the serum. On the other hand, Explain the relationship between β-arrestin 1and total protein levels in cells through its effect on Akt signaling, suggesting that it may influence protein synthesis. For example, in 3T3-L1 cells, β-arrestin 1deficiency reduced Akt activity and increased

expression of genes associated with lipogenesis, suggesting its effect on protein signaling pathways [23]. So the relationship is not direct in the sense that high β-arrestin 1will raise or lower total protein, but they share the same disease pathways (e.g., inflammation, insulin resistance, metabolic disturbance), making it useful to measure both markers when studying metabolic disorders.

**Table (3): The ROC Curve Analysis the total protein between control and metabolic disorders**

| Area Under the Curve | | | | |
|---|---|---|---|---|
| Test Result Variable(s): Total Protein | | | | |
| Area | Std. Error[a] | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
| | | | Lower Bound | Upper Bound |
| 0.857 | 0.038 | 0.000 | 0.782 | 0.933 |
| a. Under the nonparametric assumption | | | | |
| b. Null hypothesis: true area = 0.5 | | | | |

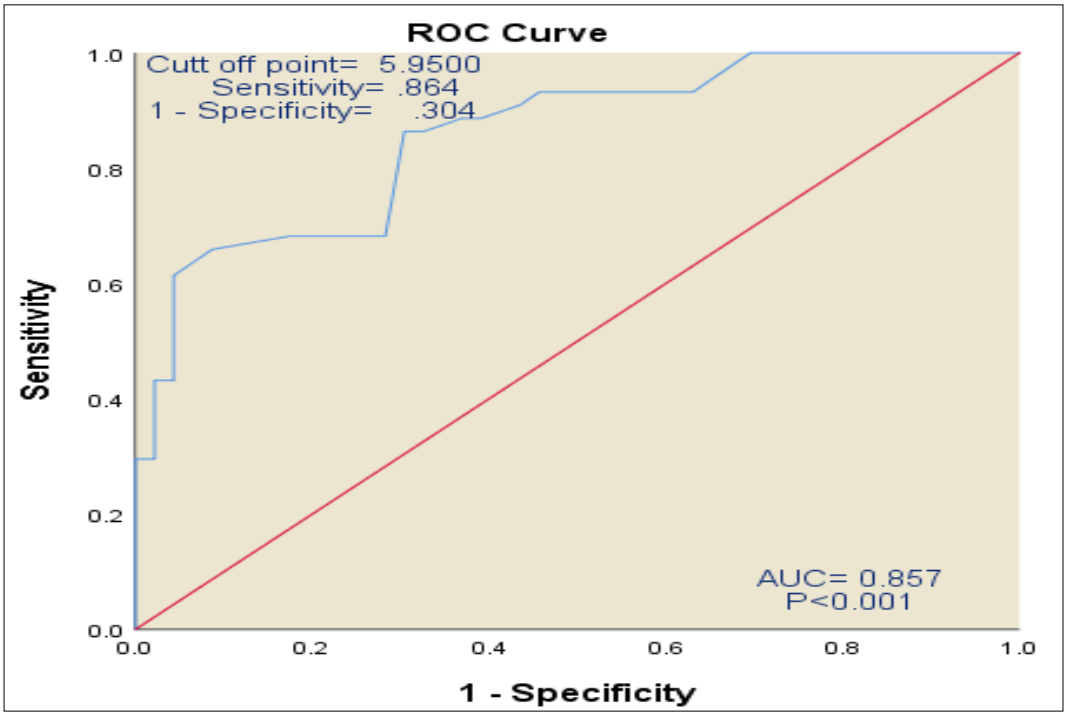


**Fig (1): ROC curve analysis of total protein between control and metabolic disorders**

In table 3, the ROC Area Under the Curve = (0.857) is a very good predictor of metabolic disorders in patients with diabetes, obesity, and dyslipidemia. Total protein in the blood is albumin + globulins, or plasma proteins in general. These proteins are influenced by several metabolic factors, such as nutrition, inflammation, liver function, protein distribution, and metabolic processes. Therefore, changes in total protein may reflect shifts in metabolic status or the onset of metabolic disorders (e.g., insulin resistance, metabolic syndrome, fatty liver disease, etc.). However, it is important to understand that total protein alone is not a definitive indicator; rather, it is often used as a component of multiple indices or models. This is consistent with a recent study in which Tang Y et al. indicated that serum protein levels are associated with an increased risk of metabolic syndrome and its components [24, 25]. The subsequent loss in antioxidant defenses and increased lipid peroxidation, insulin resistance, dyslipidemia and low-grade inflammation are indicative of a state of subclinical metabolic dysregulation [26].

**Table (4): The ROC Curve Analysis of β-arrestin 1 between control and metabolic disorders**

| Area Under the Curve | | | | |
|---|---|---|---|---|
| Test Result Variable(s): β-arrestin 1 | | | | |
| Area | Std. Error[a] | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
| | | | Lower Bound | Upper Bound |
| 0.817 | 0.049 | 0.000 | 0.722 | 0.912 |
| a. Under the nonparametric assumption | | | | |
| b. Null hypothesis: true area = 0.5 | | | | |

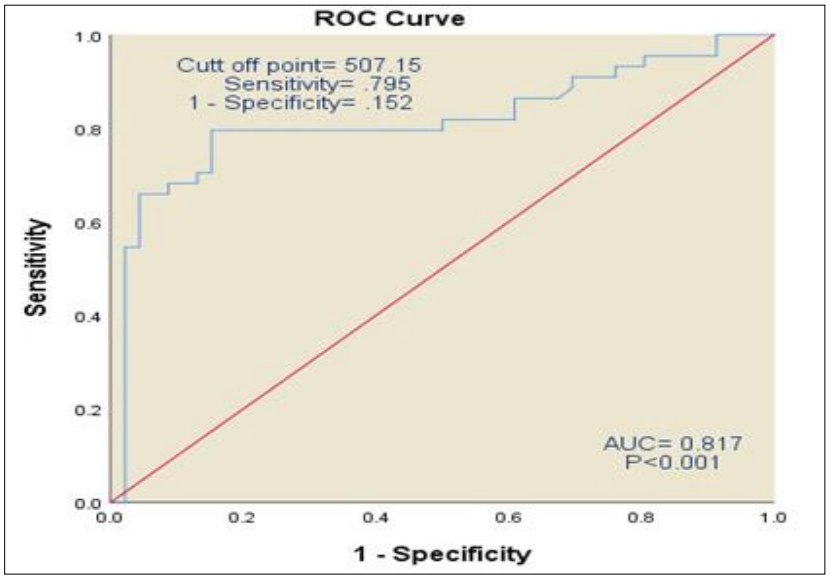


**Fig (2): ROC curve analysis of β-arrestin 1between control and metabolic disorders**

The ROC analysis of β-arrestin 1 gave a very good area under the curve (AUC) = (0.817), as it proved thatβ-arrestin 1 is a clear indicator metabolic disorder in the early stages of metabolic disorder, β-arrestin 1 expression may change in tissues before total protein begins to deviate significantly. Therefore, measuring β-arrestin 1 may provide an "early signal" for changes that will later appear in serum protein or other metabolic markers. Based on these hypotheses, it is conceivable that changes in β-arrestin 1and total protein together may provide a better indicator of a person's approach to a metabolic disorder than either of them alone. It also predicts the development of obesity, blood sugar, and lipid metabolism disorders by monitoring the impaired response of cells to lipid-regulating hormones. It also monitors protein metabolism disorders resulting from malnutrition or chronic disease through muscle growth pathways by activating $\beta_2$-adrenergic receptors and activating the IGF-1/ERK pathways, which are important in protein synthesis, muscle growth, and the balance of protein synthesis and degradation. A decrease in β-arrestin 1in cases of malnutrition or severe obesity leads to: Reduction in muscle mass, protein synthesis, and protein loss in the blood (e.g., Albumin) [27].

## 4- CONCLUSION

We conclude from this study that β-arrestin1gave a very good result area under the curve (AUC) is a biomarker for predicting metabolic disorders, and total protein levels were significantly elevated in metabolic disorders, but its utility as a standalone biomarker is limited. However, total protein alone is not a strong or specific biomarker for predicting metabolic disorders because total protein does not identify the altered protein type (albumin or globulin) and does not directly indicate a specific metabolic process. It plays a supportive role in the overall assessment. However, they share common pathological pathways (e.g., inflammation, insulin resistance, metabolic dysfunction), making it useful to measure both markers when studying metabolic disorders.

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