Evaluation of Serum Asprosin Levels in Patients with T2DM in Duhok District, Iraqi Kurdistan Region

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Abstract
Asprosin was discovered to be an innovative hormone that is complemented in “adipose tissue” as well as is abnormally elevated in human and mice which are resistant to insulin. Nevertheless, data on the contribution of asprosin in the development of DM (T2DM) is still largely missing. Consequently, the main aim of this trial was to compare the serum asprosin concentration in people with T2DM to those of apparently healthy individuals who reside in Duhok district. This investigation was carried out between Sep. 2021 and Jan. 2022 at “Duhok diabetic center in Azadi teaching and Mazi non-government laboratory”. The levels of serum asprosin were measured in 180 participants (90 confirmed as with T2DM and 90 apparently healthy persons). All of the participants’ height, weight, and biochemical variables were measured and compared. Biochemical markers including lipid panel, fasted blood sugar, hemoglobin A1c, and fasted insulin were analyzed via the “auto-analyzer system termed 6000 series COBASS”. While, the blood’s levels of asprosin were calculated through ELISA assay. The study's data was analyzed using “SPSS”. The mean age of adults with T2DM was (43.93 ± 11.95) and among those who appeared to be healthy was (41.09 ± 11.33). Serum asprosin levels were considerably higher in T2DM patients (17.21 ± 4.61) ng/ml than in healthy control (5.17 ± 2.96) (P value < 0.001). In addition, a strong relation existed among serum asprosin and BMI, TG, TCH, FBG, HbA1c, FI, and HOMAIR (P value < 0.001), whereas an inverse relationship appeared between serum asprosin and HDL-C (P value < 0.01). This investigation proves that adults with T2DM had higher serum asprosin levels than those who seemed to be healthy. Additionally, in individuals with T2DM, serum asprosin was found to be strongly linked with BMI, FBG, FI, HOMAIR, TCH and TG (P value < 0.01).

Keywords: T2DM; Asprosin; Insulin Resistance; Metabolic Disorder

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I. INTRODUCTION
Diabetes mellitus (DM) is likely one of the earliest human disorders (Ahmed, 2002). T2DM (previously known as non-insulin dependent DM) is perhaps the most common kind of DM, which is defined by elevated blood sugar levels, insulin resistant (IR), and insulin insufficiency, which may develop from the interplay of genetic, environmental, and behavioral risk factors (Olokoba et al., 2012). T2DM is characterized by relative insulin insufficiency resulting from defective pancreatic β-cells and insulin resistance in target tissues (Chatterjee et al., 2017). T2DM is a growing worldwide health issue that is intimately related to the obesity pandemic. Hyperglycemia and insulin resistance (metabolic) syndrome put people with T2DM at threat for “micro-vascular (retinopathy, nephropathy, neuropathy) and macro-vascular (cardiovascular comorbidities)” consequences (DeFronzo et al., 2015). White adipose tissue (WAT) is the source of the newly discovered peptide hormone known as asprosin, also released by this tissue. Asprosin is able to increase the amount of glucose which is released from the liver (Romere et al., 2016; Duerrschmid et al., 2017). Recent investigations on asprosin have found that it is elevated in people with T2DM compared to controls, and that the levels of asprosin are likewise linked to insulin resistance (Zhang et al., 2019; Wang et al., 2018). Profibrillin’s C-terminal domain breaks down during fasting, triggering the production of asprosin in adipocytes. Through the activation of the G protein-cAMP-PKA axis, asprosin causes a rapid liberation of glucose in the hepatocytes (Romere et al., 2016). In liver, the olfactory receptor aids to receive signals upon asprosin attachment and is also...
essential for the generation of glucose in the liver (Li et al., 2018). Several investigations have shown that asprosin concentrations in the blood are correlated with improved insulin sensitivity (Wang et al., 2019; Groener et al., 2019; Wang et al., 2018; Zhang et al., 2019). Recombinant asprosin injection raises glucose levels and promotes hyperinsulinemia, whereas anti-asprosin anti-body injection improves glucose tolerance and reduces insulin resistance (Romere et al., 2016). As a consequence, higher asprosin levels in individuals with type 2 diabetes are pathophysiological (Romere et al., 2016). Asprosin's invention proved critical to the treatment of a range of metabolic illnesses linked to insulin resistance. Asprosin has been found to have an important and complicated role in the metabolism and the development of metabolic disorders according to latest researches (Yuan et al., 2020). There are 2 studies have been conducted on asprosin in Kurdistan Region of Iraq, one in women with poly cystic ovarian syndrome (Ameen and Sulaiman, 2021) and the other in metabolic syndrome (Sulaiman, 2021). In addition, according to our knowledge, no one has conducted any study on the blood levels of asprosin in people who have T2DM in our region. More research needs to be done to find out if asprosin and T2DM are linked and if asprosin can be used as a screening tool to find and diagnose T2DM. In order to conduct additional research on the impact of asprosin on metabolic problems such as IR and T2DM, the goal of the current investigation was to assess the levels of serum Asprosin in T2DM patients in Duhok, Iraq, and to correlate these levels with those of healthy individuals.

II. MATERIALS AND METHODS

A. Subjects and study design
A cross-sectional approach was utilized as the technique of choice in order to fulfill both the protocol and the objectives of the research. A total of 180 participants (90 apparently healthy and 90 of T2DM) were chosen at random from the patients and personnel of the “Duhok diabetes center in Azadi teaching and Mazi non-government laboratory”. The research stayed conducted between Sep. 2021 and Jan. 2022. Inclusion criteria for the T2DM group included therapy for T2DM (with oral "hypoglycemic drugs"). Cancer, thyroid disease, renal illness, liver disease, congestive heart disease, and non-fasting patients were excluded from the current study.

B. Data collection and research tool
Face-to-face interviews were used to ask participants to complete a comprehensive questionnaire covering demographic information and current/past medical history. Personal information was gathered such as (phone number, age, employment, and residence), height, weight, BMI, any history of chronic illnesses. The questionnaire had categorized for oral hypoglycemic medicine history as well as insulin targeted therapies background. The ethical approval to conduct the investigation was granted by the Research Council of "Duhok Technological Campus-Shekhan", as well as the General Directorate of Health in Duhok's Ethical Committee evaluated and approved the study procedures (Code of Ethics:18082021-8-22). All participants provided their oral and written informed agreement to use personal data and samples before participation.

C. Diagnostic criteria
Patients who met the American Diabetes Association (ADA) type 2 diabetes criteria had FBG ≥ 100 mg/dL, hemoglobin A1c ≥ 6.5% or OGTT plasma sugar level 2 h after the load ≥ 200 mg/dL. Whereas, participants meeting the following criteria were considered as healthy controls: FBG < 100 mg/dL, HbA1c < 5.7 %, and OGTT-2 h post-loading plasma glucose <140 mg/dL (ADA, 2010; Thewjitcharoen et al., 2019). A systolic blood pressure that was greater than 130 mmHg or a diastolic blood pressure that was greater than 85 mmHg was considered to be hypertension.

D. Anthropometric assessment
The following anthropometric variables were evaluated: height (cm), weight (kg), and body mass index (kg/m2). Resting in a sitting position for a minimum of 10 min was required prior to taking each individual’s blood pressure. The average of the 3 blood pressure readings was used to estimate blood pressure. The BMI was determined by dividing the individual's weight in kg by their height in meters squared (Deore et al., 2012).

E. Blood samples collection
After at least 12 h of fasting overnight, blood samples (10 ml of venous blood) were taken between 8:30 and 10:30 a.m. Two ml of this blood were put in an EDTA tube for measuring HbA1c, and the other 8 ml were put in a gel tube (without clotting agents) in just below a couple of hours for serum collection. For 8 min, the gel tube was spun at 1000 rpm. In order to perform the ELISA test on the serum asprosin, one portion of the serum was placed in a deep freezer (-25 °C) while the other portion was used to measure FBG, fasting insulin, and the serum lipids.

F. Biochemical measurements
At “Mazi Private Laboratories in Duhok City”, serum samples were biochemically analyzed (FBG, TCH, serum TG, HDL-C, fasting insulin, and HbA1c) using the Autoanalyzer biochemical machine named COBASS series 6000 (Roche, Germany). Additionally, the ELISA technique was used for the assessment of serum asprosin levels. For each participant, the insulin resistance was described according to the following formula (HOMA-IR = FI (μU/ml) multiplied by fasting sugar (mg/dl) divided by 405) (Park et al., 2015). In addition, the levels of HbA1c in patients with T2DM were divided into 2 separate groups: the "good-control group," which was defined as diabetic patients with an average HbA1c of ≤ 7%, and the "poor-control group," which was distinguished as diabetic patients with a mean

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HbA1c of > 7% (Kassaian et al., 2012). These were compared to the concentration of asprosin in the serum.

G. Assessment of serum asprosin concentrations
Utilizing ELISA assay, quantitative measurements of blood asprosin concentrations were obtained and assessed (Inc. San Diego, USA from BioSource). The technique for using the kit was done in a way that was in line with what the manufacturer’s recommendations.

H. Statistical analysis
Applying version 25 of the SPSS package, the collected information was analyzed and displayed in the form (M ± SD). A comparison of proportions was carried out using the T-test. Moreover, one-way variance analysis (ANOVA) was utilized in order to contrast different groups. The Chi-square test was carried out for comparison of different categorical variables among groups. To determine the degree of connection between the data, the Pearson correlation coefficient was utilized. Furthermore, in order to establish the serum asprosin cut-off point for T2DM assessment, ROC curve analysis was performed out. Statistical significance was defined as when the p-value < 0.05.

III. RESULTS
A. Various demographic and biochemical aspects of the group under investigation
The epidemiological and chemical characteristics of the research participants are outlined in Table 1. Mean values of BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), TCH, fasting insulin, HOMA-IR, and HbA1c were substantially higher among patients with T2DM than in the healthy participants (p<0.001). With the exception, the high-density lipoprotein cholesterol level was substantially decreased in individuals having T2DM compared to the control healthy group (p<0.001). On the other hand, there was no statistically significant difference in age between the T2DM patients and the healthy groups (p value >0.05). T2DM patients’ asprosin serum levels were substantially greater than those of healthy controls (Table 1 and Figure 1).

| Variables          | T2DM patients (N=90) | Healthy adults (N=90) | P-value |
|--------------------|----------------------|-----------------------|---------|
| Age (years)        | 43.9 ± 26.12         | 41.09 ±11.33          | NS      |
| BMI (kg/m2)        | 31.24 ± 3.92         | 24.10 ± 3.04          | < 0.001*|
| SBP (mmHg)         | 125.64 ± 13.37       | 113.01 ± 11.12        | < 0.001*|
| DBP (mmHg)         | 83.78 ± 5.09         | 78.48 ± 4.91          | < 0.001*|
| TCH (mg/dl)        | 208.79 ± 23.54       | 155.52 ± 12.3         | < 0.001*|
| TG (mg/dl)         | 180.03 ± 30.88       | 91.48 ± 17.87         | < 0.001*|
| HDL-C (mg/dl)      | 40.97 ± 7.32         | 51.99 ± 8.64          | < 0.001*|
| FBG (mg/dl)        | 204.57 ± 26.47       | 88.57 ± 5.34          | < 0.001*|
| Insulin (μU/mL)    | 17.51 ± 7.06         | 6.88 ± 2.12           | < 0.001*|
| HOMA-IR            | 8.94 ± 4.07          | 1.51 ± 0.48           | < 0.001*|
| HbA1c (%)          | 8.85 ± 1.89          | 5.11 ± 0.20           | < 0.001*|
| Serum asprosin     | 17.21 ± 4.61         | 5.17 ± 2.96           | < 0.001*|
| (ng/ml)            |                      |                       |         |

Figure 1. Serum concentration of asprosin in control and T2DM groups.

Table 2. Analysis of the Pearson linking among blood asprosin levels with the potential metabolic hazardous variables with in the involved participants

| Variables          | T2DM (n=90) | Health adults (n=90) | P-value |
|--------------------|-------------|----------------------|---------|
| Age (years)        | .272**      | .616**               | < .001  |
| BMI (kg/m²)        | .679**      | .825**               | < .001  |
| SBP (mmHg)         | .346**      | .546**               | < .001  |
| DBP (mmHg)         | .295**      | .190                 | NS      |
| TCH (mg/dl)        | .338**      | .602**               | < .001  |
| TG (mg/dl)         | .217*       | .696**               | < .001  |
| HDL-C (mg/dl)      | -.271**     | -.703**              | < .001  |
| FBG (mg/dl)        | .871**      | .596**               | < .001  |
| FI (μU/mL)         | .250*       | .566**               | < .001  |
| HOMA-IR            | .505**      | .666**               | < .001  |
| HbA1c (%)          | .879**      | .661**               | < .001  |

(**) Correlation is remarkable at the 0.001 level (2-tailed). (*) Correlation is remarkable at the 0.01 level (2-tailed). NS: non- significant a p-value was >0.05.
B. Evaluation of the relationship between Asprosin quantity and other demographic and biochemical markers in the study participants

In both groups, the serum’s asprosin had a considerable positive correlation with age, BMI, TCH, TG, FBG, Fasting Insulin, HOMA-IR, and HbA1c (P<0.001), as determined by the “Pearson correlation coefficient (r)”. In addition, a considerable direct association (P value <0.01) between blood levels of asprosin and DBP, SBP, but this correlation was only found in the group of T2DM patients. In the opposite, the levels of asprosin were inversely associated with high-density lipoprotein cholesterol in both groups (P value <0.001) (Table 2).

C. Relationships among the asprosin and HbA1c groups of T2DM individuals under the investigation

Depending on a one-way ANOVA test, when the levels of serum asprosin compared to the levels of HbA1c in the good control and poor control groups, the levels of serum asprosin were significantly greater in the poor group than in the good group (P value <0.001) (Table 3). The HbA1c group levels (good control and poor control) when compared with the serum asprosin levels, there were significantly increased of serum asprosin levels in poor group than in good control group, this was according to one-way ANOVA test (P<0.001) (Table 3).

Table 3. Pattern of blood asprosin levels within different HbA1c patient groups of T2DM

| Variables | T2DM patients with HbA1c ≤7% | T2DM patients with HbA1c >7% | P-value |
|----------|-------------------------------|-------------------------------|---------|
| Serum asprosin (ng/ml) | 13.70 ± 2.15 | 19.34 ± 4.40 | < 0.001 |

*Demonstrates considerable relationship between the asprosin and HbA1c groups. Key: hemoglobin A1c=HbA1c.

D. Associations of blood asprosin levels with various demographic and biochemical characteristics of type 2 diabetes patients and the study participants

On the basis of their serum asprosin levels, all of the individuals were categorized into 1 of 3 tertiles (T1-T3). The first one was <4 ng/mL, the second was 4–13.5 ng/mL and the third was of about >13.5 ng/mL. The demographics as well as all group's biochemical characteristics are presented in (Table 4). There was a correlation between increasing tertiles and increases in indices including “age, BMI, FBG, fasting insulin, TCH, TG, HOMA-IR and HbA1c”. In correlation with the tertiles, the levels of HDL-C were declined. There was a considerable distinction between the all groups statistically. There was a considerable distinction between the all groups statistically in accordance to One-way ANOVA test (P<0.001).

According to the results of the Chi-square test, the number of patients suffering from T2DM rose with an elevation in asprosin levels among the tertiles (Figure 2). The majority of the people in our survey were located in the T1 and T2 schedules. The majority of healthy persons were found in the T1 and T2 categories. On the other hand, there were a greater number of people diagnosed with T2DM in T3 than in T2. From the other hand, the vast majority of patients with T2DM were on T3. According to the ROC analysis, the cut-off rate for blood asprosin to expect patients having T2DM was found to be (9.9 ng/ml) (P<0.001). It had a sensitivity of 1.0, a specificity of 0.9, as well as a value of 0.99 for the specific zone under the curve (AUC) (Figure 3).

Table 4. The pattern of the demographic and laboratory data in the research population among the 4 tertiles determined by the asprosin concentrations in their blood.

| Variables          | T1 (n=39) | T2 (n=67) | T3 (n=74) | p-value |
|--------------------|-----------|-----------|-----------|---------|
| Serum asprosin (ng/ml) | 2.76 ± 0.79 | 8.07±3.02 | 18.46 ±4.11 | < 0.001 |
| Age (years)        | 36.59 ± 10.99 | 43.48 ±10.94 | 44.76 ±11.83 | 0.001 |
| BMI (kg/m²)        | 22.11 ± 1.67 | 26.15 ±3.23 | 31.97 ± 3.62 | < 0.001 |
| BP(mmHg)           | 107.62 ± 10.65 | 118.36 ± 9.96 | 126.38 ± 13.91 | < 0.001 |
| DBP(mmHg)          | 78.28 ± 4.41 | 79.61 ± 5.54 | 84.00 ± 5.06 | < 0.001 |
| TCH(mg/dl)         | 157.15 ± 12.38 | 165.10 ± 23.37 | 210.77 ± 24.59 | < 0.001 |
| TG (mg/dl)         | 80.97 ± 13.84 | 119.10 ± 39.86 | 179.70 ± 32.16 | < 0.001 |
| HDL-C (mg/dl)      | 57.03 ± 3.86 | 47.60 ± 8.87 | 39.91 ± 6.93 | < 0.001 |
| FBG (mg/dl)        | 85.74 ± 4.95 | 113.09 ± 39.42 | 208.93 ± 28.61 | < 0.001 |
| Insulin(μU/mL)     | 5.93 ± 1.83 | 10.01 ± 5.44 | 17.48 ± 7.32 | < 0.001 |
| HOMA-IR            | 1.25 ± 0.37 | 3.18 ± 2.91 | 9.17 ± 4.33 | < 0.001 |
| HbA1c (%)          | 4.95 ± 0.17 | 5.70 ± 0.89 | 9.20 ± 1.8 | < 0.001 |

Figure 2. Total number of people who are present in each tertile.
It has been claimed in the past that increasing asprosin in people with T2DM may be an effective way to counteract the hyper-insulinemia that is seen in these individuals. Asprosin is usually released by the WAT, and its function is to get the liver to release more glucose. Despite this, the findings of previous research indicate that abnormally high concentrations of asprosin in the serum were discovered in both mice and humans with IR. Also, mice given an asprosin-specific monoclonal antibody had less insulin resistance and less asprosin in their serum (Romere et al., 2016; Duerrschmid et al., 2017; Ke, 2020). Thus, according to our findings, it is probable that asprosin need to be taken into consideration as one of the potential leading causes contributing the development of T2DM.

In each of the study groups, our results revealed a powerful correlation among asprosin and age, “total cholesterol, triglyceride levels, BMI, fasting blood sugar, HOMA-IR, insulin levels, and hemoglobin A1c levels” in both of the study groups. On the other hand, the serum asprosin level was found to have a negative correlation with HDL-C in both groups. According to the findings of this study, serum asprosin concentrations significantly rose with increasing HbA1c levels in both the good and the poor control groups. A potential reason of insulin resistance in T2DM is an excessive amount of asprosin, which facilitates glucose excretion from the liver into the bloodstream, causing an increase in the amount of sugar that is found in the blood, which is then followed by the production of insulin in an effort toward bring glucose levels back to its normal physiological proportions (Hoffmann et al., 2020; Rojas, 2014; Kocaman and Kuloglu, 2020; Li et al., 2018). As a consequence of this, the current findings indicate that increasing the levels of circulating asprosin in individuals with T2DM may be an effective way to counteract the hyper-insulinemia that is seen in these individuals.

It has been claimed in the past that increasing asprosin in patients with T2DM led to decreased appetite and resulted in metabolic alterations. Therefore, the effect of asprosin on metabolic markers is mostly likely caused by the fact that asprosin stimulates individual’s appetites (Zhang et al., 2020a; Li et al., 2018; Naiemian et al., 2020; Zhang et al., 2020b). In addition, a number of metabolic hormones are responsible for controlling how much glucose is released from the liver into the bloodstream (Lee et al., 2019). In addition to this, asprosin is one of the molecules that play a role in facilitating the release of sugar from the hepatocytes, which ultimately leads toward hyperglycemia (Hoffmann et al., 2020). Our findings are consistent with those of other recent investigations, which provide more support for their reliability (Deniz et al., 2021; Li et al., 2018; Alan et al., 2019). These data provide more evidence of the close connection that exists between asprosin and T2DM.
Based on the results of our study, the level of asprosin in the blood serum of the T2DM group was much higher than that of the healthy controls. The majority of healthy persons were found in the T1 and T2 categories. On the other hand, there were a greater number of people diagnosed with T2DM in T3 than in T2. It looks like people whose asprosin levels were in the third tertile were about five times more likely to get T2DM. This suggests that asprosin may be a potential risk involved with the development of T2DM.

In the present investigation, serum asprosin correlated significantly with BMI in both study groups. A rise in BMI suggested that there were large amounts of fatty tissue throughout the body, most noticeably in the abdominal region. As a consequence of this, a rise in the production of asprosin is driven by the accumulation of these fats (Silistre and Hatipoglu, 2020; Leonard et al., 2021). The findings of the current study are supported by the findings of a number of other researchers who discovered a substantial link between blood asprosin and “body mass index” in individuals diagnosed having T2DM (Leonard et al., 2021; Deng et al., 2020; Li et al., 2018; Luis et al., 2020; Deniz et al., 2021). The dysfunction of adipokines and metabolic diseases are both brought on by excessive fat accumulation (Czech, 2017; Clark and Hoenig, 2016). The results of this study also revealed that a positive association exists between serum asprosin and BMI in those who have T2DM. As a result of the elevated levels of asprosin, the BMI continued to gradually rise (Table 4). The endocrine function of adipose tissue is to control the rate of metabolism and keep the energy balance in the body stable. A number of molecules that are released by adipose tissue have the ability to either stimulate or inhibit the action of insulin (Andrade-Oliveira et al., 2015; Booth et al., 2016). Among the most prominent changes that take place with excess fat is insulin resistance, which is a leading cause of T2DM. Therefore, obesity is a causative factor in a group of physiologic problems including T2DM (Garvey et al., 2014; O’Neill and O’Driscoll, 2015).

According to the findings of this study, there is a substantial connection between “lipid profile disorder” and higher asprosin levels in those who have T2DM. This finding provides support for the hypothesis that serum asprosin has a close connection with lipid metabolism. Asprosin concentrations were shown to have a substantial positive association with cholesterol and triglyceride levels for both healthy control group and the T2DM group. In those who have T2DM, elevated lipid levels are a distinctive and pathogenic condition that can be observed; these abnormalities also play a significant role in the development of the disease (Wang et al., 2018). Dyslipidemia is a common condition, and it frequently occurs in conjunction with increased synthesis of sugar by the hepatocytes in the presence of IR in the liver (Titchenell et al., 2017; Wu and Parhofer, 2014). Given that the liver is the target organ for asprosin and insulin resistance might result in dyslipidemia (Romere et al., 2016). However, the data revealed a significant inverse connection among “HDL-C and blood asprosin in both groups of the research. It was documented in other research that increasing asprosin in individuals who having T2DM will reduce appetite with subsequent alteration in metabolic status. It is likely that the effects of asprosin on appetite were responsible for the changes in metabolic parameters (Li et al., 2018; Zhang et al., 2019). The area under the curve (AUC) of the ROC chart for asprosin in determining T2DM in the current investigation was (1.0), and it was significant statistically. This indicates that asprosin may be a valuable signal for the distinction of people in the investigated group who have T2DM from those adults who do not suffer.

The nature of our investigation has some limitations. It was a cross-sectional study that only involved a single location. Second, the study had a limited sample size, which may be one of the barriers to developing a more widespread understanding of the findings of the investigation. Third, the current study only included participants who identified as belonging to a single ethnic group among Iraqi Kurdish adults. Lastly, fasted asprosin levels were all that we were able to measure with normal glucose tolerance in addition to T2DM due to the design of our study and a lack of funding. The data collected during the OGTT (1/2, 1, 2 and 3 h) and from people who have been diagnosed as having pre-diabetes were missed.

V. CONCLUSIONS

Patients who suffer from T2DM have higher levels of asprosin in their serum. According to the findings of this study, asprosin has the potential to play a role as a hazardous leading cause in the emergence of T2DM and is considered a suitable biomarker for predicting T2DM. The outcomes of the existing investigation offer innovative and important clinical insights into the impact that asprosin plays in the pathogenesis of T2DM.

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