Circulating Ism1 Reduces the Risk of Type 2 Diabetes but not Diabetes-Associated NAFLD

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Purpose: To examine the association of serum Ism1, a new adipokine that can regulate glucose uptake, with type 2 diabetes (T2D) in a Chinese population. Considering high prevalence of Nonalcoholic Fatty Liver Disease in patients with type 2 diabetes and the regulating role of Ism1 on glucose uptake of peripheral tissues, we further explored the association between Ism1 and diabetes-associated nonalcoholic fatty liver disease.

Methods: A total of 120 newly diagnosed T2D patients and 60 control subjects with normal glucose were recruited in the case-control study. Serum Ism1 concentrations were determined by ELISA. Multivariate logistic regression analysis was used to evaluate the independent association of serum Ism1 concentration with the risk of T2D. The 120 newly diagnosed T2D patients were divided into uncomplicated T2D group and diabetes-associated NAFLD group according to the FLI score.

Results: The Ism1 level of normoglycemic controls was higher than that of T2D patients (3.91 ± 0.24 ng/ml vs 3.01 ± 0.16 ng/ml, P=0.001). Based on quartile analysis of Ism1 level, the proportion of high circulating Ism1 levels in the control group increased while T2D group decreased, and the distribution difference was statistically significant (P=0.015). Logistic regression analysis indicated that the serum Ism1 level was an independent protective factor of type 2 diabetes (OR=0.69, 95%CI: 0.54-0.89). The decrease of Ism1 level did not increase the risk of non-alcoholic fatty liver disease in diabetic patients by Binary logistic regression analysis (OR=1.08, 95% CI: 0.69-1.69).

Conclusions: The increase of serum Ism1 was associated with a decreased risk of diabetes, and it did not reduce the risk of non-alcoholic fatty liver disease in diabetic patients.

Keywords: Ism1, type 2 diabetes, NAFLD, diabetes-associated NAFLD, adipokine

INTRODUCTION

Diabetes is one of common and frequent metabolic diseases and has become the world’s third-largest chronic disease (1). The number of adults with diabetes between 20 and 79 years old worldwide has reached 463 million, and an estimated 693 million people globally will be suffering from diabetes by 2045 according to the International Diabetes Federation Survey (2). In China about 129.8 million diabetics account for nearly 12.8% of the total population, making the country...
become the most individuals and fastest-growing one in the world for diabetes (3). Such a high incidence of diabetes imposes a great burden not only to the individual but also to their family, society, and the healthcare system (4).

Type 2 diabetes is a metabolic disorder accompanied by increased insulin resistance and high blood glucose levels partly due to impaired glucose uptake and utilization by skeletal muscle, liver and adipose tissue (5, 6). Obesity is well known to be a significant risk factor for type 2 diabetes, and the increase in abdominal adipose tissue mass contributes to abnormal secretion of adipokines, which exerts important effects on glucose and lipid metabolism, insulin resistance and diabetes (7). To date, a variety of adipokines related to type 2 diabetes have been discovered and identified, including Adiponectin, Leptin, Visfatin, IL-6 and FGF21, etc (8, 9). However, the current research does not completely understand the mechanism of adipokines and new bioactive molecules remain to be discovered to predict and elucidate the pathogenesis of T2D and lead to the discovery of relevant biomarkers. Among these “adipokines” Isthmin-1 (Ism1) has received increasing attention recently.

Ism1 is a novel secreted protein unique to chordates, originally identified in the isthmus of Xenopus laevis during the early brain development in 2002 (10), and it is highly expressed in thyroid, placenta and adipose tissue (11). Previous studies have shed light on the multiple biological functions of Ism1 in embryonic development, anti-angiogenesis activity, inhibiting tumor growth and promoting apoptosis (12, 13). Recent advances have illuminated that Ism1 can regulate the glucose uptake of adipose tissue and reduce hepatic lipid synthesis in mice (14). However, to our knowledge, no one has focused on the correlation between Ism1 and T2D. Therefore, we intended to examine the difference in serum levels of Ism1 from newly-onset type 2 diabetes and normoglycemic controls, and analyzed the relationship between Ism1 level and the risk of diabetes by logistic regression.

METHOD

Study Design and Data Collection

This case-control study was approved by the Institutional Review Board of Shanghai Jiao Tong University School of Medicine Affiliated Tongren Hospital and conducted at the Department of Endocrinology from March to October 2021. Written informed consent was obtained from all participants.

The study included participants who were newly diagnosed with type 2 diabetes, based on the international classification of diabetes (ICD 10) criteria. The 120 newly diagnosed T2D patients were over 40 years old (mean age, 46.75 ± 1.20 years; BMI, 26.59 ± 0.45 kg/m²; males: females, 72:48). At the same time, from the physical examination population in the same area, 60 healthy controls subjects in Chinese population. Baseline characteristics of the T2D and control participants were summarized in Table 1. They were similar with respect to basic characteristics such as age, sex, height, weight and body mass index (BMI). Several biochemical indicators including uric acid (UA), lipids (TC, TG) and low-density lipoprotein (LDL-c) were not significantly different between the two groups. However, other biochemical parameters behaved differently. Except for high-density lipoprotein (HDL-c), creatinine that were higher in controls, T2D cases had higher levels of liver enzyme (ALT), fasting glucose (FPG) and fasting insulin (FINS). As expected, higher HOMA-IR (4.19 Vs 1.20) but lower HOMA-β (65.93 Vs 89.40) were observed in T2D than in control subjects (P<0.05), which means insulin resistance and β-cell function impairment occurred in diabetes cases.

Comparison of Ism1 Level Between Diabetes and Control Groups

Much to our surprise, we noticed that the mean of serum Ism1 concentration (CV=4.1%) decreased in T2D group (3.01 ± 0.16 ng/ml) as compared to control group (3.91 ± 0.24 ng/ml),
and the difference was statistically significant (P<0.001). To assess whether the decreased expression of serum Ism1 influenced the risk of diabetes, high and low expression levels were categorized based on quartiles. As shown in Table 2, the proportion of low circulating Ism1 levels (<3.02 ng/ml) was higher in the diabetes group than the non-diabetic groups (P=0.015).

### Binary Logistic Regression Analysis of Circulating Concentrations of Ism1, ALT, HLD-c and T2D

A multivariate analysis was performed to calculate OR value to explore the link between different variables and the occurrence of diabetes. Ism1, ALT and HLD-c were included in the regression when they were found to be significant (P<0.05). The levels of Ism1 was found to be an independent risk factor for T2D (OR=0.69, 95% CI=0.54-0.89, P=0.004), whereas ALT and HLD-c were no significant correlation with T2D (Table 3). Further, the association remained also when Ism1 was stratified by quartile, and the highest quartile level Ism1 was used as a reference. The results implied that T2D risk appeared to be significantly higher in subjects with the lowest quartile of Ism1 than in the subjects with the highest quartile of Ism1 (OR=4.69, 95% CI=1.22-17.93, P=0.024). However, compared with the highest quartile level Ism1, the second and third quartiles of Ism1 showed no significant correlation with T2D. To visualize the risk of ISM1 and type 2 diabetes, we created a nomogram (Figure 1).

### Comparison of Baseline Clinical Characteristics of T2D Patients With or Without NAFLD

T2DM is closely linked to enhanced risk of developing nonalcoholic fatty liver disease, and it had been reported that more than 50% of T2D patients were accompanied by NAFLD (15, 16). As of now, relatively less is known about the prevalence of and risk factors for NAFLD with Type 2 diabetes in China; hence, further research is required in this area. As stated above, low levels of Ism1 have been indicated as an independent risk factor for the development of T2D. The relationship between serum Ism1 levels and the development of NAFLD in diabetic patients was evaluated subsequently. FLI, a non-invasive approach for diagnosis of nonalcoholic fatty liver disease was used in our research. The score of FLI ≥60 was considered to have NAFLD. Among 120 diabetic patients, 48 patients were diagnosed with diabetes-associated NAFLD, so we matched the same number of uncomplicated diabetic cases and carried out our case-control study. There was no difference in the age and

### Table 2 | Distribution of Ism1 in the case and control groups.

| Ism1 level classification (quartile) | Non-T2D group (n = 60) | T2D group (n = 120) |
|-------------------------------------|------------------------|---------------------|
| <P25 (<2.01 ng/mL)                  | 9 (15.00)              | 36 (30.00)          |
| P25–P49 (2.01 ng/mL–)               | 11 (18.33)             | 34 (28.33)          |
| P50–P75 (3.02 ng/mL–)               | 19 (31.67)             | 26 (21.67)          |
| >P75 (>4.16 ng/mL)                  | 21 (35.00)             | 24 (20.00)          |

*x^2* = 10.40, P=0.015. Data are expressed as number of samples, n (%).
proportion of gender between the two groups of cases. Obese persons were more likely to suffer from NAFLD, especially those with abdominal obesity. As depicted in Table 4, this was indeed the case. Diabetes-associated NAFLD subjects were more likely to have abdominal obesity, with BMI of 30.97 kg/m² and waist circumference of 103.18 cm. ALT, UA and FINS were significantly higher in diabetes-associated NAFLD than diabetes. Total cholesterol, LDL-c, and HDL-c levels did not show any significant change, whereas triglycerides levels were elevated. As we know, the most important link between T2D and NAFLD is insulin resistance (IR) (17, 18), HOMA-IR levels showed an elevation in subjects with diabetes-associated NAFLD. Of note, there was no significant change in circulating Ism1 levels in either group.

Risk Factors for Diabetes-Associated Nonalcoholic Fatty Liver Disease.

The independent risk factors for concurrent diabetes-associated NAFLD were identified by a multivariate stepwise logistic regression analysis. Variables were included in the regression when they were found to be significant (P<0.05). Numerous studies have been confirmed that metabolic comorbidities such as obesity, type 2 diabetes, dyslipidemia and hypertension were strongly related to the prevalence and incidence of NAFLD (17, 19). In the present study, we found that BMI (OR=1.77, 95% CI=1.39-2.25, P<0.001) and TG (OR=1.72, 95% CI=1.02-2.88, P=0.04) were risk factors for NAFLD (Table 5). In addition, our results illustrated that low Ism1 levels did not increase the risk of NAFLD (OR=1.08, 95% CI=0.69-1.69, P=0.74) in diabetic patients.

DISCUSSION

Type 2 diabetes is a multifactorial metabolic disease that requires life-long therapy (20, 21). Although the early diagnosis of T2D is particularly important, there is still a lack of strong and effective biomarkers in the prediction of type 2 diabetes (22, 23). As such, we have explored the independent association of circulating Ism1 with the risk of T2D. To our knowledge, this is the first case-control study of Ism1 in population. Our results first demonstrated that a significant reduction of serum Ism1 level in T2D subjects when compared with control subjects. Logistic regression analysis indicated that this adipokine Ism1 is an independent protective factor for the development of T2D.

The biologically active adipokines secreted by adipose tissue have been frequently reported due to their main role in regulating metabolism, inflammation and glycolipid homeostasis to protect

**TABLE 3 | OR (95% CI) of T2D associated with ALT, HDL-c and the quartiles of Ism1.**

| Variable     | β       | Wald | P value | OR (95% CI)       |
|--------------|---------|------|---------|-------------------|
| ALT          | 0.009   | 0.13 | 0.72    | 1.00 (0.99-1.01)  |
| HDL-c        | -0.67   | 1.16 | 0.28    | 0.51 (0.15-1.73)  |
| Continuous (Ism1) | -0.30   | 0.006 | 0.004** | 0.69 (0.54-0.89)  |
| Ism1 (<P25)  | 1.55    | 5.09 | 0.024*  | 4.69 (1.22-17.93) |
| Ism1 (P25~P49) | 1.39    | 5.46 | 0.019*  | 4.86 (0.23-3.20)  |
| Ism1 (P50~P75) | 0.26    | 0.20 | 0.66    | 1.29 (0.42-4.02)  |
| Ism1 (>P75)  | /       | 8.87 | 0.031*  | 1.00              |

OR, odds ratio; CI, confidence interval; Values are given as OR (95% CI). **P value <0.01. *P value <0.05 was considered significant.
TABLE 4 | Clinical characteristics of the T2D group and T2D&NAFLD group.

| Characteristic | T2D group (n = 48) | T2DM&NAFLD group (n = 48) | P value |
|----------------|------------------|--------------------------|---------|
| Age (years)    | 43.29 ± 1.32     | 42.54 ± 1.54             | 0.56    |
| Sex (M/F)      | 29/19            | 31/17                    | 0.67    |
| BMI (kg/m²)    | 23.99 ± 0.49     | 30.97 ± 0.54             | <0.001**|
| WC(cm)         | 87.21 ± 1.52     | 103.18 ± 1.24            | <0.001**|
| FPG (mmol/L)   | 9.17 ± 0.52      | 8.60 ± 0.50              | 0.45    |
| FINs (mU/L)    | 10.70 ± 0.89     | 18.80 ± 2.02             | <0.001**|
| UA (μmol/L)    | 54.30 (47.00-60.93) | 59.00 (43.00-65.00) | 0.39    |
| Cr (μmol/L)    | 350.50 (287.75-396.50) | 370.50 (331.25-442.40) | 0.036*  |
| TC (mmol/L)    | 4.75 (4.11-5.56) | 4.96 (4.56-5.57)         | 0.13    |
| TG (mmol/L)    | 1.39 (0.88-2.16) | 2.37 (1.67-3.35)         | <0.001**|
| HDL-c (mmol/L) | 3.34 (2.58-3.86) | 3.31 (2.69-3.81)         | 0.95    |
| LDL-c (mmol/L) | 1.01 (0.89-1.21) | 0.94 (0.83-1.03)         | 0.023*  |
| ALT (μU/L)     | 23.00 (15.25-45.70) | 40.50 (25.00-65.25) | 0.002** |
| Cr(μmol/L)     | 43.71 (23.27-82.24) | 76.80 (40.51-171.41) | 0.005** |
| HOMA-IR        | 3.90 (2.08-5.40) | 5.55 (3.54-8.78)         | 0.001** |
| Ism1 (ng/mL)   | 2.50 (1.42-3.08) | 2.87 (1.84-3.48)         | 0.13    |

Values are given as OR (95% CI). **P value <0.01. *P value <0.05 was considered significant.

TABLE 5 | Binary Logistic regression analysis between level of Ism1 and T2D&NAFLD.

| Variable | β     | Wald  | P value | OR (95% CI)   |
|----------|-------|-------|---------|---------------|
| Ism1     | 0.08  | 0.11  | 0.74    | 1.08 (0.69-1.69)|
| BMI      | 0.57  | 21.45 | <0.001**| 1.77 (1.39-2.25)|
| ALT      | -0.006| 0.25  | 0.62    | 0.99 (0.97-1.02)|
| UA       | 0.003 | 0.42  | 0.52    | 1.00 (0.99-1.01)|
| TG       | 0.54  | 4.21  | 0.04*   | 1.72 (1.02-2.88)|

Values are given as OR (95% CI). **P value <0.01. *P value <0.05 was considered significant.
There were a few shortcomings in this study, one of the limitations was that it was only a case-control study, and the sample size was not large enough, with only 180 cases. The study was not comprehensive enough and was not conclusive to revealing the causative relationship between Ism1 and T2D. Therefore, further study should be evaluated by expanding the number of patients and implementing a prospective cohort. Another limitation was that this study was conducted in an age-dispersed population; therefore, research on Ism1 in elderly population with a higher T2D incidence still needs to be performed. In addition, we did not perform pathological diagnosis by using the traditional method for NAFLD, the inclusion criteria for NAFLD need to be further optimized.

In summary, our results demonstrated that the secretion of Ism1 was altered in subjects with T2D, but it was not found in patients with diabetes-associated NAFLD clearly suggesting that Ism1 was an independent protective factor for diabetes but not diabetes-associated NAFLD. Therefore, it can be a potentially useful new biomarker for the early diagnosis and management of diabetes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Tongren Hospital, Shanghai Jiao Tong University School of Medicine. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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AUTHOR CONTRIBUTIONS

XRG, WL and SH designed the research. JW performed the experiments and data analysis. JD and XXG collected the clinical data of participants and serum samples. WP assisted in research design and experiments. WL and JW prepared the paper. All authors contributed to the article and approved the submitted version.

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