Decreased Serum Relaxin-2 Is Correlated with Impaired Islet β-Cell Function in Patients with Unstable Angina and Abnormal Glucose Metabolism

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Summary
Circulating relaxin (RLX) is altered in patients with diabetes mellitus (DM) or cardiovascular diseases. This study was designed to evaluate the changes of RLX in patients with unstable angina (UA) complicated with various categories of abnormal glucose metabolism.

Patients who confirmed UA by angiographic and clinical standard were grouped according to the glucose metabolism status with oral glucose tolerance test (OGTT) and medical history categorized as normal, prediabetes, newly diagnosed type 2 DM (T2DM), and previously diagnosed T2DM. Serum RLX-2 was measured and islet β-cell function was evaluated. The severity of the coronary arterial lesions was evaluated with Syntax Scores.

Serum RLX-2 was significantly higher in UA patients with prediabetes (median [quartiles]: 9.87 [7.48, 32.58] pg/mL) and newly diagnosed T2DM (18.36 [9.52, 48.08] pg/mL), compared with those with normal glucose tolerance (6.24 [4.02, 7.27] pg/mL, both \( P < 0.05 \)). Interestingly, UA patients with previously diagnosed T2DM exhibited lower RLX-2 levels (4.17 [3.23, 5.72] pg/mL) compared with those with normal glucose tolerance (\( P < 0.05 \)). Subsequent analyses indicated that serum RLX-2 was positively associated with parameters of islet β-cell function, C-peptide, and fasting insulin levels; however, it was negatively associated with the levels of fasting glucose, 2-hour postprandial blood glucose, HbA1c, and insulin sensitivity, suggesting a potential protective role of RLX-2 during abnormal glucose metabolism in UA patients. Serum RLX-2 was not correlated with the Syntax Scores in these patients.

Serum RLX-2 is a potential marker for UA patients with early glucose metabolism abnormality, and increased RLX-2 level was correlated with preserved islet β-cell function.

Key words: Type 2 diabetes, Prediabetes, Insulin resistance, Insulin sensitivity, Syntax Scores

Type 2 diabetes mellitus (T2DM) is recognized as a systematic disease, which is initiated by loss of islet β-cells, β-cell dysfunction and insulin resistance (IR), and subsequent systematic arterial and neurological lesions.1-5) Patients with T2DM often exhibit comorbidities of cardiovascular diseases (CVD), which may eventually lead to the mortality of these patients. To emphasize the potential damage of T2DM to public health, an early status of glucose metabolic dysfunction, known as prediabetes, has been defined as impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Findings from the previous studies suggested that patients with prediabetes often exhibited β-cell dysfunction as indicated by a homeostasis model assessment (HOMA) or updated HOMA model HOMA2.6) but merely with manifestations of the arterial or neurological lesions.2-4) Accumulating evidences from the previous studies have suggested that patients with prediabetes are also at increased risk for CVDs.7,8) and a recent meta-analysis9) confirmed that patients with prediabetes are associated with 10-20% higher risks for future CVDs according to the different abnormal glucose metabolism status, such as IFG, IGT, and a combination of IFG and IGT. Therefore, early identification of patients with glucose metabolism dysfunction is of potential significance for the early prevention of arterial or neurological complications of T2DM.

Relaxins (RLX, including RLX-2 and RLX-3), are a series of novel serum biomarkers, which are structurally related to insulin and insulin-like growth factors (IGF). Although RLX was initially regarded as a pregnancy-associated hormone, it has been found to be involved in the pathogenesis and progression of T2DM. Previous studies have suggested that patients with type 1 diabetes mellitus13) or T2DM14) may have increased RLX-2 levels, and that RLX-2 is significantly correlated with the islet β-cell function in female T2DM patients.14) Moreover, recent
findings from the experimental studies suggested that recombinant human RLX-2 ameliorates systemic IR and attenuates left ventricular remodeling in diabetic rats, suggesting a potential protective role of RLX-2 against diabetes and its related CVD complications. In contrast, RLX-3 is primarily expressed in neurons of the nucleus incertus and adjacent cerebral areas, and functions as an important modulator of brain stress and mood systems. 

RLX are also suggested to be involved in CVDs. Indeed, RLX-2 and its receptor relaxin/insulin-like family peptide receptor 1 (RXFP1) have been identified in the heart, indicating a potential regulatory role of RLX-2 in the cardiovascular system. Moreover, the subsequent experimental studies have revealed the protective role of RLX-2 against CVDs via antifibrotic, antihyperpertrophic, anti-inflammatory, as well as vasodilatory actions of the systemic and coronary circulation. Notably, recent pilot clinical trials also suggested a protective role of RLX-2 for ischemic heart disease by indicating that RLX-2 administration was associated with increased myocardial salvage and improved ventricular remodeling. Moreover, the correlations of RLX-2 with islet β-cell function and other glucose metabolism related parameters were also explored. In addition, we further investigated whether serum RLX-2 was associated with the severity of coronary lesions.

Methods

The study has been approved by the Ethical Committee of Beijing Friendship Hospital (No. 2015-P2-015-01).

Patients and groups: This study included patients with unstable angina (UA), confirmed with angiographic and other clinical examinations at Beijing Friendship Hospital. UA is defined as the myocardial ischemia at rest or minimal exertion in the absence of cardiomyocyte necrosis, according to the 2015 ESC guidelines. The enrollment of the patients was performed from January 2015 to September 2015. Patients were excluded from the study if they fulfilled any one of the following criteria: type 1 DM, pregnant women, pulmonary fibrosis, pulmonary hypertension, arrhythmia including atrial fibrillation, acute or chronic liver disease, renal insufficiency, and those who had recent infections or suffered from chronic inflammatory or autoimmune disorders. All participants were free of acute or prior myocardial infarction, stable angina pectoris, coronary revascularization, chronic and acute heart failure, cardiogenic shock, or cancer. All of the consecutively included participants, who did not reveal any history of T2DM, completed the oral glucose tolerance test (OGTT) and then underwent coronary angiography. According to the results of the OGTT, patients with UA were divided into the normal glucose tolerance group (NGT, Group 2), the prediabetic group (including IGT and IFG, Group 3), and the newly diagnosed T2DM (New-DM, Group 4). Forty cases had the previously diagnosed T2DM patients (P-DM, Group 5) and 20 cases had no angiography-evidenced CVDs and normal glucose tolerance, who were hospitalized for chest pain (Controls, Group 1). In this study, IFG was defined by the American Diabetes Association as fasting plasma glucose (FPG) levels from 5.6 mmol/L to 6.9 mmol/L, and/or IGT was defined as 2-hour glucose values during OGTT of 7.8 mmol/L to 11.0 mmol/L. Clinically, the patients with newly diagnosed T2DM were considered in case of HbA1c ≥ 6.5% or an FPG ≥ 7.0 mmol/L, or a 2-hour post-OgTT or random plasma glucose value ≥ 11.1 mmol/L, according to the World Health Organization (WHO) 1999 criteria.

Clinical and biochemical measurements: The baseline characteristics of the patients were obtained during the admission interview for each patient. We collected a venous blood sample (10 mL) for each fasted patient on the day following coronary angiography. Plasma was separated and stored at -80°C for subsequent RLX measurements. Briefly, the levels of human RLX-2 were determined using enzyme-linked immunosorbent assay (ELISA) testing (Human Relaxin-2 Quantikine ELISA Kit, R&D Systems), in accordance with the manufacturers’ instructions. Serum levels of RLX-3 were measured using the commercially available ELISA Kits (Human Relaxin 3 (RLN-3) Elisa kit, BlueGene Biotech). All measurements were performed according to the manufacturer’s instructions.

Plasma glucose was measured immediately by hexokinase method (Beckman Coulter, Suzhou, China). Fasting insulin, IGF-1 and C-peptide were measured by direct chemiluminescence (Roche Diagnosis, Indianapolis, USA), and glycated hemoglobin was measured by ion-exchange high performance liquid chromatography (HPLC; BIO-RAD, California, USA). Proinsulin was measured by ELISA testing (Siemens, Tarrytown, New York, USA). Triglyceride (TG) was measured by enzymatic methods (Beckman Coulter, Suzhou, China), and high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were measured by the Rate methods (Beckman Coulter). NT-ProBNP was determined using the chemiluminescence enzyme immune assay (CLEIA) testing (LSI Medience Corporation, Japan) using the PATHFAST Cardiac Biomarker Analyzer. The β-cell function, the insulin sensitivity, and IR were calculated by homeostasis model assessment (HOMA2), which was determined from the computer model available at https://www.ocdem.ox.ac.uk. Using this model, HOMA2 was evaluated from fasting glucose and C-peptide.

Echocardiography and angiography were performed for all of the included patients. Transthoracic echocardiographic assessment was performed using a Philips IE 33 ultrasound system with X5-1 transducer. All images and measurements were acquired from the standard views according to the recommendations of the American Society of Echocardiography. Each representative value was obtained from the average of three measurements. CAG was completed by Enova-2000 DSA. Two experienced interventional cardiologists assessed the CAG results and in-
Table I. Baseline Characteristics

|                  | Controls (G1) n = 20 | NGT (G2) n = 40 | Prediabetes (G3) n = 38 | New-DM (G4) n = 35 | Previous-DM (G5) n = 40 |
|------------------|----------------------|-----------------|-------------------------|-------------------|------------------------|
| Age (years)      | 57.7 ± 8.6           | 61.2 ± 7.3      | 61.7 ± 7.6              | 59.4 ± 6.7        | 60.3 ± 6.4             |
| Male gender (%)  | 10 (50.0)            | 27 (65.9)       | 27 (73.0)               | 23 (65.7)         | 25 (62.5)              |
| Smoking (%)      | 7 (35.0)             | 22 (53.6)       | 18 (48.6)               | 15 (42.9)         | 18 (45.0)              |
| Hypertension (%) | 8 (40.0)             | 28 (68.3)       | 28 (75.7)               | 23 (65.7)         | 31 (77.5)*             |
| BMI (kg/m²)      | 23.7 ± 2.3           | 24.7 ± 3.5      | 26.0 ± 3.1*             | 27.2 ± 3.6**      | 27.3 ± 3.1**           |
| SBP (mmHg)       | 128.2 ± 22.2         | 128.3 ± 18.1    | 133.0 ± 18.2            | 130.5 ± 13.3      | 135.0 ± 20.3           |
| DBP (mmHg)       | 78.0 ± 12.7          | 74.7 ± 10.7     | 77.1 ± 9.1              | 78.7 ± 6.9        | 79.6 ± 10.8            |
| HR (bpm)         | 71.9 ± 10.3          | 71.0 ± 14.6     | 70.6 ± 10.6             | 73.8 ± 6.9        | 73.7 ± 9.0             |
| LDL-C (mmol/L)   | 2.09 ± 0.63          | 2.29 ± 0.59     | 2.61 ± 0.77*            | 2.64 ± 0.92*      | 2.35 ± 0.86            |
| HDL-C (mmol/L)   | 1.40 (1.15, 1.67)    | 1.28 (1.02, 1.49)| 1.17 (0.99, 1.33)*      | 1.12 (1.02, 1.24)*| 1.14 (0.98, 1.30)*     |
| TG (mmol/L)      | 0.95 (0.59, 1.26)    | 1.15 (0.91, 1.47)| 1.31 (1.06, 2.01)       | 1.56 (1.22, 2.22) | 1.40 (0.98, 1.70)      |
| Creatinine (μmol/L) | 78.4 ± 12.5         | 82.1 ± 13.9     | 84.7 ± 15.2             | 81.2 ± 14.7       | 82.5 ± 31.2            |
| NT-proBNP (pg/mL)| 139.5 (47.9, 254.2)  | 116.0 (69.8, 233.0) | 137.0 (62.7, 609.0)     | 167.0 (66.1, 623.3)| 189.5 (71.0, 803.5)    |

Antidiabetic medications

| Insulin (%)      | NA                   | NA               | NA                      | NA                 | 5 (12.5)               |
| Oral drugs (%)   | NA                   | NA               | NA                      | NA                 | 23 (57.5)              |
| Combined (%)     | NA                   | NA               | NA                      | NA                 | 10 (25)                |

Controls (group 1, G1); NGT (group 2, G2), Normal Glucose Tolerance; Prediabetes, (group 3, G3); New-DM (group 4, G4), New Diagnosis Type 2 Diabetes Mellitus (type 2 DM); Previous-DM (group 5, G5), Previous Diagnosis Type 2 DM. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; and HR, heart rate. * and # represents the difference was statistically significant, *Compared with G1, *Compared with G2.

Results

Clinical characteristics of patients included in the study groups: Overall, 153 patients (mean age 60.4 ± 7.2 years, 73.2% male) with UA were enrolled, and grouped according to their glucose metabolism status, including the patients with normal serum glucose levels (Group 2, n = 40), patients with prediabetes (Group 3, n = 38), patients with newly diagnosed T2DM (Group 4 or New-DM, n = 35), patients with previously diagnosed T2DM (Group 5 or P-DM, n = 40), and 20 controls (without CAD or glucose metabolic dysfunction; Group 1, n = 20). The clinical characteristics of the included patients are listed in Table I. No significant differences were noticed except for the parameters of hypertension prevalence, body mass index (BMI), LDL-C, and HDL-C. The prevalence of hypertension rate was lower in the control; meanwhile, the levels of mean BMI and LDL-C were higher, and HDL-C was lower in UA patients with glucose metabolism dysfunction (Group 3-5).

Echocardiographic and angiographic characteristics of patients: The echocardiographic and angiographic characteristics of patients are presented in Table II. Results of our research indicated that patients in UA with prediabetes and newly diagnosed T2DM revealed larger left ventricle end diastole diameter (LVEDD) than that of the controls. Moreover, the patients in UA with abnormal glucose metabolism reported larger LVEDD and left ventricle end systole diameter (LVESD) as compared to those in UA with NGT. Correspondingly, the left ventricular ejection fraction in UA with prediabetes and the newly diagnosed T2DM were lower than that of the UA with NGT. Unexpectedly, the Syntax Scores were similar in UA patients with prediabetes and previously diagnosed T2DM, whereas UA patients with newly diagnosed T2DM revealed lower Syntax Scores.

Parameters of glucose metabolism of patients: The parameters of glucose metabolism of patients are presented in Table III. We observed no significant difference regarding these parameters between the patients from the control and the NGT groups, whereas patients with glucose metabolic abnormalities revealed impaired glucose metabolism parameters.

The serum levels of RLX-2 and RLX-3 of patients: The plasma levels of RLX-2 (medians and quartiles) and
RLX-3 are presented in Table III and Figure 1. We found that patients in prediabetes and newly diagnosed T2DM with UA had higher RLX-2 compared to the controls and those in NTG with UA. Surprisingly, the levels of RLX-2 were found to be significantly reduced in the patients with previously diagnosed T2DM with UA, as compared with the controls and those in UA with NTG. As for RLX-3, the patients with newly diagnosed T2DM had lower serum RLX-3, while the patients in NTG with previously diagnosed T2DM had lower serum RLX-3 as compared with the controls.

**Correlation analyses:** The correlations between serum RLX-2, RLX-3, and clinical parameters of patients in UA with metabolic dysfunction are presented in Table IV. We found that serum RLX-2 was positively correlated with serum C-peptide, fasting insulin, and β-cell function (HOMA2%-B calculated from both fasting glucose and C-peptide concentrations) in these patients. Moreover, we found that serum RLX-2 was negatively correlated with the levels of fasting glucose, 2-hour postprandial blood glucose, and HbA1c (HOMA2%-S-calculated from fasting glucose and fasting insulin). Results of regression analyses revealed that serum RLX-2 was also significantly positively related with β-cell function (r = 0.330, P = 0.002, Table IV and Figure 2); however, we did not find a significant correlation between RLX-3 with other clinical or biochemical parameters (Table IV). Importantly, there were no significant correlations between RLX-2 or RLX-3 and Syntax Score.

**Discussion**

In this study, our results suggested that the serum level of RLX-2 was significantly higher in UA patients with prediabetes or newly diagnosed T2DM, compared to those in UA with normal glucose metabolism or controls. Moreover, we found that the serum level of RLX-2 was significantly lower in UA patients with previously diagnosed T2DM. Notably, we found that increased RLX-2 was correlated with stimulated β-cell function in UA pa-
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Patients with deregulated glucose metabolism; however, RLX-2 was not related to the severity of coronary lesions as indicated by Syntax Scores, and correlations between serum RLX-3 and other clinical parameters were not significant. These results suggested that increased RLX-2 may be an early serum marker for dysfunction of glucose metabolism in patients with UA. Our results, to the best of our knowledge, elucidated the significance of serum RLX-2 in UA patients with various dysfunction of glucose metabolism. These results provide further evidence that changes in RLX-2 may be involved in the pathogenesis and progression of glucose metabolism dysfunction.

Previous studies have suggested that changes in RLX-2 levels may be an important pathophysiological process underlying the development of DM. Indeed, some studies have suggested that patients with T2DM had increased serum RLX-2; however, whether patients with prediabetes or those with previously diagnosed T2DM had similar changes of serum RLX-2 as those with newly diagnosed T2DM is yet to be evaluated. Our observations revealed that RLX-2 was significantly increased in UA patients with prediabetes and newly diagnosed T2DM; however, it significantly reduced in UA patients with previously diagnosed T2DM who mostly received antidiabetic treatment. These results suggested that RLX-2 was sensitive for the detection of early glucose metabolism dysfunction; however, the antidiabetic treatment may inhibit the levels of increased RLX-2 as those with newly diagnosed T2DM is yet to be evaluated. Our observations revealed that RLX-2 was significantly increased in UA patients with prediabetes and newly diagnosed T2DM; however, it significantly reduced in UA patients with previously diagnosed T2DM who mostly received antidiabetic treatment. These results suggested that RLX-2 was sensitive for the detection of early glucose metabolism dysfunction; however, the antidiabetic treatment may inhibit the levels of increased RLX-2. The underlying mechanism for the regulation of the RLX-2 during the pathogenesis of glucose metabolism dysfunction deserves further investigation. A previous study by Zhang, et al. revealed that the plasma level of RLX-2 in the newly diagnosed T2DM was significantly lower than the controls. The underlying mechanisms regarding the difference between results of the present study and those by Zhang, et al. were not determined; however, the patient’s characteristics (ours included UA patients only), mean ages [(60.4 ± 7.2) years to 50 (42-61) years], and proportions of males (73.2% to 51.5%) were different between our study and Zhang’s.

Table IV. Correlation Coefficients between RLX-2 Or RLX-3 and the Clinical Parameters in Patients with Dysglycemia and UA

| Variable          | Relxin-2 Correlation coefficient (r) | P     | Relxin-3 Correlation coefficient (r) | P     |
|-------------------|-------------------------------------|-------|-------------------------------------|-------|
| Age               | 0.014                               | 0.888 | -0.089                              | 0.358 |
| Sex               | 0.083                               | 0.392 | -0.013                              | 0.892 |
| BMI               | -0.028                              | 0.775 | 0.072                               | 0.459 |
| SBP               | 0.084                               | 0.385 | 0.053                               | 0.586 |
| DBP               | 0.017                               | 0.861 | -0.117                              | 0.227 |
| HR                | -0.094                              | 0.331 | 0.049                               | 0.661 |
| LDL-C             | -0.016                              | 0.873 | -0.090                              | 0.357 |
| HDL-C             | -0.083                              | 0.397 | -0.002                              | 0.985 |
| TG                | 0.161                               | 0.100 | -0.072                              | 0.463 |
| Creatinine        | 0.135                               | 0.162 | -0.008                              | 0.938 |
| hs-CRP            | -0.040                              | 0.682 | -0.126                              | 0.198 |
| FBG               | -0.302                              | 0.001 | 0.145                               | 0.132 |
| 2h-PBG            | -0.281                              | 0.003 | -0.036                              | 0.711 |
| HbA1c             | -0.379                              | 0.000 | 0.139                               | 0.155 |
| Proinsulin        | -0.042                              | 0.693 | 0.124                               | 0.246 |
| Fasting insulin   | 0.271                               | 0.009 | 0.171                               | 0.106 |
| IGF-I             | 0.107                               | 0.316 | 0.135                               | 0.203 |
| C peptide         | 0.263                               | 0.030 | -0.088                              | 0.405 |
| %B                | 0.449                               | 0.000 | -0.196                              | 0.063 |
| %S                | -0.214                              | 0.054 | 0.070                               | 0.510 |
| HOMA2-IR          | 0.211                               | 0.057 | -0.068                              | 0.520 |
| NTpro-BNP         | 0.044                               | 0.701 | -0.136                              | 0.237 |
| LVEDD             | 0.109                               | 0.279 | 0.078                               | 0.421 |
| LVESD             | 0.106                               | 0.279 | 0.069                               | 0.483 |
| E peak            | 0.014                               | 0.887 | 0.086                               | 0.383 |
| A peak            | -0.164                              | 0.092 | 0.028                               | 0.773 |
| LVEF              | 0.113                               | 0.259 | 0.046                               | 0.640 |
| SYNTAX Score      | -0.005                              | 0.958 | 0.035                               | 0.716 |

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; FBG, fasting blood glucose; 2h-PBG, 2-hour postprandial blood glucose; IGF-1, insulin-like growth factor I; %B, β-cell function; %S, insulin sensitivity; HOMA2-IR, insulin resistance index; LVEDD, left ventricle end diastolic diameter; LVESD, left ventricle end systole diameter; and LVEF, left ventricle ejection fraction.
Figure 2. Scatter plot showing that relaxin-2 is positively related with β-cell function in patients with dysglycemia and unstable angina ($r = 0.449, P = 0.000$, by Spearman correlations analysis).

The pathophysiological significance of the upregulated RLX-2 in patients with prediabetes and newly diagnosed T2DM patients, from our point of view, may be related to a compensation response to the glucose metabolism deregulation. Our results support this since we found that increased RLX-2 was correlated with an increased β-cell function in UA patients with glucose metabolism dysfunction; however, with the extension of the T2DM duration, this compensatory function may gradually decline as the RLX-2 levels declined with prolonged diabetes. Indeed, high concentrations of glucose have been reported to be able to stimulate the expression of endogenous RLX-2, which is important for angiogenesis and endothelial repairing. Moreover, RLX-2 has been demonstrated to modify the β-cell response to glucose and increase peripheral insulin sensitivity. Similarly, studies in skeletal muscle also confirmed that insulin-stimulated whole-body glucose disappearance and percent suppression of hepatic glucose production could be corrected by chronic RLX-2 treatment. In this study, RLX-2 intervention improved the endothelial-dependent vascular reactivity and induced a two-fold proliferation in skeletal muscle capillarity (angiogenesis). Collectively, these results suggested that for patients in UA with prediabetes and newly diagnosed T2DM, increased serum RLX-2 may be a compensatory mechanism via improving the islet β-cell function and optimization of peripheral energy metabolism.

Although previous studies have indicated that changes in the serum RLX-2 are involved in the pathogenesis of CVDs, our study did not support that the serum level of RLX-2 were different among those with or without UA in the normal blood glucose patients. Moreover, the serum levels of RLX-2 were not associated with the severity of the coronary lesions in UA patients with glucose metabolism dysfunction. Although previous studies have proposed the potential cardioprotective role of RLX-2 as evidenced by attenuation of cardiac remodeling and improving endothelial function, the association between RLX-2 and severity of coronary lesions were not intensively studied. Our study is the first to evaluate the potential association between serum RLX-2 and coronary arterial lesion severity in UA patients with glucose metabolism dysfunction. Further studies are warranted to confirm the role of RLX-2 in CAD.

Regarding RLX-3, we did not report a significant association between RLX-3 levels and either clinical parameter in UA patients with glucose metabolism dysfunction, which is generally consistent with the previous findings. This is not surprising as the RLX-3 distribution and its physiological function is mainly limited to the neurological tissues.

**Limitations:** Our study has limitations, which should be noticed when interpreting the results. First, we included limited number of patients and the association between RLX-2 and certain clinical parameters may be insignificant due to the limited statistical power. Therefore, our results need to be confirmed in studies with larger sample size and adequate statistical power. Simultaneously, our study was cross-sectional, which only provides the evidence of association but not causation. Whether RLX-2
acts as a protective mechanism for UA patients and glucose metabolism dysfunction needs to be confirmed in RCTs. Eventually, the mechanisms underlying the potential association between RLX-2 and improved β-cell function needs to be clarified in the future.

Conclusions

Serum RLX-2 is a potential marker for UA patients with early glucose metabolism abnormality, and increased RLX-2 level was correlated with preserved islet β-cell function. These results provide further evidence that changes in RLX-2 may be involved in the pathogenesis and progression of glucose metabolism dysfunction.

Disclosures

Conflicts of interest: None.

References

1. Samuel CS, Hewitson TD, Zhang Y, et al. Relaxin ameliorates fibrosis in experimental diabetic cardiomyopathy. Endocrinology 2008; 149: 3286-93.
2. Perreault L, Temprosa M, Mather KJ, et al. Regression from prediabetes to normal glucose regulation is associated with reduction in cardiovascular risk: results from the Diabetes Prevention Program outcomes study. Diabetes Care 2014; 37: 2622-31.
3. Ferramini E, Gastaldelli A, Iozzo P. Pathophysiology of prediabetes. Med Clin North Am 2011; 95: 327-39.
4. Rhodes CJ. Type 2 diabetes—a matter of beta-cell life and death? Science 2005; 307: 380-4.
5. Cagliyan CE, Kirim S, Turkmen S, et al. Cardiac diastolic function is impaired at rest and worsens with exercise in otherwise healthy individuals with insulin resistance. Int Heart J 2015; 56: 345-8.
6. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 1998; 21: 2191-2.
7. Efird JT, Choi YM, Davies SW, et al. Potential for improved glycemic control with dietary momordica charantia in patients with insulin resistance and pre-diabetes. Int J Environ Res Public Health 2014; 11: 2328-45.
8. Milman S, Crandall JP. Mechanisms of vascular complications in prediabetes. Med Clin North Am 2011; 95: 309-25.
9. Kanat M, DeFronzo RA, Abdul-Ghani MA. Treatment of prediabetes. World J Diabetes 2015; 6: 1207-22.
10. Ikeda N, Hara H, Hiroi Y. Ability of 1,5-Anhydro-d-glucitol values to predict coronary artery disease in a non-diabetic population. Int Heart J 2015; 56: 587-91.
11. Shah AS, Gao Z, Urbina EM, et al. Pre-diabetes: The effects on arterial thickness and stiffness in obese youth. J Clin Endocrinol Metab 2014; 99: 1037-43.
12. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. J Am Coll Cardiol 2010; 55: 1310-7.
13. Whittaker PG, Edwards JR, Randolph C, et al. Abnormal relaxin secretion during pregnancy in women with type 1 diabetes. Exp Biol Med (Maywood) 2003; 228: 33-40.
14. Schöndorf T, Lübken G, Hoopmann M, et al. Relaxin expression correlates significantly with serum fibrinogen variation in response to antidiabetic treatment in women with type 2 diabetes mellitus. Gynecol Endocrinol 2007; 23: 356-60.
15. Shabanpoor F, Separovic F, Wade JD. The human insulin superfamily of polypeptide hormones. Vitam Horm 2009; 80: 1-31.
16. Smith CM, Walker AW, Hosken IT, et al. Relaxin-3/RXFP3 networks: an emerging target for the treatment of depression and other neuropsychiatric diseases? Front Pharmacol 2014; 5: 46.
17. Samuel CS, Hewitson TD. Relaxin in cardiovascular and renal disease. Kidney Int 2006; 69: 1498-502.
18. Teichman SL, Unemori E, Teerlink JR, et al. Relaxin: review of biology and potential role in treating heart failure. Curr Heart Fail Rep 2010; 7: 75-82.
19. Perna AM, Masini E, Nistri S, et al. Human recombinant relaxin reduces heart injury and improves ventricular performance in a swine model of acute myocardial infarction. Ann N Y Acad Sci 2005; 1041: 431-3.
20. Valle Raleigh J, Mauro AG, Devarakonda T, et al. Reperfusion therapy with recombinant human relaxin-2 (Serelaxin) attenuates myocardial infarct size and NLRP3 inflammasome following ischemia/reperfusion injury via eNOS-dependent mechanism. Cardiovasc Res 2017; 10: pii: cvw246.
21. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.
22. American Diabetes Association. Standards of medical care-2013. Diabetes Care 2013; 36: S11-66.
23. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004; 27: 1487-95.
24. Zhang X, Zhu M, Zhao M, et al. The plasma levels of relaxin-2 and relaxin-3 in patients with diabetes. Clin Biochem 2013; 46: 1713-6.
25. Wang P, Li HW, Wang YP, et al. Effects of recombinant human relaxin upon proliferation of cardiac fibroblast and synthesis of collagen under high glucose condition. J Endocrinol Invest 2009; 32: 242-7.
26. Szepietowska B, Gorska M, Szalachowska M. Plasma relaxin concentration is related to beta-cell function and insulin sensitivity in women with type 2 diabetes mellitus. Diabetes Res Clin Pract 2008; 79: e1-3.
27. Bonner JS, Lantier L, Hocking KM, et al. Relaxin treatment reverses insulin resistance in mice fed a high-fat diet. Diabetes 2013; 62: 3251-60.
28. Heringlake M, Kox T, Poeling I, et al. The effects of physical exercise on plasma levels of relaxin, NTproANP, and NTproBNP in patients with ischemic heart disease. Eur J Med Res 2009: 14: 106-12.
29. Bani D, Bigazzi M. Relaxin as a Cardiovascular Drug: A Promise Kept. Curr Drug Saf 2011; 6: 324-8.
30. Zhang J, Qi YF, Geng B, et al. Effect of relaxin on myocardial ischemia injury induced by isoproterenol. Peptides 2005; 26: 1632-9.
31. Conrad KP. Unveiling the vasodilatory actions and mechanisms of relaxin. Hypertension 2010; 56: 2-9.