Circulating levels of asprosin and its association with insulin resistance and renal function in patients with type 2 diabetes mellitus and diabetic nephropathy

Golnoosh Goodarzi1 · Leila Setayesh2 · Reza Fadaei3 · Mohammad Ebrahim Khamseh4 · Fereshteh Aliakbari5 · Jalil Hosseini5 · Nariman Moradi6

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Abstract
Introduction Adipokines play an important role in the development of type 2 diabetes mellitus (T2DM) and its complications like nephropathy. Asprosin is a newly discovered adipokine involved in glucose metabolism and inflammation process. The present study aimed to evaluate asprosin levels in patients with T2DM and T2DM + nephropathy (NP) compared to control subjects as well as investigating its relationship with insulin resistance, inflammation, and renal function markers.

Methods Serum levels of asprosin, adiponectin, IL-6, and TNF-α were measured in 55 control subjects, 54 T2DM, and 55 T2DM + NP patients using ELISA kits.

Results Asprosin was found to be higher in the T2DM (6.73 ± 1.67) and T2DM + NP (7.11 ± 1.54) patients compared to the controls (4.81 ± 1.09) (p < 0.001), while adiponectin indicated a lower concentration in both patient groups compared to the control group. Moreover, IL-6 and TNF-α indicated higher levels in the two patients group compared to the control group. Asprosin was observed to have a positive correlation with HbA1c, FBG, TC, LDL-C, IL-6, and TNF-α in the T2DM group. In the patients with T2DM + NP, asprosin was found to be positively correlated with BMI, HbA1c, insulin, HOMA-IR, Cr, UAE, IL-6, and TNF-α, and it was inversely correlated with eGFR.

Conclusion Higher concentrations of asprosin in the T2DM and T2DM + NP groups and its relationship with glucose and lipid metabolism and markers of renal function and inflammation suggested a possible role for this adipokine in the pathogenesis of both T2DM and nephropathy.

Keywords Asprosin · Type 2 diabetes · Diabetic nephropathy · Adipokine · Insulin resistance

Golnoosh Goodarzi and Leila Setayesh have contributed equally to this work.

Jalil Hosseini
Jhosseinee@gmail.com

Nariman Moradi
Nariman.Moradi@muk.ac.ir

1 Department of Nutrition, Science and Research Branch, Islamic Azad University, Tehran, Iran
2 Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran
3 Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
4 Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
5 Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
6 Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran
Introduction

In recent decades, type 2 diabetes mellitus (T2DM) becomes one of the major risks to human health, the prevalence rate of which is anticipated to rise up to 10.4% in adults in 2040 [1]. T2DM is characterized by chronic hyperglycemia and insulin resistance, and with the persistent of high levels of blood glucose and non-esterified fatty acids, which cause more damage in both function and apoptosis in pancreatic β-cell. Consequently, with a higher discharge of inflammatory factors [2], T2DM will be developed [3]. Progress in T2DM contributes to several disorders, including cardiovascular diseases (CVD), retinopathy, nephropathy, and neuropathy. Diabetic nephropathy (DN) is known as the main reason for end-stage renal failure and its association with the occurrence of both atherosclerosis and CVD in these patients.[4]. One of the important and preliminary indexes for evaluating the incidence and progression of DN is microalbuminuria [5]. Previously, pathophysiology of DN showed that it could result in arterial narrowing, and then medial hypertrophy thickens the vessel wall [6]. In the meantime, the secretion of inflammatory cytokines such as Tumor Necrosis Factor Alpha (TNF-α) and interleukin-6 (IL-6), plays an important role in the formation of inflammation in the arteries, which subsequently exacerbates this process [7].

Obesity, as one of the major independent risk factors for diabetes and CVD, was found to be related with hyperinsulinemia and insulin resistance [8]. On the other hand, adiposity induces a low grade inflammation in the body, which leads to more penetration of macrophages, especially M1 macrophages, into adipose tissue. In addition, adipose tissue has an endocrine function to secrete bioactive components called adipokines [9, 10]. Accordingly, the influence of these macrophages along with changing the secretion of adipokines from adipose tissue, can consequently affect various aspects of metabolism and inflammation [11]. Several adipokines such as resistin, adiponectin, and leptin, have been found to be related to the regulation of blood glucose levels, inflammation, and insulin sensitivity [12]. The adipokines have changed their concentrations in T2DM [13, 14], and on the other hand, excessive amount of adipocyte cells disrupted the adipokines normal functions [15]. Besides, it was indicated that the renal physiology can be affected by changes in the concentrations of adipokines including leptin and adiponectin, oxidative stress, and inflammation in obesity and insulin resistance [16]. It was also confirmed that interleukin-18 (IL-18) and high-sensitivity C-reactive protein (hs-CRP) meaningfully increase in the case of a severe nephropathy [17]. Moreover, the secretion of these adipokines and inflammatory factors are negatively related to endothelial function.

Asprosin is produced by white adipose tissue (WAT), which has been firstly recognized by Romere et al. in 2016. They have also found that asprosin is a 140-amino-acid protein encoded by FBN1 gene and it is a product of C-terminal cleavage, which is generated by profibrillin [18]. They also revealed the mediatory role of asprosin in increasing glucose and insulin levels in blood. Mechanistically, this hormone increases during starvation and controls the release of glucose from liver cells via G protein-cAMP-PKA way, in order to prevent hypoglycemia [18]. Moreover, in experimental studies, it was seen that in the insulin resistance circumstances and type 2 diabetes, the level of asprosin extremely increases in blood [19]. In contrast, the insulin resistance will be ameliorating, while the asprosin concentration is decreased by specific antibody of asprosin [18]. Moreover, the association among asprosin, inflammation (TNF phosphorylation TLR4-dependent pathway) [20], and ER stress (ER stress/inflammation-dependent pathways) [21] has been confirmed in several studies.

In order to investigate orexigenic hormonal and glucogenic function of asprosin as well as its relationship with inflammation, attenuating asprosin can be helpful in the treatment of type 2 diabetes, obesity, and metabolic syndrome with hyperinsulinemia [22].

On the other hand, insulin resistance and the increased levels of lipids in the blood, followed by the deposition in blood vessels, and especially small blood vessels like renal vessels, as well as inflammation, can play major roles in the development of diabetic nephropathy. However, no previous study has been conducted on determining whether the protein changes among patients with diabetic nephropathy, and whether the protein has the potential to be recognized as a factor in the disease or a biomarker for the disease. To the best of the authors’ knowledge, this case-control study was conducted to assess the asprosin concentration in the serums obtained from the patients with T2DM, diabetic nephropathy, and healthy control subjects and its correlation with metabolic indicators.

Methods

Study participants

This case–control study included 110 patients with type 2 diabetic who were diagnosed in terms of the criteria of American Diabetes Association as well as 56 healthy volunteers as the control group. In regard with urinary albumin excretion (UAE) levels, 54 diabetic patients who had UAE > 20 μg/min were considered as the diabetic nephropathy group. In the current study, all the individuals were recruited from outpatients referred to Shohadaie Tajrish hospital and Institute of Endocrinology and Metabolism,
Anthropometric data and biochemical measurements

The subjects’ height and weight were measured for calculating body mass index (BMI) and a standard sphygmomanometer was then utilized to determine systolic blood pressure (SBP) and diastolic blood pressure (DBP). Five milliliter (mL) of blood was taken after an overnight fasting from all the included participants. Moreover, fasting plasma sugar (FBS); lipids profiles, including total cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-C), and high density lipoprotein-cholesterol (HDL-C); Creatinine (Cr); urinary albumin excretion (UAE); alanine aminotransferase (ALT); and aspartate aminotransferase (AST) were measured using commercially available kits (ParsAzmoon, Iran). Thereafter, the traditional 4-variable Modification of Diet in Renal Disease (MDRD) equation was used to calculate Estimated glomerular filtration rate (eGFR). Insulin was also measured by ELISA kit (Monobind, USA) and HOMA-IR was calculated by the following standard formula: FBS (mg/dL)/insulin (uU/mL) × 405.

Measuring serum adipokines and cytokines

At this stage, ELISA kit was utilized to measure adiponectin levels (Adipogen, South Korea) with intra- and inter-assay coefficients of variations (CV) as 4.6% and 4.4%, respectively. The levels of asprosin were also determined using ELISA kit (AvisceraBioscience, USA) with intra- and inter-assay CV < 8%. Moreover, the levels of tumor necrosis factor-α (TNF-α) and interleukine-6 (IL-6) were determined using ELISA kits (R & D Systems, USA) with minimum detectable doses of 1.6 and 0.7 pg/mL, respectively.

Statistical analysis

All the statistical analyses were performed using SPSS software version 16. Chi-square test was then utilized for comparing categorical data, which were shown as frequency and percentage. Continuous data were also presented as mean and standard deviation (SD) and tested using student t-test. In addition, the correlation analysis was performed using Spearman correlation test. Besides, multinomial logistic regression was conducted to estimate odd ratio of diseases status according to the serum levels of asprosin. A P-value less than 0.05 was considered as the significance threshold.

Results

Basic characteristics of the study population

The study groups were matched in terms of age, sex, and BMI and no significant difference was found among the groups. Blood pressures, including SBP and DBP, indicated higher levels in both patient groups compared to the control group. As expected, the patients with T2DM and T2DM + NP indicated the elevated levels of glucose metabolism parameters, including FBS, insulin, HOMA-IR, and HbA1c. Furthermore, TG levels indicated higher levels in T2DM + NP compared to the control and T2DM groups, while TC, LDL-C, and HDL-C had no considerable differences among the groups. As well, markers of liver functions, including AST and ALT, were found to be different amongst the groups, AST demonstrated higher levels in both patient’s groups compared to the controls, while ALT was higher in T2DM + NP compared to the control group. Cr and eGFR considerably elevated in the both patient’s groups compared to the controls. In addition, these variables indicated higher concentration in T2DM + NP in comparison to the controls. Moreover, UAE was higher in T2DM + NP compared to the T2DM and control groups (Table 1).

Serum levels of cytokines and adipokines

IL-6 indicated a higher concentration in both T2DM (8.28 ± 3.5) and T2DM + NP (9.87 ± 2.98) groups compared to the control group (5.49 ± 1.76). Moreover, the T2DM + NP group indicated the elevated levels of IL-6 compared to the T2DM group (Fig. 1a). TNF-α was also found to be higher in both groups of T2DM (27.11 ± 6.58) and T2DM + NP (29.15 ± 7.77) compared to the control group (21.91 ± 7.51) (Fig. 1b). However, adiponectin decreased in both T2DM (9.53 ± 2.88) and T2DM + NP (8.56 ± 2.69) groups compared to the control group (11.79 ± 3.47) (Fig. 1c). Furthermore, levels of asprosin were found to be higher in both T2DM (6.73 ± 1.67) and T2DM + NP (7.11 ± 1.54) groups compared to the control group (4.81 ± 1.09) (Fig. 1d).

The possible effects of covariates (except age, BMI, AST and ALT) on serum levels of asprosin were adjusted using ANCOA and the results showed that serum levels of asprosin remained higher in the T2DM (6.70 ± 1.35) and T2DM + NP (7.09 ± 1.33) groups compared to the control group (4.85 ± 1.36) (p < 0.001). In addition, multinomial logistic regression was performed to estimate the odd ratio of diseases status based on one unit change in asprosin serum levels. Furthermore, the results indicate that asprosin
had a significant association with diseases’ statues in both crude and adjusted (for age, sex, and BMI) models (Table 2).

In addition, the ability of asprosin in differentiating the diseases’ status was tested using ROC curve analysis. Accordingly, asprosin indicated a relatively good ability to differentiate the T2DM (AUC [CI] 0.828 [0.751, 0.904], p < 0.001, cutoff: 5.46, sensitivity: 72% and specificity: 71%) and T2DM + NP cases (AUC [CI] 0.890 [0.831, 0.949], p < 0.001, cutoff: 5.89, sensitivity: 80% and specificity: 82%) from the controls (Fig. 2).

Association of asprosin with anthropometric and biochemical variables

Correlation analysis and multiple stepwise linear regression were separately performed in the control, T2DM, and T2DM + NP groups and the detailed results are shown in Table 3. In the control group, asprosin indicated a positive correlation with BMI, insulin, and HOMA-IR, and multiple stepwise linear regression also indicated the association between asprosin and insulin. In the patients with T2DM, asprosin was observed to be positively correlated with HbA1c, FBG, TC, LDL-C, IL-6, and TNF-α and multiple stepwise linear regression also indicated the association of asprosin with HbA1c, LDL-C, and IL-6. Moreover, in the patients with T2DM + NP asprosin, positive correlations were found with BMI, HbA1c, insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), Cr, UAE, IL-6, and TNF-α, and it was inversely correlated with eGFR. In addition, asprosin indicated independent associations with BMI, UAE, eGFR, and IL-6 (Table 3).

Discussion

The results of this case–control show that the asprosin levels in the T2DM + NP and T2DM diabetes groups were higher than that of the control group and it remained significant after adjusting for age, BMI, and sex. Moreover, the diabetic nephropathy patients had a higher asprosin concentration compared to the patients with T2DM groups; however, this difference did not reach the statistical significance level.

The regulatory roles of adipose tissue as an endocrine organ in metabolism and energy homeostasis have been confirmed previously [9]. It was shown that the insulin function can be affected by the secreted components of adipose tissue [12]. Excess adiposity can cause insulin resistance, which is known as a major reason for T2DM; therefore, obesity is associated with several metabolic disorders, including T2DM and metabolic syndrome [23, 24]. Asprosin, as a newly discovered adipokine, is secreted by white adipose tissue (WAT) and plays an important role in the discharge of glucose from hepatic cells to maintain serum glucose level under normal condition. In addition, it was indicated that the level of asprosin increases under pathological conditions such as insulin resistance and T2DM, whereas in an animal study, it was shown that the reduced asprosin concentration through the treatment with its specific antibody results in ameliorating insulin resistance [18]. Nevertheless, due to diversity in race and sample types, the definite association of asprosin in T2DM has not been well-established yet.

The results of this study show that asprosin concentration is positively correlated with T2DM and T2DM + NP, which was in line with the results of the Romere et al.’s study [18].

Table 1 Anthropometric and biochemical characteristics of the study population

| Variables               | Control (n = 55) | T2DM (n = 54) | T2DM-NP (n = 55) | p    |
|-------------------------|-----------------|---------------|------------------|------|
| BMI (kg/m²)             | 25.72 ± 3.45    | 26.72 ± 4.21  | 26.47 ± 4.27     | 0.401|
| Age (year)              | 58.71 ± 7.93    | 61.83 ± 7.78  | 61.84 ± 9.36     | 0.082|
| Sex (male)              | 36 (65.5%)      | 32 (59.3%)    | 35 (63.6%)       |      |
| SBP (mm Hg)             | 126.13 ± 15.3   | 137.56 ± 19.82| 145.71 ± 18.73   | < 0.001|
| DBP (mmHg)              | 78.00 ± 12.46   | 86.30 ± 15.2  | 92.76 ± 13.56    | < 0.001|
| HbA1c (%)               | 4.52 ± 0.92     | 8.19 ± 1.43   | 8.17 ± 1.26      | < 0.001|
| FBG (mg/day)            | 93.55 ± 11.5    | 163.02 ± 22.75| 167.64 ± 21.45   | < 0.001|
| Insulin (µU/mL)         | 4.34 ± 2.46     | 10.29 ± 5.09  | 11.66 ± 5.63     | < 0.001|
| HOMA-IR                 | 1.02 ± 0.62     | 4.27 ± 2.47   | 4.86 ± 2.5       | < 0.001|
| TG (mg/dL)              | 126.76 ± 49.56  | 150.56 ± 44.57| 175.73 ± 60.33   | < 0.001|
| TC (mg/dL)              | 174.82 ± 39.8   | 180.44 ± 45.99| 193.07 ± 47.53   | 0.092 |
| LDL-C (mg/dL)           | 106.51 ± 32.33  | 107.13 ± 36.38| 119.33 ± 35.92   | 0.099 |
| HDL-C (mg/dL)           | 47.24 ± 6.86    | 44.44 ± 7.37  | 44.60 ± 5.6      | 0.050 |
| Cr (mg/dL)              | 1.03 ± 0.18     | 1.28 ± 0.18   | 2.57 ± 0.79      | < 0.001|
| AST (U/L)               | 19.60 ± 5.66    | 22.66 ± 5.72  | 24.05 ± 6.96     | 0.001 |
| ALT (U/L)               | 19.43 ± 7.79    | 22.1 ± 7.67   | 25.01 ± 8.18     | 0.001 |
| UAE (µg/min)            | 10.35 ± 4.48    | 11.07 ± 5.16  | 254.31 ± 147.3   | < 0.001|
| eGFR (mL/min/1.73 m²)   | 82.02 ± 25.00   | 65.20 ± 15.37 | 32.41 ± 13.31    | < 0.001|
Correspondingly, they reported that the levels of asprosin in the serum of newly diagnosed T2DM patients more elevated compared to the controls. Zhang et al. also reported that the levels of asprosin considerably increased in insulin resistance and T2DM patients [19]. Overall, it may be proposed that the higher asprosin concentration in serum is a risk factor related to the development of T2DM. In line with this concept, the results of the present study indicate that asprosin is positively associated with the markers of glucose metabolism and insulin resistance.

Despite the unclear mechanism of the increased level of asprosin in T2DM, the glycogenic role of this adipokine was proposed as a cause of this phenomenon. Of note, Glucose acts as a suppressor of asprosin in a negative-feedback axis. According to previous studies’ results, the asprosin is extremely increases in the insulin resistance subjects and insulin sensitivity is improved by lowering the asprosin [18]. In addition, it was shown that the abnormal secretion of asprosin by WAT leads to higher levels of asprosin in T2DM [19]. The asprosin also increases the glucose production in liver cells, and then due to hyperinsulinemia, the insulin resistance will consequently exacerbate [18]. Glucose dysregulation in individuals with insulin resistance was observe to be narrowly associated with the pathogenesis of T2DM [25, 26], so further studies are warranted to explore the exact mechanism.

The current study also showed a positive association between asprosin and BMI. Moreover, it was proposed that excessive adipose tissue can disrupt the normal function, secretion of adipokines, and metabolic dysfunction [15, 27]. Therefore, it can be concluded that obesity is a pivotal factor for the elevated serum levels of asprosin.

Furthermore, the results show that serum asprosin is associated with lipid metabolism. In the T2DM patient group, the level of asprosin was positively and independently related to both LDL-C and TC. The target organ for asprosin is hepatic cells; therefore, it is assumed that asprosin may be related to dyslipidemia [19]. Previously, an animal study showed that using antibody against asprosin could reduce lipid profile, including TG, TC, and LDL-C, which could be resulted from the effect of asprosin on insulin sensitivity. These results need more studies to dissect the possible underlying mechanisms in this regard.

Strikingly, the results of the present study show the association of asprosin with the markers of kidney function (eGFR, UAE, and Cr) in patients with T2DM+NP. A previous study has shown that asprosin is associated with the markers of kidney function in diabetic patients, while the present study showed that the relationship of asprosin with the markers of

![Fig. 1](https://example.com/fig1.png)

**Fig. 1** Serum levels of cytokines and adipokines. a Serum levels of IL-6 increased in both T2Dm and T2DM + NP compared to controls as well as T2DM + NP compared to T2DM group. b TNF-α indicated higher concentration in both patient groups in comparison to controls. c Adiponectin serum levels were found to be lower in the both patient groups compared to controls. d Asprosin serum levels increased in T2DM and T2DM + NP groups compared with controls.
Fig. 2 ROC curve analysis of diagnostic ability of asprosin to differentiate diseases status from control. a T2DM from control and b T2DM + NP from control.

Table 3 Spearman correlation and multiple linear regression of asprosin with anthropometric and biochemical measurement

| Variables  | Control | T2DM | T2DM + NP |
|------------|---------|------|-----------|
|            | r       | B (95% CI) | r       | B (95% CI) | r       | B (95% CI) |
| BMI        | 0.273*  |         | 0.259    |         | 0.314*  | 0.095 (0.016, 0.174)* |
| Age        | 0.154   | −0.076 | 0.062    |         | 0.104   |         |
| SBP        | 0.206   | 0.050  |          |         | 0.175   |         |
| DBP        | 0.206   | 0.050  |          |         | 0.175   |         |
| HbA1c      | 0.105   | 0.422**| 0.014 (0.003, 0.024)* | 0.314*  |         |
| FBG        | 0.161   | 0.317* |         | 0.262   | 0.357** |
| Insulin    | 0.292*  | 0.202 (0.094, 0.311)** | 0.171   |         |
| HOMA-IR    | 0.309** |         | 0.241    |         | 0.409** |
| TG         | 0.070   | 0.144  | 0.121    |         |
| TC         | −0.177  | 0.345* | −0.060   |         |
| LDL-C      | −0.143  | 0.374**| 0.346 (0.064, 0.624)* | −0.090  |         |
| HDL-C      | 0.006   | 0.078  | 0.046    |         |
| Cr         | 0.060   | 0.153  | 0.453**  |         |
| UAE        | −0.037  | −0.050 | 0.363**  | 0.003 (0.000, 0.005)* |
| eGFR       | −0.114  | −0.194 | −0.446** | −0.042 (−0.068, −0.016)** |
| AST        | 0.073   | 0.068  | 0.132    |         |
| ALT        | 0.043   | 0.035  | 0.049    |         |
| IL-6       | −0.113  | 0.329* | 0.014 (0.046, 0.274)** | 0.392**  | 0.135 (0.020, 0.249)* |
| TNF-α      | 0.131   | 0.311* |         | 0.334*  |
| Adiponectin| −0.051  | −0.159 | −0.239   |         |

*p < 0.05, **p < 0.01
kidney function only exists in T2DM+NP. In diabetic patients, several factors, including hyperglycemia, oxidative stress, and renin-angiotensin system are the initiators of the inflammatory procedure in the kidneys and micro-inflammation was also proposed as a major mechanism for the development of diabetic nephropathy [28]. Furthermore, asprosin was indicated to have a positive correlation with inflammatory cytokines. The effect of asprosin on inflammation has been confirmed, as well. Asprosin upregulates JNK phosphorylation TLR4-dependent pathway, which causes inflammation in the body [20]. On the other hand, it was reported that several adipokeins such as resistin and adiponectin, have the regulatory effect on the insulin action and are also associated with inflammation [28].

Altogether, it was shown that asprosin is positively associated with inflammatory markers, insulin resistance obesity, and renal function indicators in T2DM+NP, while in the T2DM patients, asprosin was found to be associated with glucose and cholesterol metabolism markers and inflammation. These results suggest a possible role for asprosin in the pathogenesis of T2DM and T2DM+NP through their pathological mechanism such as inflammation, insulin resistance, and obesity. In regard with the cross-sectional design of this study, we were limited to conclude a causal relationship between asprosin and the above-mentioned factors; however, further studies are needed in this regard in the future.

Author contributions NM and JH: conceptualization, methodology. GG and LS: data curation, writing--original draft preparation. MEK and FA: visualization, investigation. JH and NM: supervision. RF: statistical analysis, validation. NM and RF: writing--reviewing and editing.

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Data availability The data that support the findings of this study are available from corresponding authors, [J.H, N.M.], upon reasonable request.

Declarations

Conflict of interest There is no conflict of interest for authors to declare in this study.

Consent to participate Informed written consent was signed by all studied participants.

Ethical approval The study was approved by the Ethics committee of Shahid beheshti University of Medical Sciences.

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