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The association of new inflammatory markers with type 2 diabetes mellitus and macrovascular complications: a preliminary study

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Abstract. – AIM: Type 2 diabetes mellitus (T2DM) is not simply a disease of hyperglycemia, but also is an inflammatory disorder. This study aimed to observe the expression of inflammation-related factors in elderly T2DM patients with or without macrovascular disease (MVD).

PATIENTS AND METHODS: A total of 64 T2DM patients participated in this study, including 31 patients with MVD (group A) and 33 patients without MVD (group B); and 30 healthy volunteers were recruited as normal control (group C). The levels of serum irisin, retinol-binding protein 4 (RBP4) and adiponectin expression were all detected and compared between groups.

RESULTS: The demographic and clinical characteristics were comparable between T2DM patients and healthy volunteers. For patients in group A, the serum levels of irisin, RBP4 and adiponectin were 12.05 ± 2.12 pg/mL, 2.13 ± 0.83 μg/mL and 45.65±20.13 ng/mL, respectively. While the corresponding parameters were 26.11 ± 4.09 pg/ml, 1.54 ± 0.54 μg/ml and 57.93 ± 23.47 ng/mL for patients in group B; and were 40.25 ± 2.73 pg/mL, 0.98 ± 0.36 μg/mL and 60.03 ± 20.26 ng/mL for healthy volunteers in group C, respectively. As compared to healthy volunteers, the levels of irisin, RBP4 and adiponectin were all significantly changed in T2DM patients; and the difference in irisin, RBP4 and adiponectin between T2DM patients with and without MVD were all significant (p = 0.000, p = 0.001, and p = 0.029, respectively). Multivariate regression analysis showed that irisin and RBP4 are both independent predictors for MVD in T2DM patients.

CONCLUSIONS: Inflammatory disorder is significantly in T2DM patients with MVD, and serum irisin and RBP4 would be reasonable new markers of MVD.

Key Words:

Inflammatory disorder, Macrovascular complications, Type 2 diabetes mellitus, Irisin, Retinol-binding protein 4.

Abbreviations

T2DM = type 2 diabetes mellitus; MVD = macrovascular disease; DM = diabetes mellitus; RBP4 = retinol-binding protein 4; PAI-1 = plasminogen activator inhibitor-1; CRP = C-reactive protein; hs-CRP = high-sensitivity C-reactive protein; BMI = body mass index; FBG = fasting blood glucose; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TC = total cholesterol; WHR = waist-to-hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Introduction

Vascular complication is more prevalent in subjects with diabetes mellitus (DM), and previous studies have reported that chronic hyperglycemia could likely be an independent and important determinant for the occurrence and development of vascular complications. For the inadequate insulin secretion by pancreatic beta cells, hyperglycemia is significantly in type 2 diabetes mellitus (T2DM), and the microvascular and macrovascular complications are relatively common in poorly controlled T2DM[1,2].

It has been proven that insulin resistance is one of the typical characteristics to T2DM patients, and insulin resistance would be attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma. Indeed, more and more recent evidences show that DM is a pro-inflammatory state[3], and the active inflammation would participate in the progression of vascular complications of T2DM patients[4]. Currently, the inflammation-related factors such as high-sensitivity C-reactive protein (hs-CRP), Toll-like receptor 2 (TLR2), TLR4, and plasminogen activator inhibitor-1 (PAI-1), soluble cell adhesion molecules, interleukin-1b (IL-1b), IL-6, tumor necrosis factor-a and adipocyte-de-

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rived protein adiponectin have been widely concerned, and their abnormal expression would indicate a pro-inflammatory state in a certain degree[5-9]. However, the predictive value of above inflammation-related factors on the occurrence and progression of vascular complications is still limited.

Recently, irisin has been identified as a novel myokine that drives brown-fat-like conversion of white adipose tissue[10], and it also has been regarded as an anti-inflammatory factor, which is correlated to diabetes and severity of insulin resistance[11-13]. So it is speculated that the macroangiopathy in diabetic patients may also correlated with the lower levels of irisin. Additionally, more and more studies reported that lipocalin family protein retinol-binding protein 4 (RBP4) was closely associated with obesity-related metabolic disorders, and the circulating levels of RBP4 were positively correlated with carotid intima-media thickness and subclinical atherosclerosis in T2DM[14,15]. All those findings suggest that RBP4 may participate in the pathogenesis of vascular complications of diabetes.

There are also some reports on inflammatory markers in predicting vascular complications of T2DM[9,16,17]; however, majority of these studies are forced on ancient indicators (such as serum adiponectin, PAI-1 and hs-CRP) and limited to specific populations, which may be not representative of other regions or ethnic population. Thus, their findings still need to be further verified and new serological predictors should be investigated. Therefore, in this study, we have evaluated a series of inflammatory markers in T2DM patients with or without macrovascular complications, and our findings would provide reasonable new markers of macrovascular disease (MVD) in T2DM.

Patients and Methods

Patients

This was a prospective and controlled study, and 64 participants with diagnosed T2DM, who hospitalized in Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital between January 1 of 2007 and December 31 of 2012, were recruited. In order to investigate whether there were difference in the expression of inflammation-related factors in elderly T2DM patients with or without MVD, thirty-one T2DM patients with MVD were designated as group A, and another 33 body mass index (BMI)-matched T2DM patients without MVD were assigned to group B. And 30 healthy volunteers were recruited as normal control and they were designated as group C.

In this study, T2DM patients had one of the following criteria should be excluded: (1) evidence of nephropathy, retinopathy, acute or chronic infection, fever, or any inflammatory condition; (2) co-existence of microvascular complications of DM; (3) congenital MVD or MVD caused by trauma; (4) MVD diagnosed prior to T2DM.

This study was conducted in accordance with the 1975 Declaration of Helsinki and approved by the institutional Review Board of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital. Informed consents were also obtained from all participants.

Data Collection and Laboratory Assessment

The detailed information of demographic parameters (such as age, gender, duration of diabetes, BMI and waist-to-hip ratio) and physical examination (including systolic blood pressure and diastolic blood pressure) were collected.

The examination of fasting blood glucose (FBG), glycosylated haemoglobin (HbA1c), lipid profiles [including total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) and triglycerides] were performed by automatic biochemical analyzer (Olympus AU400, Tokyo, Japan) according to standard laboratory procedures, and the remaining serum samples were cryopreserved at –80°C. In this study, the serum level of irisin (BioVendor, Modrice, Czech Republic), RBP4 (AssayMax, Yurok Circle San Iose, CA, USA), adiponectin (Biovision, Milpitas, CA, USA), PAI-1 (BioVendor, Czech Republic), and hs-CRP (Cusabio, Wuhan, China) were detected by enzyme-linked immunosorbent assay using commercially available reagents.

Definition of Macrovascular Disease (MVD)

MVD should include coronary artery disease (CAD) proven by coronary angiography, peripheral vascular disease (PVD) proven by Doppler ultrasound of lower limb vessels, cardiovascular disease (CVD) proven by computed tomography (CT) scan of brain and carotid Doppler examination, respectively.

Statistical Analysis

Quantitative variables were expressed as mean and standard deviation, and categorical variables were presented as counts and percentages. Comparisons between groups of quantitative and qualitative variables were performed using the Student t test and Chi-square test (or Fisher's exact test), respectively. And multiple logistic regression analysis was used to find predictors of MVD in T2DM patients. A *p*-value of less than 0.05 (two-tailed) was considered to indicate a significant difference. All statistical analyses were performed using the SPSS software package version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

As Table I showed that there were significant lipid and inflammatory disorders among T2DM patients in this study. For example, the levels of serum irisin, RBP4 and adiponectin were all significantly changed in T2DM patients as compared to healthy volunteers. Additionally, the age and sex distribution, BMI, waist-to-hip ratio (WHR), systolic (SBP) and diastolic blood pressures (DBP) of the T2DM patients with or without MVD were also presented in Table II, whereas the distribution of FBG, HbA1c, lipid profile parameters (such as total cholesterol, LDL, HDL, and triglycerides) were summarized in Table III. And the difference in above parameters were not statistic significantlly between two groups.

Of patients with MVD in group A, high to 67.7% (21/31) patients received angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARBs) treatment, 64.5% (20/31) patients received aspirin, 58.1% (18/31) patients received aspirin and 16.1% (5/31) patients received b-blockers. Of patients without MVD in group B, only 12.1% (4/33) patients received ACEI/ARBs and 6.1% (2/33) patients received b-blockers, whereas none received statins or aspirin.

The levels of serum irisin, RBP4, adiponectin, PAI-1 and hsCRP in T2DM patients with or without MVD were also presented in Table III. For patients with MVD in group A, the serum levels of irisin, RBP4 and adiponectin were 12.05 ± 2.12 pg/mL, 2.13 ± 0.83 mg/mL and 45.65 ± 20.13 ng/mL, respectively; while the corresponding parameters were 26.11 ± 4.09 pg/ml, 1.54 ± 0.54 mg/ml and 57.93 ± 23.47 ng/mL for T2DM patients without MVD in group B. As compared to patients without MVD in group B, serum irisin (p = 0.001), and adiponectin (p = 0.029) was both significantly decreased in patients with MVD in group A; while serum RBP4 (p = 0.001), PAI-1 (p = 0.004) and hs-CRP (p = 0.040) were all elevated significantly. And these findings indicated that inflammatory disorder was significant in T2DM patients with MVD. It is worth mentioning that the levels of serum irisin, RBP4, adiponectin, PAI-1 or hsCRP among CAD, PVD and CVD were not significantly in this cohort.

Table I. The demographic and laboratory parameters between T2DM patients and health volunteers.

Parameter	T2DM	Healthy control	*p* value
Sample size	64	30	
Age, years	59.54 ± 10.85	58.72 ± 10.26	0.729
Gender, male/female	45/19	21/9	
BMI, kg/m^2	22.61 ± 2.71	22.45 ± 2.61	0.788
WHR	0.96 ± 0.06	0.95 ± 0.08	0.501
Blood pressure, mmHg			
SBP	135.43 ± 22.17	128.26 ± 19.88	0.135
DBP	79.67 ± 8.42	75.84 ± 8.56	0.044
FBG, mmol/L	8.41 ± 2.01	4.81 ± 0.58	0.000
HbA1c, %	9.37 ± 2.25	5.45 ± 0.46	0.000
Total cholesterol, mmol/L	1.81 ± 0.72	4.47 ± 0.43	0.000
LDL, mmol/L	2.99 ± 0.54	2.29 ± 0.35	0.000
HDL, mmol/L	1.25 ± 0.29	1.43 ± 0.22	0.003
Triglycerides, mmol/L	1.82 ± 0.75	1.14 ± 0.33	0.000
Irisin, pg/mL	18.89 ± 3.78	40.25 ± 2.73	0.000
RBP4, μg/mL	1.86 ± 0.62	0.98 ± 0.36	0.000
Adiponectin, ng/mL	51.42 ± 21.32	60.03 ± 20.26	0.067
PAI-1, mg/ml	29.21 ± 8.97	–	
Hs-CRP, ng/mL	9.87 ± 7.42	–	

Table II. The demographic and general clinical parameters in T2DM patients with or without MVD.

Parameter	MVD	Non-MVD	*p* value
Sample size	31	33	
Age, years	61.36 ± 10.61	58.43 ± 11.35	0.291
Gender, male/female	21/10	24/9	0.786
Duration of diabetes, years	5.13 ± 3.28	4.99 ± 3.52	0.870
BMI, kg/m^2	22.42 ± 2.65	22.87 ± 2.83	0.515
WHR	0.98 ± 0.03	0.95 ± 0.08	0.054
Blood pressure, mmHg			
SBP	138.65 ± 20.31	130.85 ± 22.54	0.152
DBP	81.33 ± 9.86	78.65 ± 8.61	0.251
Treatment			
ACEI/ARBs	21 (67.7%)	4 (12.1%)	
β-blockers	5 (16.1%)	2 (6.1%)	
Statins	20 (64.5%)	–	
Aspirin	18 (58.1%)	–	

Given the difference in parameters observed between patients with or without MVD, we performed a multivariate logistic regression analysis, controlling for all covariates simultaneously (Table IV). The result of analysis revealed that both serum irisin (OR = 0.509, 95%CI=0.342-0.758, p = 0.002) and RBP4 (OR = 0.323, 95%CI = 0.174-0.612, p = 0.001) were significant independent predictors of MVD in T2DM patients.

Discussion

The global prevalence of diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025, and T2DM is the most common form of diabetes constituting 90% of the diabetic population[18,19]. One important pathogenetic factor of the diabetic macrovascular complications is represented by a decreased uptake of glucose into muscle and adipose tissue that leads to chronic extra cellular hyperglycemia, with the appearance of a chronic vascular damage. Currently, large evidences showed microvascular and macrovascular complications have become more prevalent in patients with DM[2,9,20]; how to prevent and treat vascular complication has been highly concerned by clinicians.

Considering the pro-inflammatory state of diabetes, we analyzed several inflammation-related factors such as irisin, RBP4, adiponectin, PAI-1 and hs-CRP in T2DM patients with and without MVD. And our findings were basically consistent with previous reports from other studies[9,17,21,22]. Thus, our data further suggested that patients with T2DM patients with MVD may have a more inflammatory disorder in vascular tissue as compared to those without MVD.

Recently, several studies reported that the occurrence and progress of diabetes may be correlated to irisin; and experiments had already re-

Table III. The biochemical and inflammatory parameter in T2DM patients with or without MVD.

Parameter	MVD (group A)	Non-MVD (group B)	*p* value
Sample size	31	33	
FBG, mmol/L	8.45 ± 2.63	8.31 ± 2.26	0.820
HbA1c, %	9.16 ± 2.05	9.41 ± 2.33	0.651
Total cholesterol, mmol/L	1.82 ± 0.74	1.80 ± 0.65	0.909
LDL, mmol/L	2.87 ± 0.68	3.11 ± 0.58	0.133
HDL, mmol/L	1.21 ± 0.21	1.28 ± 0.32	0.308
Triglycerides, mmol/L	1.83 ± 0.68	1.81 ± 0.62	0.903
Irisin, pg/mL	12.05 ± 2.12	26.11 ± 4.09	0.000
RBP4, μg/mL	2.13 ± 0.83	1.54 ± 0.54	0.001
Adiponectin, ng/mL	45.65 ± 20.13	57.93 ± 23.47	0.029
PAI-1, mg/ml	34.66 ± 12.81	26.25 ± 9.42	0.004
Hs-CRP, ng/mL	11.24 ± 7.6	7.63 ± 6.14	0.040

Table IV. Multiple logistic regression analysis of predictors for MVD in T2DM patients.

Parameter	OR	95% CI	*p* value
Irisin	0.509	0.342-0.758	0.002
RBP4	0.323	0.174-0.612	0.001
Adiponectin	1.403	0.678-2.889	0.348
PAI-1	0.727	0.356-1.506	0.404
Hs-CRP	0.562	0.321-1.022	0.065

vealed that injecting irisin into obese, pre-diabetic laboratory mice could improve glucose tolerance when fed a high-fat diet[23]. In this work, we found a significant decrease of serum irisin in T2DM patients, which further confirmed the potential role of irisin in glucose metabolism regulation and diabetes occurrence. Additionally, when compared the serum levels of irisin between T2DM patients with and without MVD, we have found that irisin decreased more significantly when MVD existed. Though large, multicentre, prospective, case-control studies were required to verify present study, our findings, still suggested that irisin would be a potential target for monitoring and intervention of T2DM and its associated vascular complications

At present, more and more evidences showed that the levels of serum RBP4, a protein secreted by adipocytes, were increased in insulin-resistant states, which had a causal role in T2DM. Experiments in mice suggested that elevated RBP4 levels could cause insulin resistance[24]. In addition, elevated serum RBP4 was also associated with cardiovascular risk factors in subjects with varied clinical presentations[22]. In our study, we have found there was an elevated serum RBP4 in T2DM and this elevation was more significant in T2DM patients with MVD than patients without MVD. Thus, we speculated that lowering serum RBP4 levels should be a useful tool for T2DM patients to prevent the appearance of MVD.

Adiponectin is an approximately 30-kDa protein specifically secreted from adipose tissue that circulates as oligomeric complexes in healthy human subjects at relatively high concentrations[25]. This protein has provided a novel link between obesity, insulin resistance, and vascular disease. In respect to previous investigations, it had been reported that the level of adiponectin was low in diabetic patients[9].

Adiponectin has been shown to have important effects in the vasculature, as well as in insulin signaling, glucose metabolism, and energy balance[26]. The significant decline of adiponectin in T2DM patients may contribute to the deterioration of inflammatory disorder and the occurrence of MVD. In this study, the decline of adiponectin was observed in T2DM patients with MVD; and as compared to patients without MVD, we also found that the level of adiponectin decreased significantly in patients with MVD. However, multiple logistic regression analysis showed that the decline of adiponectin was not an independent predictor of MVD in T2DM patients. Thus, more research was still needed to verify the predicting role of adiponectin for MVD in T2DM patients.

At present, both hs-CRP and PAI-1 were well-established markers of inflammation. Serum hs-CRP test not only accurately detects low concentrations of C-reactive protein to predict a healthy person's risk of cardiovascular disease[17], but also contributes to evaluate vascular inflammation, especially in combination with lipid metabolism related proteins. However, someone also reported that hs-CRP and PAI-1 tests would not be meaningful if people already with chronic inflammation, as their CRP and PAI-1 levels would already be very high. In this study, though the serum levels of hs-CRP and PAI-1 were significantly higher in patients with MVD than patients without MVD, multiple logistic regression analysis indicated that either hs-CRP or PAI-1 was not predictor for MVD in T2DM. Thus, we speculated that monitoring the elevation of serum hsCRP or PAI-1concentration had limited value to evaluate the severity of vascular inflammation and predict the risk of MVD occurrence.

Conclusions

Though these preliminary findings still need to be verified, our results still indicate that inflammatory disorder is significant in T2DM patients with MVD, and serum irisin and RBP4 would be new markers of MVD.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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