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# Estimation of Adropin and its correlation with glycemic indices in patients with type 2 diabetic mellitus.

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**Abstract**

Adropin is a newly identified protein involved in the regulation of energy balance and carbohydrate metabolism; it has also been implicated in the development of insulin resistance. Despite the fact that it may offer a potential link to T2DM, conflicting reports exist in the literature with respect to the association between adropin and T2DM; further investigation was thus conducted. The aim of this study is to assess the association between serum Adropin levels and glycemic indices in patients with T2DM. This study included 100 participants; fifty of them had T2DM without any complications, compared with 50 apparently healthy subjects representing control group. The age range for the T2DM patients was 18-75 years, while the control group ranged from 22-58 years, with an equal distribution of sexes in both groups. Adropin and fasting insulin hormone were measured by ELISA kits. Glycated hemoglobin (HbA1c) Fasting Blood Sugar (FBS) levels were also measured while Insulin resistance (IR) and glycemic indices were calculated. The concentrations of Adropin were higher with significance ($P<0.05$) in T2DM group when compared with control group and a positive correlation was found between Adropin and insulin levels in both groups. The Receiver Operating Characteristic analysis (ROC) showed that Adropin can predict T2DM when its level >1250.7 pg/ml with AUC=97.9%, sensitivity of 100% and specificity of 96.1%. Measurement of glycemic indices include (Insulin, HOMA-IR, S%, B%, G/I ratio, QUICKI, McAuley, and TyG index) revealed that IR and TyG index were higher in T2DM while B%, S%, QUICKI index, and McAuley index were lower in T2DM. Adropin is connected to T2DM and may be used as prognostic marker for T2DM. Further studies with larger sample sizes are recommended confirm these results.

**Keywords:** Type 2 diabetic mellitus, Insulin resistance, Adropin, Glycemic indices, Receiver Operating Characteristic.

# تقدير مستوى الأدروبين وعلاقته بمؤشرات نسبة السكر في الدم لدى مرضى السكري النوع الثاني

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**الخلاصة**

الأدروبين هو بروتين تم التعرف عليه حديثًا ويشارك في تنظيم توازن الطاقة واستقلاب الكربوهيدرات؛ كما ثبت تورطه في تطور مقاومة الأنسولين. وعلى الرغم من حقيقة أنه قد يقدم رابطًا محتملًا لمرض السكري

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من النوع 2، إلا أن هناك تقارير متضاربة في الأدبيات فيما يتعلق بالارتباط بين الأدروبين ومرض السكري من النوع 2؛ وبالتالي تم إجراء مزيد من التحقيق. والهدف من هذه الدراسة هو تقييم الارتباط بين مستويات الأدروبين في المصل ومؤشرات نسبة السكر في الدم لدى مرضى السكري من النوع 2. شملت هذه الدراسة 100 مشارك؛ كان خمسون منهم مصابين بمرض السكري من النوع 2 دون أي مضاعفات، مقارنة بخمسين مشاركًا يتمتعون بصحة جيدة يمثلون مجموعة التحكم. كان النطاق العمري لمرضى السكري من النوع 2 18−75 عامًا، بينما تراوحت مجموعة التحكم من 22 إلى 58 عامًا، مع توزيع متساوٍ للجنسين في كلتا المجموعتين. تم قياس الأدروبين وهرمون الأنسولين الصائم بواسطة مجموعات ELISA. كما تم قياس مستويات الهيموجلوبين السكري (HbA1c) وسكر الدم الصائم (FBS) بينما تم حساب مقاومة الأنسولين (IR)ومؤشرات نسبة السكر في الدم. كانت تركيزات Adropin أعلى مع دلالة ($P < 0.05$) في مجموعة T2DMعند مقارنتها بمجموعة التحكم وتم العثور على ارتباط إيجابي بين مستويات Adropin والأنسولين في كلتا المجموعتين. أظهر تحليل خصائص التشغيل المستقبل (ROC) أن Adropin يمكن أن يتنبأ بمرض السكري من النوع 2 عندما يكون مستواه> 1250.7 بيكو جرام / مل معAUC = 97.9 ٪ وحساسية 100٪ وخصوصية 96.1٪. كشف قياس مؤشرات نسبة السكر في الدم (الأنسولين و HOMA−IR وS ٪ وB ٪ ونسبة G / I و QUICKI و McAuley ومؤشر (TyG أن مؤشر IR و TyG كانا أعلى في T2DM بينما كانتB ٪ وS ٪ ومؤشر QUICKI ومؤشر McAuley أقل في T2DM. يرتبط الأدروبين بمرض السكري من النوع الثاني ويمكن استخدامه كعلامة تشخيصية لمرض السكري من النوع الثاني. يوصى بإجراء المزيد من الدراسات مع أحجام عينات أكبر لتأكيد هذه النتائج.

## Introduction

Hyperglycemia, resulting from inadequate insulin production, activity, or both, is a sign of diabetes mellitus (DM), which is a metabolic illness [1]. Today, DM is recognized as a prevalent illness in modern societies [2]. Diabetes occurs when the body fails to use insulin or when insulin is not sufficiently produced by the pancreas [3]. However, insulin resistance (IR) leads to decreased glucose absorption in adipose tissue, muscle, and the liver, as well as increased glucose synthesis in the liver [4, 5].

Metabolic imbalances or the risks associated with insulin resistance (IR) can lead to hyperglycemia, hypertension, dyslipidemia, visceral adiposity, and elevated inflammatory markers [6]. Insulin resistance can be determined by mathematical equation depending on the levels of glucose and insulin or by using HOMA calculator which gives other information such as sensitivity of β cell to insulin (S%), and β cell percent (B%) [7]. The significant of glucose to insulin ratio (G/I) was used as IR pointer [8]. Additionally, the McAuley index was used as predictor for IR in an indirect way using insulin and triacylglycerol (TG) [9, 10]. An index based on TG- glucose levels was suggested as predictive value for IR, which also was used in clinical practice to screen patients with heart problems [11].
Other glycemic indices were used to predict insulin sensitivity such as Quantitative Insulin sensitivity Check Index (QUICKI) which represent the invers of HOMA-IR [12, 13].

The bioactive protein Adropin, which is expressed in the liver and brain, is encoded by the Energy Homeostasis Associated gene (*Enho*). It has a molecular weight of 4.5 kDa and 76 amino acids [14]. Adropin has been detected in the kidney, lung, testes, stomach, skeletal muscle, endothelial cells, peripheral blood mononuclear cells, and other regions of the central nervous system. It is also found in the circulatory system [15]. Adropin improves insulin sensitivity, glucose metabolism, endothelial function, and motor coordination *via* controlling a number of signaling pathways [16]. However, as has been suggested more recently, Adropin may function as a membrane-bound protein that regulates cell-cell communication [17].

In addition to enhancing insulin signaling pathways and shifting fuel preference to favor glucose while inhibiting fat oxidation, skeletal muscle plays a critical role in mediating the whole-body effects of Adropin. It has also been suggested that Adropin may enhance insulin-induced glucose uptake in muscle [16]. Given the importance of Adropin, it is recommended that more prospective and interventional human studies will be able to evaluate the therapeutic effects of Adropin in people with T2DM [18].

Level of Adropin showed lower values in T2DM [19].and the same results were found in patients with metabolic dysfunction-associated fatty liver disease (MAFLD) which lead to suggest that Adropin may be a potential biomarker for predicting the development of MAFLD, especially in T2DM individuals [20]. Lower serum Adropin level was also found in a study connected to coronary atherosclerosis and acute myocardial infarction which suggested that low serum Adropin level is an important predictor of stable coronary artery disease [21]. Conflicting results were obtained regarding Adropin levels in patients with T2DM; lower levels [19, 22] or higher levels [23] were observed when compared with that of the control group.

Since previous studies did not provide adequate data on the relationship between glucose homeostasis markers and serum Adropin levels, this study aimed to find the association of Adropin with T2DM and glycemic indices.

## Experimental Part

### Subjects

This case-control study included 50 patients with T2DM of both sex (male: 25, female: 25), aged between18-75 year. Samples were collected from Al-Zahraa Teaching Hospital in Kut Province during the period between November 2023 and January 2024. The study received approval from the ethical committee at the Faculty of Science, Baghdad University (Ref. CSES/1223/0138 on December 23, 2023) and an informed consent was achieved from each participant. Duration of the disease was one month to 20 years; the percentage of duration of T2DM more than 10 years was (12%). The percentage of patients who were under metformin treatment was 26% while, 74% of patients were under Sitagliptin (Januvia) treatment. The exclusion criteria were: pregnant women, patients who had any acute or chronic inflammatory diseases; T2DM with complications and chronic or hereditary diseases. A control group of 50 apparently healthy participants was also included, aged between 22 and 58 years, and with an equal distribution of sexes. They were considered healthy depending on their history, physical examination, and other biochemical tests.

The exclusion criteria were: pregnant women, and patients who had other acute or chronic inflammatory diseases.

### Collection of Blood Samples

After an overnight fast, approximately 5 ml of blood samples were collected from each participant. One milliliter from each blood sample was used to measure Glycosylated hemoglobin (HbA1c), while the remaining sample was placed in a gel tube for 10 min at room temperature to clot. After coagulation, serum was separated by centrifugation at 1500 x g for 10 min; the separated serum was kept in Eppendroff tubes at –20°C.

### Methods

This study included measuring Adropin and fasting insulin levels using a sandwich ELISA kit. The HbA1c% level was measured using CLOVER A1c® Plus**.** Fasting Blood Sugar (FBS) level was measured by an automated colorimetric/ enzymatic method. HOMA- IR, S%, and B% were calculated by Homeostatic Model Assessment of Insulin Resistance (HOMA) calculator program (Fig 1) [24].

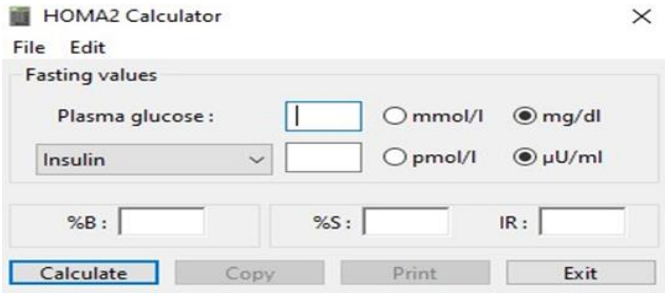


**Figure 1:** The HOMA calculator [24].

The G/I ratio, QUICKI, McAuley and TyG indices were calculated by special equations as shown below:

The G/I ratio [8] = Fasting glucose (mg/dl)/ fasting insulin (µIU/ml)

McAuley Index [9, 10] = exp [2.63-0.28 ln (fasting insulin (µU/ l) -0.31 ln ( TG (mmol/l)]

Triglyceride Glucose (TyG) index [11]= ln [(TG (mg/dl) x fasting glucose (mg/dl) /2)]

Quantitative Insulin Sensitivity Check Index (QUICKI)[12,13]=

1/ ((log fasting glucose (mg/dl) +log (fasting insulin (µIU/ml))

**Statistical Analysis**

Results are presented as means ± SD for the comparison of variables in both groups. Statistical analysis was performed with SPSS 25 software. Normally of the data was assessed based on Shapiro-Wilk test. The independent sample student's-test was used to compare means of the parameters between groups. Correlation between parameters was assessed by Pearson correlation analysis. Receiver operating characteristic (ROC) curve analysis was constructed for Adropin level as a predictor for T2DM patients. The P value for significance was set at less than 0.05 or below 0.001for highly significance.

**Results**

The study compared the biochemical parameters and glycemic indices of the T2DM and control groups. The results indicated that the mean levels of FBS, HbA1c%, insulin, HOMA-IR, and TyG index were significantly higher (P<0.001) in T2DM group when compared with the controls. Conversely, the mean levels of B%, S%, QUICKI index, and McAuley index were significantly lower in T2DM group than that in control group. The G/I ratio showed non- significant difference, as shown in Table 1.

**Table 1**: Glycemic indices and biochemical parameters were compared between the T2DM group and the control group**.**

| Parameters | Study Groups | | P – Value < or = |
|---|---|---|---|
| | T2DM Group (Mean ± SD) (n=50) | Control Group (Mean ± SD) (n=50) | |
| **FBS (mg/dL)** | 186.5 ± 48.7 | 91.38 ± 33.23 | **0.001**** |
| **HbA1c %** | 8.62 ± 2.27 | 5.14 ± 0.54 | **0.001**** |
| **Insulin (µIU/mL)** | 14.56 ± 2.19 | 7.47 ± 1.33 | **0.001**** |
| **HOMA-IR** | 3.19 ± 1.58 | 0.97 ± 0.17 | **0.006**** |
| **B%** | 60.24 ± 12.91 | 93.99 ± 24.80 | **0.001**** |
| **S%** | 45.08 ± 13.26 | 106.2 ± 20.57 | **0.001**** |
| **G/I Ratio** | 13.04 ± 7.12 | 12.65 ± 2.93 | **0.723** |
| **QUICKI** | 0.29 ± 0.01 | 0.35 ± 0.01 | **0.001**** |
| **McAuley Index** | 4.29 ± 0.70 | 6.22 ± 0.90 | **0.001**** |
| **TyG Index** | 5.09 ± 0.38 | 4.48 ± 0.20 | **0.001**** |

** Student's t-test at P <0.001 levels was used for significant difference between two independent means

The effect of sex on the levels of the parameters between the patients and control groups was listed in Table 2. All biochemical parameters showed no significant difference ($P \geq 0.05$) between male and female.

**Table 2:** Comparison of biochemical parameters according to sex in T2DM group.

| Parameters | T2DM group | | P – Value < or = |
|---|---|---|---|
| | Male Group (Mean ± SD) (n=25) | Female Group (Mean ± SD) (n=25) | |
| **FBS (mg/dL)** | 192.1± 71.76 | 199.4 ± 69.54 | 0.327 |
| **HbA1c %** | 8.28 ± 1.79 | 8.92 ± 2.63 | 0.324 |
| **Insulin (µIU/mL)** | 14.05 ± 2.13 | 15.01 ± 2.19 | 0.125 |
| **HOMA-IR** | 3.67 ± 0.96 | 2.68 ± 1.01 | 0.492 |
| **B%** | 59.60 ± 13.56 | 60.80 ± 16.13 | 0.920 |
| **S%** | 47.79 ± 14.75 | 43.68 ± 11.54 | 0.172 |
| **G/I Ratio** | 15.47 ± 6.45 | 14.54 ± 7.76 | 0.596 |
| **QUICKI** | 0.30 ± 0.016 | 0.29 ± 0.018 | 0.164 |
| **McAuley Index** | 4.30 ± 0.72 | 4.28 ± 0.71 | 0.913 |
| **TyG Index** | 5.07 ± 0.38 | 5.01 ± 0.41 | 0.747 |

Student's t-test at $P < 0.05$ levels was used for significant difference between two independent means.

Adropin levels were significantly higher in T2DM group compared to control group ($P<0.001$). The analysis of gender's effect on Adropin levels revealed a non-significant difference, as shown in Table 3.

**Table 3:** Comparison of Adropin level between the study groups

| | T2DM Group (Mean ± SD) | Control Group (Mean ± SD) | P-value < or = |
|---|---|---|---|
| **Adropin (pg/mL)** | 1760.1 ± 170.55 | 1040.1 ± 150.76 | 0.001** |
| | T2DM Group **Male** | T2DM Group **Female** | |
| | 1750.5±230.34 | 1700.4±320.74 | 0.403 |

* Significant difference between two independent means using Student t-test at $P < 0.001$ levels.

### Correlation of Adropin and Glycemic Indices

Pearson correlation analysis was employed to explore the possible correlation of Adropin and glycemic indices of T2DM group and control group. In the control group, there was a significant positive correlation between Adropin levels and insulin (P= 0.001), HOMA-IR (P= 0.001), and B% (P= 0.002). On the other hand, Adropin levels were negatively correlated with S% (P= 0.001), G/I ratio (P= 0.001), QUICKI (P= 0.001), and McAuley index (P= 0.001), as shown in Table 4 and Figure 2.

**Table 4:** Pearson correlation analysis of Adropin levels with biochemical parameters in the Control group.

| Parameters | Adropin (pg/mL) | |
|---|---|---|
| | r | P – Value < or = |
| **BMI (kg/m$^2$)** | 0.075 | 0.604 |
| **Age (year)** | –0.055 | 0.565 |
| **FBS (mg/dL)** | - 0.170 | 0.237 |
| **HbA1c %** | 0.013 | 0.928 |
| **Insulin (µIU/mL)** | 0.563 | 0.001** |
| **HOMA-IR** | 0.530 | 0.001** |
| **B%** | 0.420 | 0.002** |
| **S%** | - 0.531 | 0.001** |
| **G/I Ratio** | - 0.569 | 0.001** |
| **QUICKI** | - 0.405 | 0.004** |
| **McAuley Index** | - 0.450 | 0.001** |
| **TyG Index** | 0.209 | 0.145 |

*Correlation is significant at $P<0.001$ level.

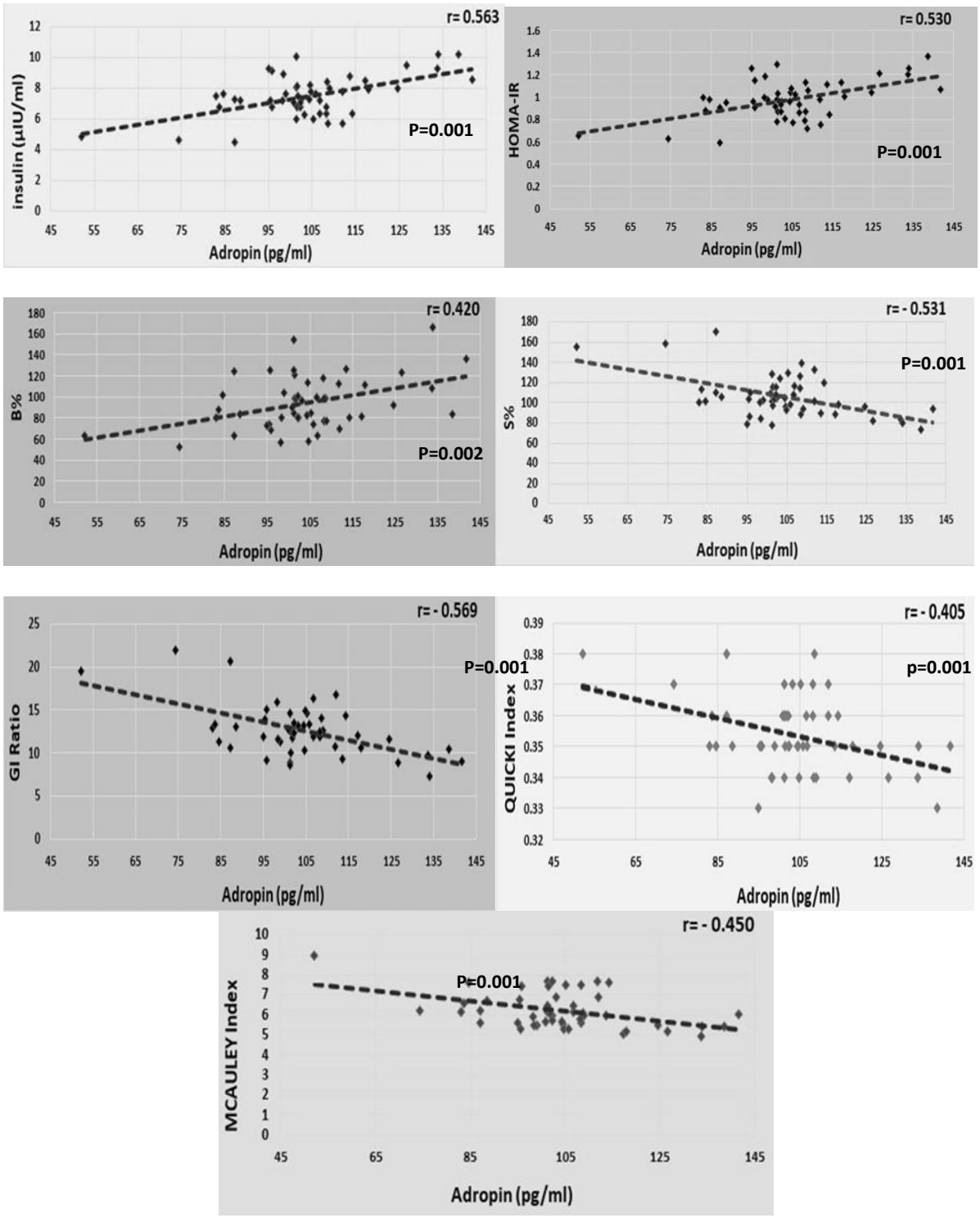


**Figure 2:** Pearson correlation analysis of Adropin with: insulin, HOMA-IR, B%, S%, G/I ratio, QUICKI and McAuley indices in the Control group.

In T2DM group, a significant positive correlation was observed between Adropin levels and insulin (P= 0.001). No significant correlations were found between Adropin levels and the other variables, as shown in Table 5 and Figure 3.

**Table 5:** Correlation of Adropin levels with glycemic indices in T2DM group.

| Parameters | Adropin (pg/mL) | |
|---|---|---|
| | r | P – Value < or = |
| **BMI (kg/m$^2$)** | 0.007 | 0.963 |
| **Age (year)** | –0.006 | 0.774 |
| **FBS (mg/dL)** | - 0.108 | 0.449 |
| **HbA1c %** | - 0.133 | 0.351 |
| **Insulin (µIU/mL)** | 0.433 | 0.001** |
| **HOMA-IR** | - 0.038 | 0.790 |
| **B%** | 0.115 | 0.421 |
| **S%** | - 0.079 | 0.581 |
| **G/I Ratio** | - 0.172 | 0.227 |
| **QUICKI** | - 0.044 | 0.761 |
| **McAuley Index** | - 0.102 | 0.460 |
| **TyG Index** | - 0.049 | 0.732 |

**Correlation is significant at P<0.001 level.

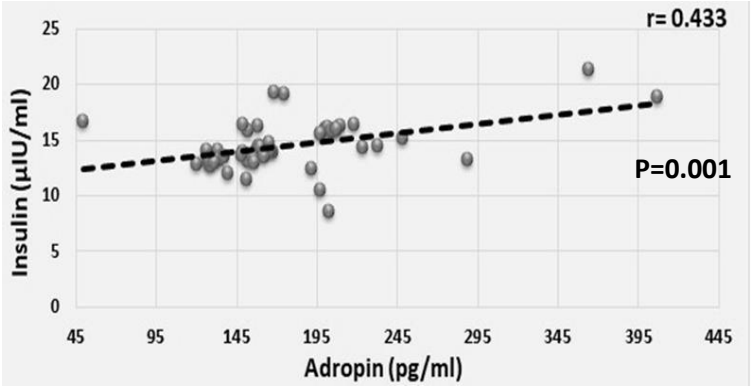


**Figure 3:** Pearson correlation between Adropin and insulin levels in T2DM group.

**Receiver Operating Characteristic of Adropin**

Receiver operating characteristic (ROC) curve analysis was constructed for Adropin level as a predictor for the disease. The optimal cut-off value of Adropin level for prediction of T2DM was 1250.7pg/ml. Hence, Adropin level > 1250.7 pg/ml is a predictor for T2DM, as a large significant area under the curve (AUC= 97.9%) was observed indicating a significant association between the higher level of Adropin and having T2DM disease. This cut-off value was associated with a sensitivity (SN) of 100% and specificity (SP) of 96.1%, with accuracy of 97.8%. The positive predictive value (PPV) of Adropin was 95.2% and negative predictive value (NPV) was 100%, as shown in Figure 4 and Table 6.

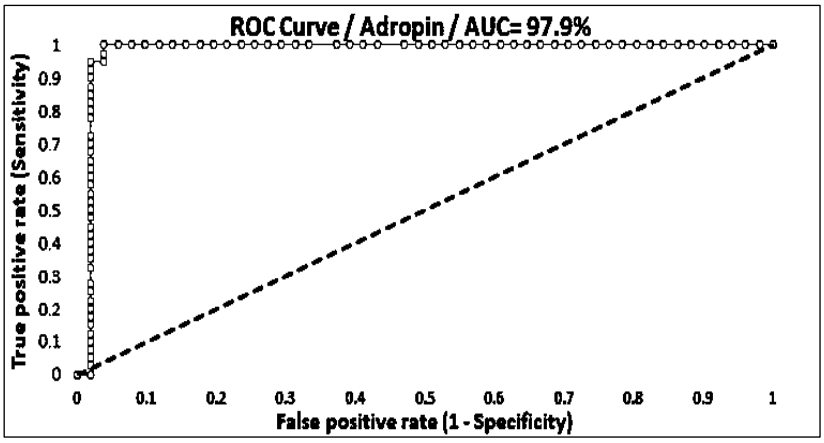


**Figure 4:** ROC curve of Adropin levels in prediction of T2DM.

**Table 6:** Diagnostic accuracy of Adropin level to predict T2DM.

| Adropin (pg/ml) | Cut-off value | AUC | SN | SP | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|
| | 1250.7 | 97.9% | 100% | 96.1% | 95.2% | 100% | 97.8% |

## Discussion

In this study, HbA1c levels were significantly higher in T2DM group, a finding consistent with a study by Yuan *et al*.,(2023), which demonstrated that their HbA1c prediction model had superior prediction ability [25]. Insulin was considerably greater in the T2DM group than in the control group, this result was in disagreement with that of a study by Ahmed and Hatam (2023), who reported a significant decrease in insulin ($P<0.05$) in T2DM compared to control group [7].

A study by Abbas *et al.,*(2020) found that increase HOMA-IR is a significant risk factor for the development of T2DM and cause a hyperglycemic condition [26]. Their result agrees with that in this study. The TyG index was significantly higher in T2DM group, the outcome matched that of a research conducted by Chamroonkiadtikun *et al*.,(2020) who found that, although FPG seemed to be a more reliable predictor of diabetes, the TyG index was strongly linked to the probability of diabetes incidence and could be a useful biomarker of developing diabetes [27].

The T2DM is characterized by a persistent loss of β-cell function, which is correlated with elevated HbA1c levels and an extended duration of T2DM, this explanation was to clarify the lower B% levels of T2DM patients found by Wysham and Shubrook, (2020) [28], which agree to that in this study.

The lower S% levels observed in T2DM group agree with that of a study by Al-Musawi *et al*., (2021) study who suggested that patients with T2DM who have inactive lifestyle, have poor glycemic control, and overeating contributed to the abundant accumulation of glucose in their muscles, adipose tissues, and pancreatic cells [29]. McAuley and QUICKI indices were significantly lower in T2DM group, which agree with Pandit *et al.*, (2020) study. They found that the QUICKI level was 0.358±0.041 in normal population while in the lean metabolic syndrome (MetS) and obese metabolic syndrome were 0.334±0.037 and 0.316±0.026 respectively. However, the McAuley index result was in disagreement with this study. They found McAuley index in normal population was 0.49±0.26 while in lean MetS and obese MetS was 0.75±0.25 and 0.79±0.17 respectively. In the same study, IR indices were higher in MetS than in the normal population; however, there is no difference in the indices between

lean and obese MetS. Given that waist circumference varies little in relation to IR level, its applicability may need to be reevaluated [30]. In the current study, Adropin levels were significantly higher in the T2DM group compared to controls, which is consistent with findings by Ugur *et al*., (2015). Increased endothelial function and energy homeostasis are linked to the reason of these peptides' elevated activity. The same result was found by another study [31].

However, a disagreement was found with that of a study by Shah *et al*., (2021) who found lower Adropin level in T2DM compared to control. Also, they observed an inverse correlation between Adropin with FBS and HOMA-IR in T2DM patients [32]. Serum Adropin level and metabolic-related indicators showed a significant inverse connection, suggesting that Adropin may have a preventive effect against the development of metabolic illnesses, particularly diabetes [33, 34].
According to Kumar *et al.*, (2012) hypothesis, Adropin played a role in maintaining metabolic homeostasis and that Adropin deficiency affected glucose homeostasis negatively and increased the risk of IR and the advancement of T2DM [35].The ROC analysis has been carried out to assess whether Adropin might be a new biomarker for identifying T2DM as compared with healthy control groups. Results of the ROC analysis are displayed in Table 6 and Figure 4. The optimal cut-off value of adropin level was 1250.7 pg/ml. Hence, adropin level > 1250.7 pg/ml is a predictor for T2DM, as a large significant area under the curve (AUC= 97.9%) indicates a significant association between the higher level of adropin and having T2DM. Shanaki (2016) observed that a cut-off value of >2.25 ng/mL of Adropin can predict T2DM [23].

## Conclusion

The current study found that the levels of Adropin were elevated in T2DM group than in the healthy control group. This suggests that Adropin may be involved in the pathogenesis of the development of diabetes and could be used as a biomarker for early detection of the disease.

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