Article

J. Biol. Regul. Homeost. Agents. 2022; 36(4): 1091–1098
https://doi.org/10.23812/j.biol.regul.homeost.agents.20223604.119

The Value of Asprosin on the Development in Prediabetic Individuals: A Prospective Study

Jiao Huang[1,2], Xiaoying Ding[3], Yuhang Ma[3], Shumei Li[4], Yongde Peng[1,*]

[1]Department of Endocrinology and Metabolism, Shanghai General Hospital of Nanjing Medical University, 200000 Shanghai, China
[2]Department of Rheumatology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, 310000 Hangzhou, Zhejiang, China
[3]Department of Endocrinology and Metabolism, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, 200000 Shanghai, China
[4]Department of Endocrinology and Metabolism, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, 200000 Shanghai, China
*Correspondence: pengyongde0908@126.com (Yongde Peng)
Published: 20 August 2022

Background: A asprosin and Meteorin-like (Metrnl) are related to diabetic. The aim of this study was to assess the impact of asprosin or Metrnl on the development of diabetes in pre-diabetics.
Methods: This is a prospective study. Subjects were divided into two groups: Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) based on the results of an oral glucose tolerance test. Two years later, subjects were divided into three groups based on blood glucose outcome: Normal, pre-diabetic and diabetic groups. Biochemical methods were used to detect blood glucose, blood lipids, liver function, kidney function and thyroid function. Radioimmunoassay was used to detect tumor markers. The levels of Asprosin and Metrnl were detected by ELISA (enzyme-linked immunosorbent assay).
Results: A total of 403 subjects were enrolled in this study. At baseline, fasting blood glucose (FBG) and triglyceride (TG) were higher as well as 2-h postprandial blood glucose (PBG) and high-density lipoprotein (HDLC) were lower in IGT group than in IFG group ($p < 0.05$). Two years later, glycation hemoglobin (HbA1c), FBG, PBG, TG, kidney function related indexes creatinine (CREA) and Asprosin were lower while CHOL (total cholesterol) and HDLC were higher in prediabetic group than in diabetic group ($p < 0.05$). Asprosin and not Metrnl, positively correlated with HbA1c, PBG and CREA in diabetic patients ($p < 0.001$).
Conclusions: Asprosin is related to blood glucose levels and markers of renal function in patients with diabetes.

Keywords: asprosin; Metrnl; diabetes mellitus; biomarkers

Introduction

Diabetes mellitus is a common metabolic disease. Diabetic patients suffer a chronic hyperglycemic due to insufficient insulin secretion or insulin resistance. It increases the risk of blood glucose and protein metabolism disorders and growth of adipose tissue [1]. Prediabetic individuals are characterized by periods of elevated blood glucose that do not reach diagnostic thresholds. They may experience impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) [2]. Whereas type 1 diabetes mellitus (insulin dependent) can be hereditary, type 2 diabetes mellitus is acquired and hence can be avoided. Therefore, patients with type 2 diabetes can be benefited by an early diagnosis of the disease that may prevent its appearance [3].

Tests like oral glucose tolerance test (OGTT) are impractical for type 2 diabetes mellitus large scale studies. Furthermore, to screen high-risk non-diabetic individuals, China has produced different type 2 diabetes mellitus risk prediction models, but all face some limitations, including, the lack of accountancy for lifestyle variations, based on small and inappropriate cohort selection, or with a short-term follow-up [4]. Thus, finding more convenient and promising methods is of great clinical convenience to effectively identify prediabetic patients to avoid the appearance of type 2 diabetes mellitus due to an early detection and management of the disease.

Studies reported that the annual progression rate of prediabetes individuals is 5%–10%. From these individuals 70% of them will develop diabetes [5–8]. Furthermore, prediabetic people has associated an increased risk of cardiovascular and microvascular disease [9–11]. The transition from prediabetes to diabetes is related to the patient's long-term diet and lifestyle. Prediabetes is reversible when individuals achieve and maintain normal blood glucose levels.

Adipokines play an important role in the pathophysiology of diabetes mellitus and affect its occurrence and development. Higher asprosin level is an important marker for predicting the development of diabetes, and can be used as a target molecule to treat in diabetes [12,13]. One study showed that the depletion of Meteorin-like (Metrnl) in fat

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

cells increases insulin resistance after following a high-fat diet. However other studies, on the contrary, have shown that the overexpression of Metrnl reduces insulin resistance induced by leptin deficiency or a high-fat diet [14,15]. At present, it is unknown whether asprosin or Metrnl are able to predict the progression of prediabetes to diabetes. The aim of this study is to evaluate the role of asprosin and Metrnl on the development of diabetes mellitus in prediabetic individuals.

Materials and Methods

Study Design

This study was carried out in Sijing Community, Songjiang District, Shanghai, China. Prediabetic patients (diagnosed with IFG or IGT) with an age between 40 and 67 years old that had common pre-diabetic symptoms, such as polydipsia, polyuria, polyophagia were included in the study. Patients diagnosed with diabetes mellitus of any type that had endocrine and metabolic diseases, such as Cushing's syndrome, osteoporosis, lipid dysemia, primary hypothyroidism that led into secondary obesity, severe organic diseases in liver, kidney, heart, and brain, surgical operation in the preceding 3 months, malignant tumors, blood system diseases, acute and chronic infections, history of neurological or psychiatric diseases, history of antidiabetic drug use or were during pregnancy or lactation were excluded from the study. Patients avoided alcohol consumption for 7 days prior to the study participation and did not take insulin and sulfonamides 14 days prior to the study participation.

Diagnostic Criteria

Diagnosis of diabetes was made according to the World Health Organization (WHO) 1999 diagnostic criteria (Table 1). The subjects without diagnosis of diabetes underwent an OGTT [16], while the previously diagnosed with diabetes underwent the steamed bread meal test (SBMT) in the observations after two years of follow-up. For the OGTT patients consumed a standard drink (75 g anhydrous glucose dissolved in water) after fasting overnight, to assess glucose tolerance. Two hours later blood samples were collected to measure glucose concentration. In the case of SBMT glucose concentrations were measured after an oral administration of 100 g steamed bread meal test (equal to 75 g of glucose) following the same procedure as for OGTT.

Observations on First Enrollment and after Two Years of Follow-Up

On enrollment, patients were divided in two groups according to the tests results. (1) Impaired glucose tolerance group (IGT) and (2) impaired fasting glucose group (IFG). After two years of follow-up, the patients were divided into three groups according to their disease outcomes: Normal group, prediabetic group, and diabetic group, as shown in Fig. 1.

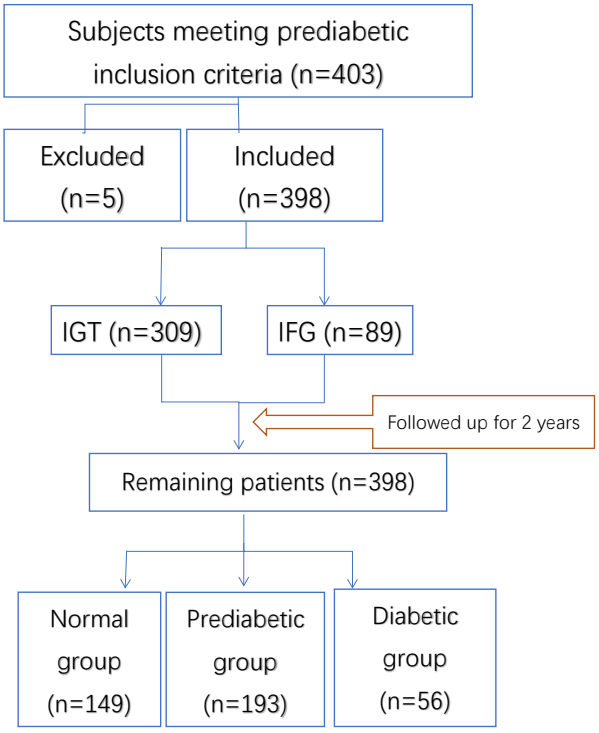

Fig. 1. Flow chart of the study population. IGT, impaired glucose tolerance; IFG, impaired fasting glucose.

Table 1. Group allocation criteria.

Criteria	Glucose levels in venous plasma
T2DM	Self-reported diagnosed T2DM FBG >7.0 mmol/L PBG >11.1 mmol/L
IFG	6.1 mmol/L ≤ FBG <7.0 mmol/L and PBG <7.8 mmol/L
IGT	FBG <6.1 mmol/L and 7.8 ≤ PBG < 11.1 mmol/L
NGT	FBG <6.1 mmol/L and PBG <7.8 mmol/L

T2DM, type 2 diabetes mellitus; FBG, fasting blood glucose; PBG, 2-h postprandial blood glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, Normal Glucose Tolerance.

To prevent the transition from prediabetes mellitus to diabetes mellitus is important to intervene the lifestyle of patients (diet and physical activity) with health education. A lifestyle intervention based the guidelines for prevention and treatment of type 2 diabetes mellitus in Chinese was used to change lifestyle behaviors in patients. After the intervention, those patients who met the World Health Organization (WHO) diagnostic criteria for diabetes were assigned to the diabetic group. The patients who were diagnosed as IFG or IGT were assigned to the prediabetic group. The subjects whose blood glucose was under normal levels (NGT) were assigned to the normal group. The diagnostic criteria are shown in Table 1.

Outcome Assessment

Collection of Clinical Data

At enrollment from July 2012 to March 2013, and follow-up visit from July 2014 to March 2015, the demographic characteristics, medical history, and family history of participants were recorded by trained staff through face-to-face interviews, using standard proformas. All subjects received a comprehensive examination, including blood pressure measure, pulse rate counting, height, weight, BMI, waist and hip circumference and waist-hip ratio estimation.

Detection of Biochemical Indicators

All subjects were required to fast for at least 8 hours overnight and avoided high-glucose and high-fat diet the day before blood samples collection. Venous blood was collected from the elbow. One mL of blood sample was placed in an anticoagulation tube, and glycated hemoglobin meter was used to detect HbA1c (glycation hemoglobin). Further 5 mL of venous blood was placed in a coagulation promoting tube for static mixing and centrifuged at 1000 g at –3 °C for 15 minutes. The serum was separated and stored in a 1.5 mL EP (eppendorf) tube at –80 °C.

Fasting insulin (INS) was measured by chemiluminescence. Automatic biochemical analyzer was used to measure.

- Blood glucose indicators: Fasting blood glucose (FBG), 2-h postprandial blood glucose (PBG),
- lipid metabolism indicators: Total cholesterol (CHOL), triglyceride (TG), high density lipoprotein (HDLC), low density lipoprotein (LDLC);
- Liver function: Alanine aminotransferase (ALT);
- Renal function (urea (UREA), creatinine (CREA), uric acid (UA).
- Thyroid function free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH).

Radioimmunoassay was used to detect tumor markers (CA, glycoprotein antigen; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199).

Determination of Serum Asprosin and Metrnl Levels

The levels of asprosin and Metrnl were estimated using enzyme-linked immunosorbent assay (ELISA); Asprosin ELISA kit and Metrnl ELISA kit (Yazai Biotechnology Co., LTD, Shanghai, China), following manufacturer's instructions.

Statistical Analysis

Statistical Product and Service Solutions (SPSS; version 22.0; SPSS Inc., Chicago, IL, USA) software package was used for statistical analysis. Continuous data were checked for normality of distribution, using Shapiro-Wilk test. Normally distributed continuous data is presented as mean ± standard deviation and compared between groups using student t test, resorting to F tests when comparing more than two groups. Categorical data were described as frequency (%) and compared between groups using the chi-squared test (χ^2), resorting to the Mann-Whitney test when the expected frequencies were <5 in >20% of cells and Fisher's exact test for comparisons that fitted 2 × 2 tables. Correlations were assessed using Pearson's correlation coefficient. A $p < 0.05$ was considered as statistically significant result.

Results

Baseline Values

On baseline examination, 403 subjects were enrolled and screened and were assigned to IGT (n = 309) and IFG (n = 89) groups. Five subjects dropped out due to follow-up interruption. The remaining 398 patients were invited to attend follow-up examination. At follow up visit patients were assigned to normal (n = 149), prediabetic (n = 139) and diabetic group (n = 56). No statistically significant differences were found in background features between IGT group and IFG group (Table 2). Glucose metabolism, lipid metabolism, tumor markers, liver and kidney function, thyroid function, and blood indicators values are shown in Table 3. FBG and HDLC was lower, and PBG and TG was higher in the IGT group compared to IFG group ($p < 0.05$).

Follow-Up Values

Clinical characteristics of patients are shown in Table 4. Diabetic group showed higher BMI and waist-hip ratio compared to normal and prediabetic group ($p < 0.001$). Biochemical indicators of patients at follow-up are presented in Table 5. Prediabetic group showed higher levels of FBG, PBG, CHOL, TG and asprosin compared to normal group ($p < 0.05$), diabetic group showed higher levels of HbAlc FBG, PBG, TG, HDLC, CREA and asprosin compared to prediabetic and normal population and higher levels of CHOL, CA199, UA, FT4, HGB and HCT compared to normal group. The asprosin adipocytokine level was significantly different between different groups, while Metrnl level showed no statistical difference.

Then, the correlation between asprosin level at follow-up and biochemicals with significant differences between groups (HbA1c, FBG, PBG, TG, HDLC, CREA and HGB) was assessed. It was found that asprosin level positively correlated with HbA1c (R = 0.148, $p < 0.003$), PBG (R = 0.191, $p < 0.001$) and CREA (R = 0.396, $p < 0.001$) (Fig. 2, Table 6). According to the results at 2-year follow-up, the asprosin adipocytokine level was significantly different between different groups, while Metrnl level showed no statistical difference.

Discussion

The aim of this study was to reveal the correlation between the expression level of asprosin or Metrnl at 2-year

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Table 2. The distribution and comparison of basic clinical features of IGT and IFG groups at enrollement.

Observation index		IGT group (n = 309)	IFG group (n = 89)	χ^2/t	p
Gender	Male	128 (%)	49 (%)	0.351	0.554
	female	181 (%)	40 (%)		
Age (years)		60.98 ± 8.89	59.83 ± 7.62	1.108	0.268
Systolic blood pressure (mmHg)		138.65 ± 17.33	135.61 ± 15.85	1.485	0.138
Diastolic blood pressure (mmHg)		81.73 ± 28.23	79.63 ± 10.12	0.689	0.491
Heart rate (BPM)		84.16 ± 13.56	83.90 ± 11.57	0.164	0.869
BMI (kg/m^2)		25.09 ± 3.31	24.51 ± 2.91	1.495	0.136
Waist-hip ratio		0.91 ± 0.07	0.90 ± 0.06	1.224	0.222

Data is presented as N (%) or mean ± SD. IGT, impaired glucose tolerance; IFG, impaired fasting glucose; BMI, Body Mass Index; BPM, beat per minut.

Table 3. The distribution and comparison of biochemical indicators of IGT and IFG groups at enrollement.

Observation index	IGT group (n = 309)	IFG group (n = 89)	t	p
HbA1c (%)	5.86 ± 0.23	5.82 ± 0.19	1.500	0.135
FBG (mmol/L)	5.92 ± 0.52	6.36 ± 0.20	–7.812	<0.001*
PBG (mmol/L)	9.08 ± 0.91	6.36 ± 1.21	22.964	<0.001*
CHOL (mmol/L)	5.35 ± 0.91	5.34 ± 0.85	0.093	0.926
TG (mmol/L)	1.99 ± 1.35	1.66 ± 1.49	1.984	0.048*
HDLC (mmol/L)	1.49 ± 0.36	1.58 ± 0.39	–2.039	0.042*
LDLC (mmol/L)	3.09 ± 0.74	3.06 ± 0.73	0.338	0.736
CEA (ng/mL)	2.93 ± 1.60	2.73 ± 1.40	1.168	0.244
CA199 (U/mL)	12.83 ± 8.88	12.01 ± 6.74	0.807	0.420
ALT (U/L)	22.84 ± 14.47	21.00 ± 10.42	1.119	0.264
UREA (μmol/L)	5.50 ± 1.36	5.67 ± 1.31	–1.048	0.296
CREA (μmol/L)	65.63 ± 15.69	67.02 ± 13.90	–0.755	0.451
UA (μmol/L))	337.75 ± 83.15	329.60 ± 85.50	0.810	0.419
FT3 (pg/mL)	5.13 ± 0.70	5.29 ± 0.70	–1.900	0.058
FT4 (ng/dL)	15.99 ± 2.40	16.46 ± 3.79	–1.411	0.159
TSH (mIU/L)	2.68 ± 2.05	2.31 ± 1.26	1.616	0.107
HGB (g/L)	140.98 ± 13.88	141.79 ± 13.23	–0.490	0.624
HCT (%)	40.46 ± 3.41	40.64 ± 3.31	–0.442	0.659
Asprosin (ng/mL)	89.55 ± 41.62	88.05 ± 44.19	0.295	0.768
Metrnl (pg/mL)	506.47 ± 226.54	479.52 ± 206.60	1.008	0.314

Data is presented as N (%) mean ± SD. IGT, impaired glucose tolerance; IFG, impaired fasting glucose; HbA1c, glycation hemoglobin; FBG, fasting blood glucose; PBG, 2-h postprandial blood glucose; CHOL, cholesterol; TG, triglyceride; HDLC, high density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; ALT, alanine aminotransferase; UREA, urea; CREA, creatinine; UA, uric acid; FT3, thyroid function free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; HGB, hemoglobin; HCT, hematocrit. *Denotes significant difference between groups ($p < 0.05$).

follow-up with biochemical indicators in patients transitioning from prediabetes to diabetes. The study showed that asprosin positively correlated with HbA1c, PBG and CREA in the diabetic group at 2-year follow-up and these biochemical indicators were higher in the diabetic group compared to normal and prediabetic group. The results showed that asprosin could identify the occurrence of diabetes, while Metrnl not.

Most studies have pointed out that pancreatic β-cell damage and insulin resistance are the main physiological and pathological changes in prediabetic population. Moreover, prediabetes is dominated by IFG and IGT [17]. Although impaired glucose regulation is a necessary stage in the progression of normal glucose tolerance to diabetes, it is reversible. Early interventions provide a reliable basis to prevent the appearance of diabetes [18,19]. Some researchers believe that multiple biomarkers may be involved in the occurrence and development of prediabetes [20–22]. This study looked at multiple perspectives, including blood glucose indicators, lipid metabolism indicators, tumor markers, liver function, kidney function and thyroid function indicators. The study showed that FBG, PBG, TG and HDLC were significantly higher in prediabetic patients compared to normal patients at follow-up.

Table 4. The distribution and comparison of basic clinical features of normal, prediabetic and diabetic groups at 2-year follow-up.

Observation index		Normal group (n = 149)	Prediabetic group (n = 193)	Diabetic group (n = 56)	χ^2/F	p
Gender	Male	64	83	30	0.335	2.185
	Female	85	110	26		
Age (years)		60.97 ± 9.11	60.40 ± 8.25	61.16 ± 8.70	0.267	0.766
Systolic blood pressure (mmHg)		133.27 ± 16.18	134.60 ± 14.42	137.79 ± 17.02	1.738	0.177
Diastolic blood pressure (mmHg)		81.83 ± 8.78	82.08 ± 8.27	84.34 ± 10.19	1.797	0.167
Heart rate (BPM)		76.51 ± 6.63	77.90 ± 9.48	80.32 ± 16.99	3.004	0.051
BMI (kg/m^2)		24.64 ± 3.35	25.21 ± 3.17	26.84 ± 3.33^{ab}	9.268	<0.001*
Waist-hip ratio		0.88 ± 0.05	0.90 ± 0.07^{a}	0.93 ± 0.08^{ab}	12.561	<0.001*

Data is presented as mean ± SD. BMI, Body Mass Index. *Denotes significant differences between groups ($p < 0.05$). ^{a}Denotes $p < 0.05$ vs. normal group. ^{b}Denotes $p < 0.05$ vs. prediabetic group.

Table 5. The distribution and comparison of biochemical indicators of normal, prediabetic and diabetic groups at 2-year follow-up.

Observation index	Normal group (n = 149)	Prediabetic group (n = 193)	Diabetic group (n = 56)	F	p
HbA1c (%)	5.77 ± 0.43	5.83 ± 0.30	6.13 ± 0.46^{ab}	19.023	<0.001*
FBG (mmol/L)	5.50 ± 0.38	6.02 ± 0.55^{a}	6.95 ± 0.91^{ab}	137.630	<0.001*
PBG (mmol/L)	6.33 ± 1.15	8.32 ± 1.50^{a}	11.75 ± 2.72^{ab}	233.170	<0.001*
CHOL (mmol/L)	5.21 ± 0.94	5.45 ± 1.01^{a}	5.52 ± 0.96^{a}	3.303	0.038*
TG (mmol/L)	1.42 ± 0.75	1.72 ± 1.12^{a}	2.05 ± 1.33^{ab}	8.334	<0.001*
HDLC (mmol/L)	1.62 ± 0.44	1.59 ± 0.46	1.44 ± 0.41^{ab}	3.409	0.034*
LDLC (mmol/L)	3.12 ± 0.81	3.23 ± 0.84	3.28 ± 0.91	1.050	0.351
CEA (ng/mL)	2.52 ± 1.43	2.28 ± 1.23	2.35 ± 1.39	1.384	0.252
CA199 (U/mL)	10.88 ± 7.92	11.27 ± 7.72	13.48 ± 8.92^{a}	2.245	0.107
ALT (U/L)	21.33 ± 12.84	23.44 ± 16.40	25.59 ± 15.33	1.837	0.161
UREA (μmol/L)	5.65 ± 1.26	5.61 ± 1.43	5.74 ± 1.49	0.196	0.822
CREA (μmol/L)	68.59 ± 15.38	67.80 ± 15.17	73.66 ± 17.13^{ab}	3.142	0.044*
UA (μmol/L)	319.17 ± 79.88	331.23 ± 83.24	348.54 ± 101.37^{a}	2.554	0.079
FT3 (pg/mL))	4.70 ± 0.59	4.84 ± 0.55	5.09 ± 1.32	0.086	0.918
FT4 (ng/dL)	15.59 ± 1.96	15.80 ± 2.34	16.36 ± 2.59^{a}	2.603	0.076
TSH (mIU/L)	2.58 ± 1.47	2.81 ± 1.94	2.57 ± 1.32	0.065	0.938
HGB (g/L)	141.10 ± 14.28	144.27 ± 13.30	149.39 ± 15.16^{a}	6.661	0.002*
HCT (%)	42.30 ± 4.08	43.12 ± 3.83	43.82 ± 4.25^{a}	2.792	0.064
Asprosin (ng/mL)	80.98 ± 41.59	90.60 ± 37.92^{a}	106.38 ± 51.62^{ab}	7.850	0.001*
Metrnl (pg/mL)	523.49 ± 227.64	494.48 ± 230.32	459.67 ± 169.47	1.820	0.163

Data is presented as N (%) and mean ± SD. HbA1c, glycation hemoglobin; FBG, fasting blood glucose; PBG, 2-h postprandial blood glucose; CHOL, cholesterol; TG, triglyceride; HDLC, high density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; ALT, alanine aminotransferase; UREA, urea; CREA, creatinine; UA, uric acid; FT3, thyroid function free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; HGB, hemoglobin; HCT, hematocrit. *Denotes significant differences between groups ($p < 0.05$). ^{a}Denotes $p < 0.05$ vs. normal group. ^{b}Denotes $p < 0.05$ vs. prediabetic group.

Table 6. Correlation analysis between serum asprosin level and clinical indicators at 2-year follow up.

Index		HbA1c	FBG	PBG	TG	HDLC	CREA	HGB
Asprosin	R	0.148	0.044	0.191	–0.017	0.065	0.396	–0.043
	p	0.003	0.383	<0.001	0.735	0.196	<0.001	0.394

HbA1c, glycation hemoglobin; FBG, fasting blood glucose; PBG, 2-h postprandial blood glucose; TG, triglyceride; HDLC, high density lipoprotein cholesterol; CREA, creatinine; HGB, hemoglobin.

It is well known that absolute or relative insulin deficiency and/or resistance plays a unique role in the development of diabetes [23,24]. Insulin resistance *in vivo* is an important factor that leads to lipid metabolism disorder. At

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

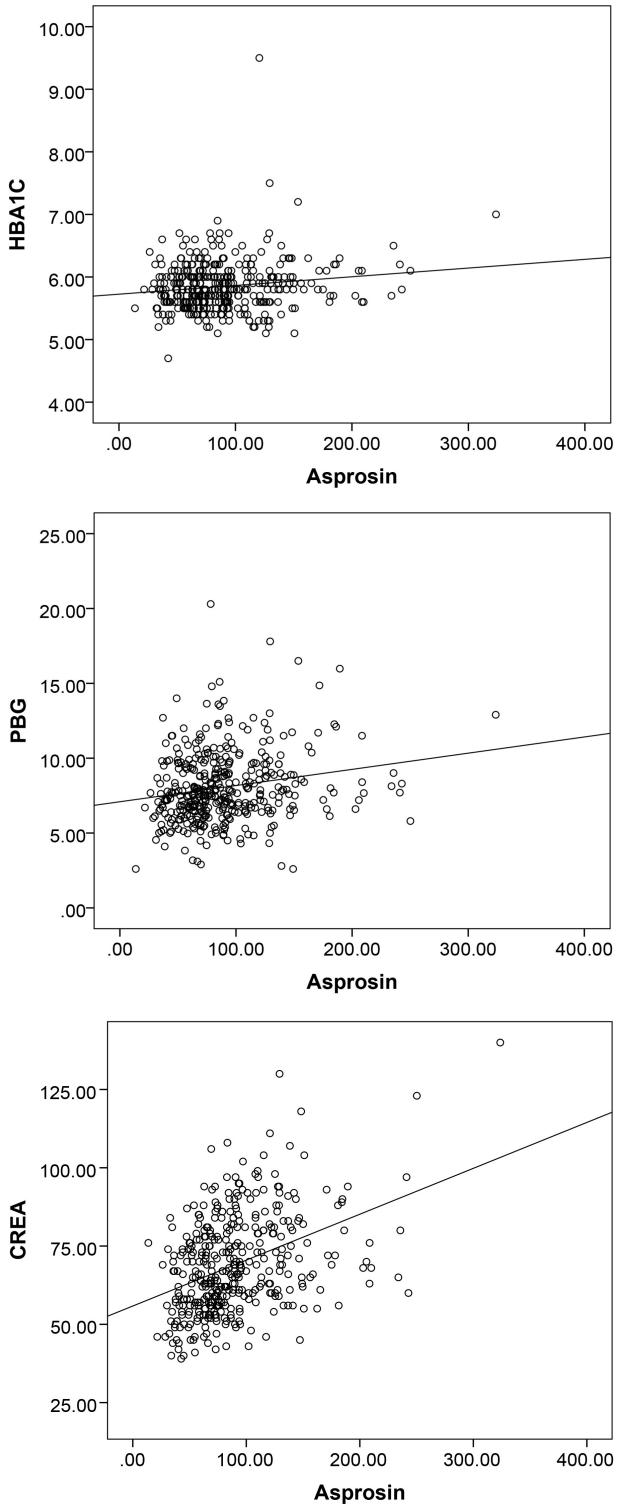

Fig. 2. Correlation analysis between serum asprosin level and various biochemical indicators. HbA1c, glycation hemoglobin; FBG, fasting blood glucose; CREA, creatinine.

the same time, lipid metabolism disorder can promote insulin resistance [25] what makes of this physiological process a vicious cycle. Studies have shown that when insulin secretion is too low, lipid metabolism is enhanced, which in a short time will lead to an increase in the synthesis of lipid metabolism-related factors TG, and HDLC, and a decrease in the expression level of LDLC [26]. Therefore, it is not surprising that FBG, PBG, TG and HDLC at 2-year follow-up are higher in prediabetic patients compared to normal patients and may be used for the identification of prediabetes.

The risk of T2DM (type 2 diabetes mellitus) is positively associated with rapid weight gain, early age of obesity onset and greater obese years among middle-aged women [27]. However, greater BMI in young children were not associated with later T2DM [28]. In the study of Li *et al.* [29] in the year 2020, it was found that the increase of waist-hip ratio lead to the risk of diabetes, which is consistent with our results. Similar to our findings, Zhang *et al.* [30] in the year 2019 found that the concentration of asprosin was significantly higher in newly diagnosed T2DM compared to normal glucose tolerance population in a study with a population in the southern China. Similarly, the results of Wang *et al.* [31] in the year 2018 showed that plasma asprosin concentration was significantly correlated with IGR and newly diagnosed T2DM, especially in the IGR population, suggesting that asprosin may be involved in the development of diabetes. Additionally, a previous study has shown that asprosin is positively correlated with insulin resistance [12]. Other study found that asprosin is positively correlated with BMI and TG, suggesting that asprosin is closely related to insulin resistance and blood lipids [30]. Furthermore, it has been observed that asprosin positively correlated with fasting blood glucose, HbAlc and Homeostasis Model-Assessed Insulin Resistance Index (HOMA-IR) in patients with T2DM [32]. Consistent with our findings, asprosin was positively correlated with PBG and HbA1c in patients with T2DM. Metrnl was found to be related to blood glucose, blood pressure and blood lipids in diabetic patients in a previous study [33]. However, in this study, Metrnl did not show significant difference among normal, prediabetic and diabetic patients.

The results of this study show that asprosin level is significantly correlated with clinical indicators (HbA1c, PBG and CREA) in patients that transitioned from prediabetes in diabetes in two years. High levels of asprosin that led into higher blood glucose and poorer renal function in diabetes mellitus patients might be one of the reasons for the development of the disease. In addition, the sample size and population of this study are limited due to all subjects were from the same district. Further studies are needed with longer term follow up and larger sample size.

Conclusions

This study showed that asprosin level is significantly correlated with blood glucose levels and renal function related indicators (HbA1c, PBG and CREA) in patients transitioning from prediabetes to diabetes at 2-year follow-up.

Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Author Contributions

JH—has made the design of the work and written this article; XD, YM, SL and YP—have done the acquisition, analysis, and interpretation of data. All authors have drafted the work and substantively revised it. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study protocol received ethical approval by the Committee on Human Research at Shanghai General Hospital (project no. 2013KY083). Written informed consent was obtained from each participant. The study fulfilled Declaration of Helsinki principles for medical research involving humans.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, *et al.* Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999–2002. Diabetes Care. 2006; 29: 1263–1268.

[2] Hackworth N, Moore S, Hardie E, Critchley C, Buzwell S, Kyrios M, *et al.* A Risk Factor Profile for Pre-Diabetes: Biochemical, Behavioural, Psychosocial and Cultural Factors. E-Journal of Applied Psychology. 2007; 3: 14–26.

[3] Govind G, Akhtar MJ. Design of an ELC resonator-based reusable RF microfluidic sensor for blood glucose estimation. Scientific Reports. 2020; 10: 18842.

[4] Shao X, Wang Y, Huang S, Liu H, Zhou S, Zhang R, *et al.* Development and validation of a prediction model estimating the 10-year risk for type 2 diabetes in China. PloS One. 2020; 15: e0237936.

[5] Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, *et al.* Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: A systematic overview and meta-analysis of prospective studies. Diabetes Research and Clinical Practice. 2007; 78: 305–312.

[6] Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet (London, England). 2012; 379: 2279–2290.

[7] Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, *et al*. Impaired Fasting Glucose and Impaired Glucose Tolerance. Diabetes Care. 2007; 30: 753–759.

[8] Hostalek U. Global epidemiology of prediabetes—present and future perspectives. Clinical Diabetes and Endocrinology. 2019; 5: 5.

[9] Brannick B, Dagogo-Jack S. Prediabetes and Cardiovascular Disease: Pathophysiology and Interventions for Prevention and Risk Reduction. Endocrinology and Metabolism Clinics of North America. 2018; 47: 33–50.

[10] Ford ES, Zhao G, Li C. Pre-Diabetes and the Risk for Cardiovascular Disease. Journal of the American College of Cardiology. 2010; 55: 1310–1317.

[11] Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ (Clinical Research ed.). 2016; 355: i5953.

[12] Wang M, Yin C, Wang L, Liu Y, Li H, Li M, *et al.* Serum Asprosin Concentrations are Increased and Associated with Insulin Resistance in Children with Obesity. Annals of Nutrition & Metabolism. 2019; 75: 205–212.

[13] Gozel N, Kilinc F. Investigation of plasma asprosin and saliva levels in newly diagnosed type 2 diabetes mellitus patients treated with metformin. Endokrynologia Polska. 2021; 72: 37–43.

[14] Jamal MH, Abu-Farha M, Al-Khaledi G, Al-Sabah S, Ali H, Cherian P, *et al*. Effect of sleeve gastrectomy on the expression of meteorin-like (METRNL) and Irisin (FNDC5) in muscle and brown adipose tissue and its impact on uncoupling proteins in diet-induced obesity rats. Surgery for Obesity and Related Diseases. 2020; 16: 1910–1918.

[15] Li ZY, Song J, Zheng SL, Fan MB, Guan YF, Qu Y, *et al.* Adipocyte Metrnl Antagonizes Insulin Resistance Through PPARγ Signaling. Diabetes. 2015; 64: 4011–4022.

[16] Wang C, Pan Y, Song J, Sun Y, Li H, Chen L, *et al.* Serum Metrnl Level is Correlated with Insulin Resistance, but Not with β-Cell Function in Type 2 Diabetics. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2019; 25: 8968–8974.

[17] Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. Journal of Clinical Investigation. 1999; 104: 787–794.

[18] Li N, Wang J, Wang X, Sun J, Li Z. Icariin exerts a protective effect against d-galactose induced premature ovarian failure via promoting DNA damage repair. Biomedicine & Pharmacotherapy = Biomédecine & Pharmacothérapie. 2019; 118: 109218.

[19] Zhou QX, Wang ZY, Zhao HF, Wang S. The effects of GLP-1 analogues on pre-diabetes of the children. Experimental and Therapeutic Medicine. 2017; 13: 1426–1430.

[20] Luc K, Schramm-Luc A, Guzik TJ, Mikolajczyk TP. Oxidative stress and inflammatory markers in prediabetes and diabetes. Journal of Physiology and Pharmacology: An Official Journal of the Polish Physiological Society. 2019; 70: 809–824.

[21] Lee H, Park T, Kim J, Yun JH, Yu H, Kim Y, *et al*. Identification of metabolic markers predictive of prediabetes in a Korean population. Scientific Reports. 2020; 10: 22009.

[22] Gar C, Rottenkolber M, Prehn C, Adamski J, Seissler J, Lechner A. Serum and plasma amino acids as markers of prediabetes, insulin resistance, and incident diabetes. Critical Reviews in Clinical Laboratory Sciences. 2018; 55: 21–32.

[23] Sims EK, Carr ALJ, DiMeglio LA, Evans-Molina C, Oram RA. 100 years of insulin: celebrating the past, present and future of diabetes therapy. Nature Medicine. 2021; 27: 1154–1164.

[24] Tandon R, Luxami V, Dosanjh HS, Tandon N, Paul K. Insulin

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Therapy for Diabetes Epidemic: A Patent Review. Current Drug Delivery. 2018; 15: 777–794.

[25] Bódis K, Roden M. Energy metabolism of white adipose tissue and insulin resistance in humans. European Journal of Clinical Investigation. 2018; 48: e13017.

[26] Wang X, Wu J, Wu Y, Wang M, Wang Z, Wu T, *et al*. Pleiotropic Effects of a KCNQ1 Variant on Lipid Profiles and Type 2 Diabetes: a Family-Based Study in China. Journal of Diabetes Research. 2020; 2020: 1–7.

[27] Luo J, Hodge A, Hendryx M, Byles JE. BMI trajectory and subsequent risk of type 2 diabetes among middle-aged women. Nutrition, Metabolism and Cardiovascular Diseases. 2021; 31: 1063–1070.

[28] Sabin MA, Magnussen CG, Juonala M, Shield JPH, Kähönen M, Lehtimäki T, *et al*. Insulin and BMI as Predictors of Adult Type 2 Diabetes Mellitus. Pediatrics. 2015; 135: e144–e151.

[29] Li ZT, Wang XN, Liu XL, Ke JZ, Ruan XN, Qiu H, *et al*. [Relationship of body mass index, waist circumference and waist-to-hip ratio with diabetes mellitus in community residents aged 15 years old and above in Pudong new district, Shanghai]. Zhonghua Liu Xing Bing Xue Za Zhi = Zhonghua Liuxingbingxue Zazhi. 2020; 41: 326–330.

[30] Zhang L, Chen C, Zhou N, Fu Y, Cheng X. Circulating asprosin concentrations are increased in type 2 diabetes mellitus and independently associated with fasting glucose and triglyceride. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2019; 489: 183–188.

[31] Wang Y, Qu H, Xiong X, Qiu Y, Liao Y, Chen Y, *et al*. Plasma Asprosin Concentrations are Increased in Individuals with Glucose Dysregulation and Correlated with Insulin Resistance and first-Phase Insulin Secretion. Mediators of Inflammation. 2018; 2018: 1–7.

[32] Chen Y, Tang H, Wang L, He J, Guo Y, Liu Y, *et al*. Fertility Enhancement but Premature Ovarian Failure in esr1-Deficient Female Zebrafish. Frontiers in Endocrinology. 2018; 9: 567.

[33] Chung HS, Hwang SY, Choi JH, Lee HJ, Kim NH, Yoo HJ, *et al.* Implications of circulating Meteorin-like (Metrnl) level in human subjects with type 2 diabetes. Diabetes Research and Clinical Practice. 2018; 136: 100–107.