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# Determination of adropin, body mass index and other biochemical parameters in Iraqi type II diabetic patients

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***Abstract***---Evidence suggests a hormone peptide named adropin, is involved in lipid metabolism, insulin resistance, and obesity. However, its role in pathogenesis of type 2 diabetes mellitus (T2DM) is still unclear in humans. Therefore, we investigated whether adropin levels are altered in T2DM patients, and evaluated its association with diabetes- related parameters. Samples which collected from 180 subjects were divided into case group [n = 90] and control groups [n = 90]. The mean age was [43.17 ±11.13] years. Men (n=81) and femanl (n=99) were participated in case-control study. Serum adropin levels were determined by ELISA. The mean serum adropin level was significantly higher [P<0.01] in the control group compared to case group [6.9±1.3 vs. 5.8±1.2] respectively. The result shown there was a significant difference [P-value<0.001] between body mass index and adropin. adropin with high significant negative correlation [P-value<0.001] between adropin and body mass index, fasting blood sugar, glycated hemoglobin, insulin, and homeostatic model assessment for insulin resistance also a significant negative correlation was found between the adropin and low-density

lipoprotein, triglyceride, very low-density lipoprotein and no significant with cholesterol, high-density lipoprotein. We showed that T2DM patients have lower adropin levels, and serum level of adropin is inversely associated with and body mass index, insulin resistance; therefore indicating a close association between adropin and T2DM. However, further studies are necessary to establish the role of adropin in diabetes.

***Keywords*---**adropin, type 2 diabetes mellitus (T2DM), hemoglobin.

## Introduction

T2DM is the furthermost common of DM which is identified via hyperglycemia, insulin resistance, and relative insulin deficiency (1). T2DM represents approximately 90% of all types of diabetes(2). In T2DM, hyperglycaemia is the outcome of insufficient production of insulin and inability of the body to react fully to insulin, a case that is well-defined as insulin resistance(3) . The risk of developing T2DM rises with obesity, age, and physical inactivity. It occurs more recurrently in those with dyslipidemia or hypertension (4). It was appraised that in 2017 there were 451 million (age 18–99 years) individuals with diabetes worldwide (5). The prevalence of T2D in Iraq reached epidemical proportions in 2007, impacting about 2 million people or 7.43% of the total Iraqi population (6). In recent years, much attention has been focused on potential role of molecules involved in regulation of metabolic homeostasis and complicated interactions between its components in pathogenesis of T2DM(7) .

Adropin is one of the most important adipose tissue derived hormones originally identified in 2008(8). Adropin (ADR, molecular weight 7.927 kDa) is a 76 amino acid peptide(9).This hepatokine is encoded by the energy homeostasis-associated gene (Enho), which is located in chromosome 9 in humane and is expressed mainly in the brain and the liver(10). It was recently demonstrated that adropin is a membrane-associated protein that regulates cell-cell communication(11). However, it is also detected in peripheral tissues such as in the heart, lung, kidney medulla and muscles. Furthermore, adropin protein is present in the circulatory system of humans(12).

Adropin levels has direct correlation with amount of body fat and body mass index (BMI)(13). It was found that the biological effects of adropin are conferred through the activation of G protein-coupled receptor 19 (GPR19) a member of the orphan G protein-coupled receptors family, is considered as a candidate for an adropin receptor(8).

Adropin is a multifunctional peptide implicated in various physiological processes, recent studies have suggested that plays a pivotal role in metabolic homeostasis, including fatty acid metabolism, as well as energy expenditure, insulin resistance prevention, and development of dyslipidemia and hyperinsulinemia associated with obesity(14).

Adropin of enhances glucose tolerance, ameliorates insulin resistance and promotes preferential use of carbohydrate over fat in fuel selection and enhanced insulin-induced cell surface expression of GLUT4 without altering the whole cell level(15). Skeletal muscle is a key organ in mediating adropin's whole-body effects, sensitizing insulin signaling pathways and altering fuel selection preference to favor glucose while suppressing fat oxidation , suggest adropin has the potential to promote insulin-induced glucose uptake in muscle(16).

The significance of adropin provides information for future prospective and interventional human studies to assess adropin therapeutic roles in human individuals with T2DM(11). Also, studies the serum level of adropin in diabetic patients in comparison with healthy individuals have shown a decreased level of adropin in diabetic patients(17). Therefore, the objective of this study was to investigate adropin concentration its association with BMI and its association as well as with metabolic and anthropometric parameters in patient with T2DM compared with healthy controls .

## Materials and Methods

### *Chemicals*

Sandwich enzyme-linked immunosorbent assay [ELISA] method is used to quantitatively determine blood insulin and irisin hormones by employing an automated ELISA reader [PKL PPC 230]. FBS, HbA1c, CH., TG, HDL, LDL, and VLDL were quantified in this investigation using the COBAS INTEGRA® 400 plus automatic biochemistry analyzer [Roche/Hetachi Diagnostics Ltd Company, Japan]. Automated biochemistry analyzer COBAS INTEGRA® 400 plus may perform colorimetric, immunoturbidimetric, and ion-selective assays depending on the type of test needed.

### *Study design*

A total of 90 Iraqi T2DM patients[ 48 females and 42 males] were selected from those attending the Dr. Ali Muneeb Al- Rubaie's lab in [Baghdad- Iraq] from December 2021– February 2022 . The diagnosis of T2DM was performed on the basis of the recommended criteria by WHO[12]..For the purpose of comparisons, 90 Iraqi control subjects who were comparable to the diabetes mellitus patients in respect to gender [51 females and 39 males] were included. The mean age of both groups was [43.17±11.13] years.

### *Statistical analysis*

Analysis of data was carried out using the available statistical package of SPSS-24(Statistical Packages for Social Sciences-version 24). Data were presented in simple measures of frequency, percentage, mean and standard deviation . The significance of the difference of different means (quantitative data) was tested using Students t-test for difference between two independent means or Paired t-test for difference of paired observations (or two dependent means) , ROC, and Tukey test were utilized . Statistical significance was considered whenever the p-value was less than 0.05.

**Results**

The results included a total of 180 participants were enrolled in the current study but the mean age was 43.17 (±11.13) years who diagnosed with type II diabetic and there was a significant difference between the study groups regarding the mean age as in figure 1

The results found the females constituted the largest percentage of the sample (55%), with no significant difference between the study groups regarding the gender distribution (P-value=0.765), as shown in table 1.

The results of the BMI distribution showed there was a significant difference between the study groups. In the control group, 23.3% of the participants were obese and 6.7% of them had marked obesity, while in the case group, 38.9% of the participants were obese and 30% had marked obesity as shown in table 2.

Results showed there was a significant higher [P-value <0.05] level of FBS, HbA1c, LDL, CH, TG and IR in the case group compared to the control group, while no significant difference [P-value <0.442] was obtained between the study groups in HDL , also the means of irisin were significantly lower [P-value <0.05] among the participants in the case group compared to those in the control group, as shown in table 3. Moreover, the results showed there was a significant negative correlation [P-value <0.001] between irisin and BMI, as shown in table 4, and figure 3. Moreover, the results showed there was a significant negative correlation between adropin and BMI, as shown in table 4 and figure 3

The results reported there was a significant negative correlation between correlations were found between adropin and FBS, HbA1C, and HOMA-IR. As shown in table 5 and figure 4. According to the receiver operating characteristic cut-off point, the SN was 83.3% with an SP of 51.1%. While the cut-off point of the adropin was 147.8 (ng/L) with an SN of 80% and SP of 50% as shown in figure 5. Finally, the results showed significant negative correlation was A significant negative correlation was found between adropin and triglyceride and VLDL, as shown in table 6

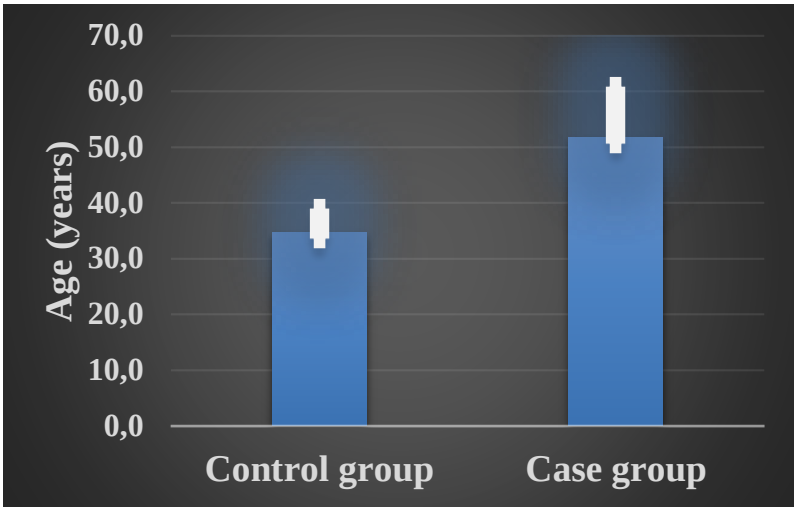


Figure 1: Age distribution of the participant

Table 1: Gender distribution according to the study groups

| Gender | Groups | | Total | P-value |
|---|---|---|---|---|
| | Control group | Case group | | |
| | N (%) | N (%) | | |
| Female | 51 (56.7) | 48 (53.3) | 99 (55.0) | 0.765 |
| Male | 39 (43.3) | 42 (46.7) | 81 (45.0) | |
| Total | 90 (50.0) | 90 (50.0) | 180 (100.0) | |

Table 2: The distribution of the BMI according to the study groups

| BMI | Groups | | Total | P-value |
|---|---|---|---|---|
| | Control group | Case group | | |
| | N [%] | N [%] | | |
| Normal | 42 [46.7] | 12 [13.3] | 54 [30.0] | <0.001 |
| Overweight | 21 [23.3] | 16 [17.8] | 37 [20.6] | <0.001 |
| Obesity | 21 [23.3] | 35 [38.9] | 56 [31.1] | <0.001 |
| Markedobesity | 6 [6.7] | 27 [30.0] | 33 [18.3] | <0.001 |

Table 3: The distribution of the study markers according to the study groups

| Variables | Groups | | P-value |
|---|---|---|---|
| | Control group | Case group | |
| | Mean (±SD) | Mean (±SD) | |
| Fasting blood sugar (mmol/L) | 5.4 [±0.4] | 9.8 [±2.9] | <0.001 |
| HbA1C | 4.3 [±0.6] | 8.3 [±2.5] | <0.001 |
| Cholesterol (mg/dl) | 163.2 [±21.1] | 208.5 [±54.0] | <0.001 |

| | | | |
|---|---|---|---|
| Triglycerides (mg/dl) | 78.1 [±19.7] | 216.5 [±85.9] | <0.001 |
| LDL (mg/d) | 100.8 [±21.3] | 132.4 [±33.2] | <0.001 |
| HDL (mg/dl) | 48.1 [±6.6] | 50.5 [±28.6] | 0.442 |
| VLDL (mg/dl) | 18.1 [±8.3] | 36.9 [±20.7] | <0.001 |
| Fasting Insulin (mIU/L) | 9.0 [±0.8] | 10.7 [±4.4] | <0.001 |
| Insulin resistance | 2.1 [±0.3] | 4.5 [±1.5] | <0.001 |
| Adropin (ng/L) | 149 [±16.9] | 139.8 [±19.9] | **<0.001** |

Table 4: Correlation between adropin and BMI

| | **Adropin (ng/ml)** | |
|---|---|---|
| | Pearson Correlation | P-value |
| BMI (kg/m$^2$) | -0.462 | <0.001 |

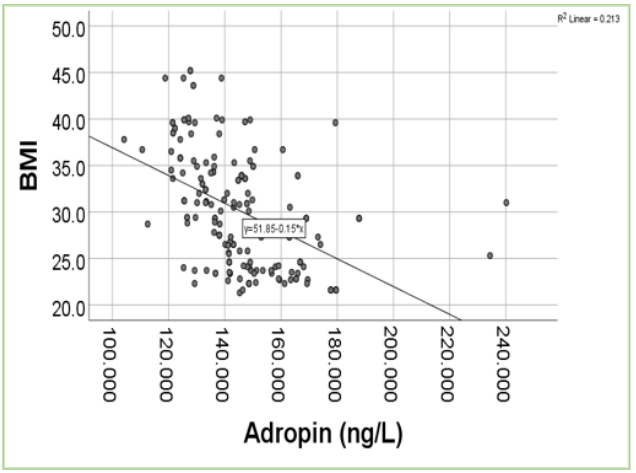


Figure 3: Correlation between adropin and BMI

Table 5: Correlation between adropin and other diabetic variables

| | Adropin (ng/ml) | |
|---|---|---|
| | Pearson Correlation | P-value |
| FBS (mmol/L) | -0.167 | 0.025 |
| HbA1C | -0.168 | 0.024 |
| Insulin(mIU/L) | -0.117 | 0.118 |
| HOMA-IR | -0.207 | 0.005 |

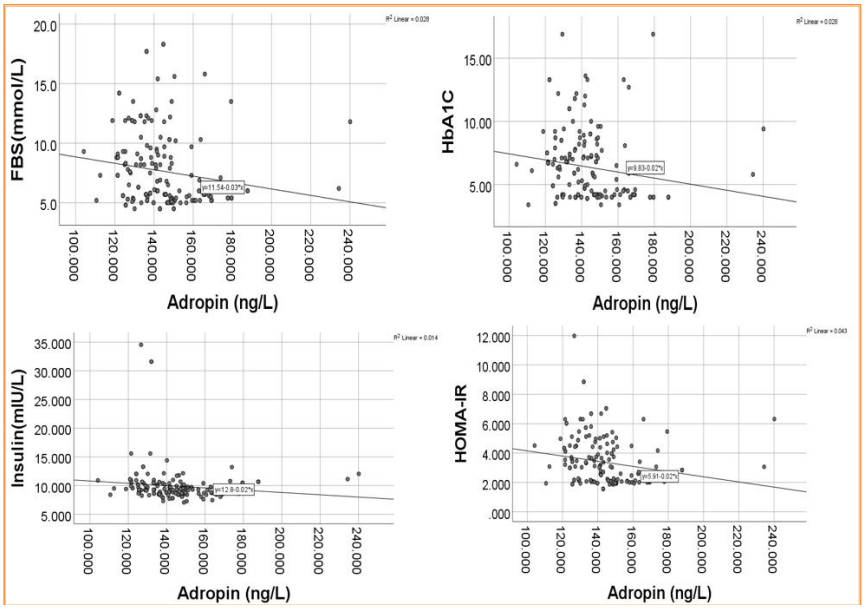


Figure 4: Correlation between adropin and diabetic variables

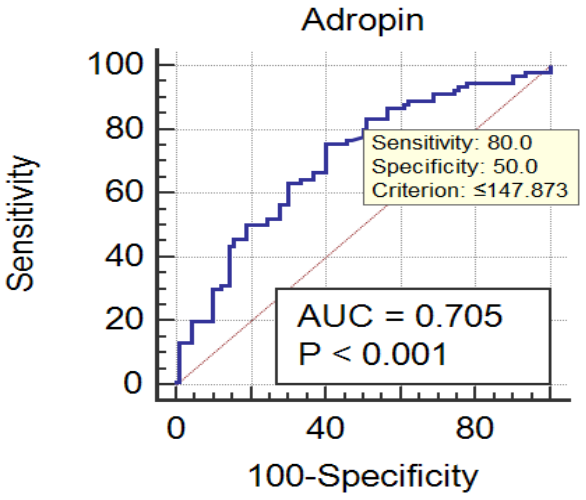


Figure 5: Receiver operating characteristic curve for adropin

Table 6: Correlation between adropin and lipids

| | Adropin (ng/ml) | |
|---|---|---|
| | Pearson Correlation | P-value |
| Triglyceride (mg/dl) | -0.250 | 0.001 |
| Cholesterol (mg/dl) | -0.039 | 0.605 |
| LDL (mg/d) | -0.162 | 0.030 |
| HDL (mg/dl) | -0.062 | 0.407 |
| VLDL (mg/dl) | -0.204 | 0.006 |

**Discussion**

The study findings were in agreement with those of(18) , who found that age and gender had an impact on biochemical, hormone, and adipocytokine parameters in Iraqi T2DM patients. Furthermore, these findings were in agreement with those of Wong et al. as well. There was a rise in the prevalence of glucose intolerance (both pre-diabetes and T2DM) as people aged 45 and older, according to a study by(19). When it comes to aging and glucose intolerance, there are several contributing factors to consider. When it comes to age-related changes in insulin sensitivity as well as beta cell function, aging is a major contributor(20) . Aging is associated with reduced beta cell proliferation capacity and increased sensitivity to apoptosis(21).

It was found that diabetes was more common in women than men in Basra, Iraq(22) , although the findings were at odds with those of(23), who found that diabetes appeared to diminish the more favorable cluster of risk factors that women have in general compared to men(23). As a result of this, testosterone has been linked to a bidirectional modulation of diabetes risk in men and women. Diabetes can be prevented in men by testosterone, which acts as an antidote. While insulin sensitivity is improved and cardiovascular risk is reduced in hypogonadal males, testosterone administration has the opposite effect. In women, testosterone's effects are quite different. Initial β -cell hyper-function in women with testosterone excess may lead to secondary β -cell failure and T2DM (24). Differences in disease risk between men and women can be traced to a variety of factors, including differences in human biology, behavior, or anatomical structure.

According to some experts, nearly all human diseases are sexually dimorphic, ranging from their prevalence, age of onset to their severity or duration. Females are thought to be diagnosed with T2DM at a younger age because puberty occurs earlier in women. When boys reach puberty, those ratios tend to reverse in a dramatic fashion. Women's hormones change as they get older and enter menopause, affecting insulin utilization once more(25).

These findings matched those of(26), who found that BMI was one of the factors that increased diabetes According to another study, the key causes of type 2 diabetes are personal lifestyle and eating habits that contribute to overweightness and obesity(18). Obesity and diabetes epidemics are increasing at the same time. Both of these metabolic illnesses are characterized by insulin action abnormalities, with obese persons resistant to insulin and their pancreatic -cells failing, eventually leading to diabetes ,People are more likely to develop visceral versus peripheral adiposity, which is connected to insulin resistance and type 2 diabetes, than total adiposity (27).

The results were agreed with (2)who found there was increasing in obesity and overweight among people with type 2 diabetes compared to the normal people , as well as the study agreed with (28). As well as the current study agreed with results previously reported by (29)that found Elevated BMI was also associated with progressively higher risk for all DM2 complications The relationship between

excess weight and being diagnosed with a DM2 complication was stronger for women than for men.

However, the association between diabetes mellitus and obesity due the type 2 diabetes is described as a combination of low amounts of insulin production from pancreatic β-cells and peripheral insulin resistance(30). Insulin resistance leads to elevated fatty acids in the plasma, causing decreased glucose transport into the muscle cells, as well as increased fat breakdown, subsequently leading to elevated hepatic glucose production. Insulin resistance and pancreatic β-cell dysfunction must occur simultaneously for type 2 diabetes to develop. Anyone who is overweight and/or obese has some kind of insulin resistance, but diabetes only develops in those individuals who lack sufficient insulin secretion to match the degree of insulin resistance. Insulin in those people may be high, yet it is not enough to normalize the level of glycemia(31).

On the other hand , the current The current finding agreed with results previously reported by (32) the findings an increase in the levels of fasting blood glucose, HbA1C, cholesterol, triglycerides, LDL, as well as VLDL, but the levels of HDL was opposite to the current study which was decreased in patients with T2DM compared to control, some other studies also showed the HDL was increasing in T2DM(33).

Hemoglobin is glycated by a non-enzymatic interaction between glucose and the beta-N-terminal chain's end. This result in a Schiff base (pre-A1c), which is then transformed into Amadori products, including HbA1c. The amount of glycated haemoglobin increases as the average plasma glucose rises (and thereby HbA1c). HbA1c is a good indicator of glucose control across the lifespan of a red blood cell (usually 120 days)(34).

As well as the results agreed with (35)showed that mean cholesterol was found to be statistically significant ($p<0.05$) in Group 1 (newly diagnosed group) when compared with control groupin , (32)who found that patients with T2DM have significantly higher serum concentrations of cholesterol, also the results of HDL revealed that mean HDL-C was found to be significantly different ($p<0.05$) in diabetic patients compared with control group. Type 2 diabetes is characterized by low HDL cholesterol (HDL-C) and HDL dysfunction and results of LDL was found to be significantly different ($p<0.05$) when compared with control group.

In addition , the results also agreed with (20)that reported the overweighted people with T2DM recorded high value of fasting insulin and insulin resistance ,In addition , the Insulin resistance has a major role in the pathogenesis of diabetic dyslipidemia as there is evidence of increased release of free fatty-acid from insulin resistance fat cells. The free fatty acids entering into the liver in the presence of glycogen promotes triglyceride production and also secretion of apolipoprotein B and VLDL cholesterol, thus resulting in fatty liver. Similarly, higher levels of circulating insulin is also associated with low HDL levels(36).

Furthermore, there was agreement with (17) also agreed with(37), notably several studies indicated an inverse association between circulating adropin levels and body mass index . There was emerging evidence that energy homeostasis is

modulated by brown adipose tissue(8)

Adropin, associated with glucolipid homeostasis and insulin sensitivity, may implicate in the pathogenesis of DM2, and disagree with (38)that found the adropin is maintaining glucose homeostasis and regulation of lipid metabolism; and provides information for future prospective and interventional human studies to assess adropin therapeutic roles in human individuals with DM2, The level of adropin changes in different physiological and pathophysiological conditions. A decreased concentration of adropin is associated with many diseases such as insulin resistance associated with obesity and T2DM(39).In addition ,Adropin of enhances glucose tolerance, ameliorates insulin resistance and promotes preferential use of carbohydrate over fat in fuel selection and enhanced insulin-induced cell surface expression of GLUT4 without altering the whole cell level (11) . In muscle, adropin increased insulin-induced Akt phosphorylation and cell-surface expression of GLUT4 suggesting sensitization of insulin signaling pathways. Also, studies the serum level of adropin in diabetic patients in comparison with healthy individuals have shown a decreased level of adropin in diabetic patients(13).

Given the increase in the prevalence of diabetes, insulin action as a major contributor should be enhanced; adropin has been recognized as a secreted peptide that enhances glucose tolerance, oxidative glucose metabolism, and insulin receptor signaling in skeletal muscles in diet-induced obese(40).An inverse association between adropin levels and body mass index (BMI) has also been reported in human studies(41). The first evidence indicating a link between adropin, obesity and the risk of metabolic syndrome in humans was presented by (41)who reported that low adropin levels were found in obese patients and weight loss increased its levels.In adipose tissue, lipogenesis depends upon the availability of carbohydrates in circulation, as well as their uptake by adipocytes, demonstrate that adropin may affect intracellular lipid content by the suppression of lipid accumulation during adipogenic differentiation and by promoting the lipolytic activity of white mature adipocytes(42).The regulation of lipolysis in white adipocytes is complex, and it is modulated by numerous metabolic, hormonal and environmental signals .showing that adropin protects from adiposity. Adropin promotes the proliferation of white preadipocytes and suppresses their differentiation into adipocytes. By contrast, the effects of adropin on mature white adipocytes are unknown. So the adropin deficiency may lead to adiposity. By contrast, administration or overexpression of adropin protects against body weight gain in human fed a high-fat diet(8).

The finding of the current study agreed with results previously reported by (43) that found serum Adropin levels were inversely correlated with adverse metabolic parameters including FBS, HbA1C, HOMA-IR and fasting insulin and agreed with(44), as well as (45)showed opposite to current study which reported Serum adropin has negative correlation with HbA1C and fasting insulin and BMI , one possible reason that adropin plays an important role in maintaining metabolic homeostasis, increasing glucose utilization at the expense of fatty acids, improving glucose tolerance, and reducing insulin resistance. The differences between the studies it was highly probable that our observations in T2DM were confounded by variations in disease duration, diabetic complications

Metabolically, adropin regulates the activities of the principal pancreatic hormones that control the fate of glucose and fatty acids. In the liver, adropin enhances insulin signaling. while suppressing glucagon signaling .Adropin also regulates insulin signaling and glucose metabolism in skeletal and cardiac muscle(46)

according to the receiver operating caracteristic while the cut-off point of the adropin was 147.8 (ng/L) Agreed with (Es-Haghi, et al.,2021), Receiver operating characteristic (ROC) curve demonstrated adropin concentration could be used as a possible optimal cut-off value to identify T2DM from non-T2DM , Howevr Receiver operating characteristic (ROC) curve was drawn to ascertain whether serum adropin levels would become a biomarker of T2DM and determine the area under curve (AUC) and cut-off value.

This finding agreed with results previously reported by (47)that found patients have lower serum Adropin and high levels of lipid,as well as disagreed with(48) . In human subjects, circulating adropin was negatively correlated with the levels of plasma TG, apolipoprotein B, and LDL-c and was positively correlated with the HDL-c level) mentioned in their study that serum adropin concentrations were inversely associated with these indices of blood lipid. It is important to note that liver TG and TC was inversely correlated with serum adropin level, but only liver TG was significantly negative correlated with liver *ENHO* mRNA expression. We believed that two reasons might explain these differences, circulating adropin levels may associate with the discrepancy of the equilibrium between cholesterol synthesis and processing of circulating lipoprotein particles (10). On the other hand, liver ENHO mRNA expression is regulated by the biological clock and nutrition status. Experiments based on mice overexpressing adropin unable to prove the role for adropin in regulating cholesterol uptake from the diet, clearance from the circulation or cholesterol biosynthesis (14).The precise effect of adropin in lipid metabolism is still unclear. Further studies examining the relationship between adropin expression in liver tissues and intrahepatic TG and TC are required (49). Overall, these results collectively suggest that adropin deficiency may contribute to abnormalities in lipid metabolism, glucose homeostasis and insulin sensitivity.

**Conclusion**

The study demonstrate the the avge females displayed high percentage than male with T2DM and the mean average old of patient was + 40 year old also levels of irisin in patient with T2DM was decreased compared with healthy controls ,Moreover, serum adropin levels were negative correlated with anthropometric and metabolic markers of obesity and T2DM. also we found a negative correlation between adropin and BMI and certain lipid profile parameters adropin is a novel and promising peptide hormone for insulin resistance ,therefore it can be used as a prognostic marker for estimation of the T2DM.

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