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The plasma levels of relaxin-2 and relaxin-3 in patients with diabetes

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ABSTRACT

Objectives: Relaxin-2 has been found to alleviate fibrosis in experimental diabetic cardiomyopathy. In addition, the levels of serum relaxin-3 were increased and correlated with all the component traits of metabolic syndrome. We investigated the levels of plasma relaxin-2 or relaxin-3 and their relationship to component traits in patients with diabetes.

Design and methods: We studied 33 newly diagnosed type 2 diabetes patients and 38 age-matched healthy subjects. Blood samples were taken at study entry, and relaxin-3, relaxin-2, fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, serum insulin and hemoglobin A_{1c} (HbA_{1c}) levels were measured.

Results: Relaxin-2 levels were significantly lower in patients with diabetes than in controls: the median plasma relaxin-2 concentration was 34.68 pg/mL (range, <29.00–50.81 pg/mL) in patients with diabetes and 45.80 pg/mL (range, <37.42–54.46 pg/mL) in controls ($p = 0.0150$). However, no differences in relaxin-3 levels were observed between the diabetes group and controls ($p = 0.6550$). The plasma levels of relaxin-2 or relaxin-3 were not correlated with systolic blood pressure (BP), diastolic BP, total cholesterol, LDL-C, HDL-C, triglyceride, fasting blood glucose, fasting insulin and HbA_{1c} in patients with diabetes. Additionally, there was no correlation between the plasma concentrations of relaxin-2 and relaxin-3 in patients with diabetes ($r_s = 0.225$; $p = 0.208$).

Conclusions: We conclude that the plasma levels of relaxin-2 in diabetes patients were lower than in controls, however, there are no difference in plasma relaxin-3 concentrations between controls and patients with diabetes. Relaxin-2 or relaxin-3 levels are not related to component traits in patients with diabetes.

Introduction

Diabetes mellitus is a highly prevalent disease. More than 80% of diabetes patients are due to type 2 diabetes mellitus, which typically affects older, overweight, and sedentary individuals and those who have a complex pathophysiology involving resistance to the action of insulin in the body and inadequate insulin secretion from the pancreas [1]. Diabetes promises to become an even larger public health issue with significant social and economic burden with clinical practice and public health policy implications [2].

Relaxin-3 and relaxin-2 are two members of the relaxin family of peptides [3]. Recent researches reported that relaxin-2 ameliorated fibrosis in experimental diabetic cardiomyopathy and inhibited proliferation of cardiac fibroblasts under the high glucose condition [4,5]. Clinical study has been undertaken to examine that endogenous relaxin-2 was positively related with insulin sensitivity and negatively to beta-cell function in patients with diabetes [6]. However, it is not clear that the levels of endogenous relaxin-2 in patients with diabetes compared with controls. Relaxin-3 is recognized as the 'ancestral' member of the relaxin peptide family and appears to be capable of modulating essential functions, such as appetite regulation, increasing food intake and body weight [7–9]. Recent studies provide evidence that relaxin-3 levels were significantly higher in the metabolic syndrome patients than controls and related with all the component traits of metabolic syndrome [10]. It is not clarified that the levels of endogenous relaxin-3 in patients with diabetes and relation with the component traits of diabetes.

However, the exact changes of endogenous relaxin-2 or relaxin-3 in patients with diabetes remain unknown. In addition, it is undetermined whether endogenous relaxin-2 or relaxin-3 plays a major role as a circulating hormone in patients with diabetes. In this study, we

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, hemoglobin A_{1c}; HOMA2, homeostasis model assessment.

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investigated plasma relaxin-3 and relaxin-2 levels and their relation to component traits in patients with diabetes.

Methods

Patients

Newly diagnosed type 2 diabetes patients ($n = 33$) were studied. For the type 2 diabetes group, inclusion criteria were: 1) to be diagnosed with type 2 diabetes according to the 2006 WHO criteria [11]; and 2) to have no diabetic complication. Furthermore, newly diagnosed type 2 diabetes patients had to never have received any diabetes therapy, including medication and insulin. Pregnant women and patients with ketoacidosis, recent infections, severe liver or renal disease, malignant tumors, cardiovascular disease, sodium disorder or suffered from chronic inflammatory or autoimmune disorders were excluded. Healthy subjects ($n = 38$) with no clinical problems who were undergoing a health checkup in hospital served as controls. The study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Harbin Medical University and complied with the Declaration of Helsinki, and informed consent was obtained from subjects before the initiation of the study.

Sample collection

Blood was drawn into tubes that contained Na2-EDTA (1 mg/mL) and 500 kIU/mL aprotinin (Sigma, St. Louis, MO, USA). Plasma was obtained by centrifugation at 3000 rpm for 10 min at 4 °C and stored at −80 °C until the assay.

Radioimmunoassay for relaxin-3 and relaxin-2

Relaxin-3 and relaxin-2 levels were measured by radioimmunoassay (RIA). In brief, samples were extracted through a Sep-Pak C18 cartridge and assayed using an RIA kit (Phoenix Pharmaceuticals, Belmont, CA, USA).

Measurement of other parameters

The levels of fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, serum insulin and hemoglobin A_{1c} (HbA_{1c}) were assessed by routine biochemical analysis.

Insulin sensitivity was calculated by homeostasis model assessment (HOMA2). HOMA2 was calculated from computer model available on the Internet web at www.ocdem.ox.ac.uk [12]. Using this model, HOMA2 was evaluated from fasting glucose and insulin for both beta-cell function and insulin resistance. HOMA2%B calculated from fasting insulin and glucose concentrations, and HOMA2%S calculated from fasting insulin.

Statistical analysis

Data were reported as the means (standard deviations) or medians (interquartile range) for continuous variables and as numbers (percentages) for categorical variables. The differences between two groups were analyzed using Student's t test or the nonparametric Wilcoxon test for continuous variables and the χ^2 test for categorical variables. Associations between the plasma relaxin-2 or relaxin-3 levels and other variables were evaluated using the Spearman correlation test. A p-value of <0.05 was considered statistically significant.

Table 1
Clinical and biochemical characteristics of the study groups.

Variables	Controls ($n = 38$)	Diabetes ($n = 33$)
Age (years)	46 (42.75–55.25)	50 (42–61)
Gender (male/female, n)	22/16	17/16
Systolic BP (mmHg)	125.50 ± 14.62	134.39 ± 16.29*
Diastolic BP (mmHg)	86 (80–90)	85(80–90)
Total cholesterol	4.86 (4.15–5.74)	5.20 (4.52–5.71)
Triglycerides	1.32 (1.02–1.94)	2.00 (1.20–3.04)*
HDL-C	1.39 ± 0.19	1.19 ± 0.29*
LDL-C	3.30 ± 0.78	2.84 ± 0.84*
Fasting blood glucose	5.07 (4.87–5.45)	8.18 (6.22–13.74)**
Fasting insulin	7.15 (5.70–10.20)	11.70 (6.10–23.00)*
HbA_{1c}	5.35 (5.10–5.50)	8.40 (7.30–10.40)**

BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, hemoglobin A_{1c}; *$p < 0.05$ vs. controls; **$p < 0.01$ vs. controls.

Results

Plasma relaxin-3 and relaxin-2 in patients with diabetes

The baseline clinical and demographic characteristics of the study population are shown in Table 1. No significant differences in age and gender were observed between the control and diabetes groups. Patients with diabetes showed significantly higher systolic BP, triglycerides, fasting blood glucose, fasting insulin, and HbA1c with a significantly lower level of HDL-C and LDL-C than the control group. Notably, the plasma relaxin-2 levels were significantly lower in patients with diabetes than in controls: the median plasma relaxin-2 concentration was 34.68 pg/mL (range, <29.00–50.81 pg/mL) in patients with diabetes and 45.80 pg/mL (range, <37.42–54.46 pg/mL) in controls ($p = 0.0150$) (Fig. 1). The median plasma relaxin-3 was 69.72 pg/mL (range, <65.53–74.18 pg/mL) in patients with diabetes and 69.37 pg/mL (range, <63.90–72.97 pg/mL) in controls, and there were no statistically significant differences between the diabetes group and controls ($p = 0.655$) (Fig. 2). Additionally, there was no correlation between the plasma concentrations of relaxin-3 and relaxin-2 in patients with diabetes ($r_s = 0.225$; $p = 0.208$) (Fig. 3).

The relationship between plasma relaxin-3 or relaxin-2 levels and component traits in patients with diabetes

The plasma levels of relaxin-2 or relaxin-3 showed no statistically significant associations with systolic BP, diastolic BP, total cholesterol, LDL-C, HDL-C, triglycerides, fasting blood glucose, fasting insulin, HbA_{1c}, HOMA2%B and HOMA2%S (Table 2).

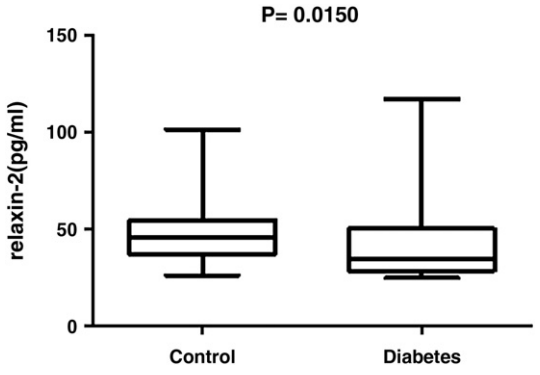

Fig. 1. Relaxin-2 levels in controls and patients with diabetes.