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Clinical Trials Study

Postprandial glucagon-like peptide 1 secretion is associated with urinary albumin excretion in newly diagnosed type 2 diabetes patients

Song LL *et al*. Postprandial GLP-1 and microalbuminuria

Abstract

BACKGROUND

Microalbuminuria is an early and informative marker of diabetic nephropathy. Our study found that microalbuminuria developed in patients with newly diagnosed type 2 diabetes mellitus (T2DM).

AIM

To investigate the association between glucagon-like peptide 1 (GLP-1) and microalbuminuria in newly diagnosed T2DM patients.

METHODS

In total, 760 patients were recruited for this cross-sectional study. The GLP-1 levels during a standard meal test and urinary albumin-creatinine ratio (UACR) were determined.

RESULTS

Patients with microalbuminuria exhibited lower GLP-1 levels at 30 min and 120 min during a standard meal test than patients with normal albuminuria (30 min GLP-1, 16.7 ± 13.3 pmol *vs* 19.9 ± 15.6 pmol, $P = 0.007$; 120 min GLP-1, 16.0 ± 14.1 pmol *vs* 18.4 ± 13.8 pmol, $P = 0.037$). The corresponding area under the curve for active GLP-1 (AUCGLP-1) was also lower in microalbuminuria patients (2257, 1585 to 3506 *vs* 2896, 1763 to 4726. pmol × min, $P = 0.003$). Postprandial GLP-1 levels at 30 min and 120 min and AUCGLP-1 were negatively correlated with the UACR ($r = 0.159$, $r = 0.132$, $r = 0.206$, respectively, $P < 0.001$). The prevalence of microalbuminuria in patients with newly diagnosed T2DM was 21.7%, which decreased with increasing quartiles of AUCGLP-1 levels (27.4%, 25.3%, 18.9% and 15.8%). After logistic regression analysis adjusted for sex, age, hemoglobin A1c, body mass index, systolic blood pressure, estimated glomerular filtration rate, homeostasis model assessment of insulin resistance, $AUC_{glucose}$ and $AUC_{glucagon}$, patients in quartile 4 of the AUCGLP-1 presented a lower risk of

microalbuminuria compared with the patients in quartile 1 (odds ratio = 0.547, 95% confidence interval: 0.325-0.920, P = 0.01). A consistent association was also found between 30 min GLP-1 or 120 min GLP-1 and microalbuminuria.

CONCLUSION

Postprandial GLP-1 levels were independently associated with microalbuminuria in newly diagnosed Chinese T2DM patients.

Key Words: Microalbuminuria; Glucagon-like peptide 1; Type 2 diabetes; Nephropathy

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Core Tip: The association between the microalbuminuria and glucagon-like peptide 1 (GLP-1) response after a standard meal load in newly diagnosed Chinese type 2 diabetes mellitus patients was identified. Patients with microalbuminuria showed lower postprandial GLP-1 levels than those without microalbuminuria. The prevalence of microalbuminuria decreased with increasing quartiles of 30 min and 120 min and area under the curve for active GLP-1 levels after a standard meal. The highlights of our study are that the patients were newly diagnosed, which excluded the influence of glucose-lowering therapies. Furthermore, we assessed the fasting and postprandial GLP-1 levels in response to a standard meal, not oral glucose. Third, the GLP-1 determined in our study was active GLP-1, not total GLP-1.

INTRODUCTION

Microalbuminuria, defined as a urine albumin-creatinine ratio (UACR) of 30 to 300 mg/g, is a highly predictive marker of structural damage in the kidneys in the early stages of diabetic nephropathy when the glomerular filtration rate (GFR) is preserved

(higher than 60 mL/min)[1]. In fact, microalbuminuria appears as early as the early stage of diabetes and even prediabetes. An increased prevalence of microalbuminuria has been observed in patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Compared with that in subjects with normal glucose tolerance, urinary albumin excretion is approximately 70% higher in obese subjects with IFG or IGT[2]. A German study reported that the prevalence of microalbuminuria in individuals with isolated IFG, isolated IGT, IFG + IGT and unknown type 2 diabetes mellitus (T2DM) was 5.3%, 9.7%, 5.8% and 13.2%, respectively[3]. The presence of microalbuminuria is associated with atherosclerotic vascular disease, cardiovascular events, ischemic stroke and premature mortality in both individuals with or without diabetes[4-7].

Multiple mechanisms are involved in the increase in glomerular basement membrane permeability, resulting in increased urinary albumin excretion[8,9]. It has been reported that endocrine hormones also participate in the pathogenesis of microalbuminuria[10-13]. The development of T2DM is accompanied by disordered secretion of endocrine hormones, such as insulin, incretins, glucagon, and leptin. Glucagon-like peptide 1 (GLP-1) has been reported to be an important hormone that regulates nutrition metabolism. Impairment in GLP-1 secretion is associated with abnormally elevated blood glucose levels and increased body weights. Decreased GLP-1 secretion not only accounts for diabetes development but also may take part in the development and progression of related microvascular complications.

However, there is a lack of evidence on the associations of active GLP-1 levels and GLP-1 response to a meal with microalbuminuria in T2DM patients. Newly diagnosed T2DM patients are good subjects for risk factor studies of microalbuminuria because the influence of glucose-lowering therapy is avoided and the impact of disease duration is minimized. In this cross-sectional study, we investigated the association of fasting and postprandial plasma GLP-1 levels with microalbuminuria in patients newly diagnosed with T2DM.

MATERIALS AND METHODS

Study design and participants

For this multicenter study, patients were recruited from 11 clinical centers. All patients had been diagnosed with T2DM within the past 12 mo. The major inclusion criteria included: Met World Health Organization 1999 T2DM diagnostic criteria; aged between 18 and 75 years; and were not treated with antidiabetic medicine or received treatment for less than 30 d and stopped three months before entering this study. The detailed criteria can be found in a previously published article[13]. The study flowchart is displayed in Supplementary Figure 1.

Ethical principles

This study was reviewed and approved by China-Japan Friendship Hospital Institutional Review Board (Approval No. 2008-23). All patients provided informed consent prior to study enrollment and the trial was implemented in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. This trial registration was registered at ChiCTR (Registration No. ChiCTR-TRC-08000231).

Clinical data collection

The general clinical measurements included body weight, height, body mass index (BMI), waist circumference, and systolic/diastolic blood pressure (SBP/DBP). The glucose metabolism variables included hemoglobin A1c (HbA1c), fasting blood glucose and postprandial glucose in a standard meal test. The lipid metabolism variables included low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). The indexes of insulin sensitivity and insulin secretion were calculated with the following equations: Homeostasis model assessment of insulin resistance (HOMA-IR) = FINS (μIU/mL) × FBG (mmol/L)/22.5; HOMA-B = 20 × FINS (μIU/mL)/[FBG (mmol/L)-3.5]; UACR = urinary albumin (mg/L)/urinary creatinine (g/L).

Evaluation of plasma hormones related to glucose metabolism during the standard meal tolerance test

Levels of glucose, insulin, glucagon and GLP-1 were measured during a standard test at 0 min, 30 min, 120 min and 180 min. The area under the curve (AUC) during a standard meal test was calculated with the following equations: $AUC_{glucose}$ = ($glucose_{0\ min}$ + $glucose_{30\ min}$) × 30/2 + ($glucose_{30\ min}$ + $glucose_{120\ min}$) × 90/2 + ($glucose_{120\ min}$ + $glucose_{180\ min}$) × 60/2; $AUC_{glucagon}$ = ($glucagon_{0\ min}$ + $glucagon_{30\ min}$) × 30/2 + ($glucagon_{30\ min}$ + $glucagon_{120\ min}$) × 90/2 + ($glucagon_{120\ min}$ + $glucagon_{180\ min}$) × 60/2; $AUC_{insulin}$ = ($insulin_{0\ min}$ + $insulin_{30\ min}$) × 30/2 + ($insulin_{30\ min}$ + $insulin_{120\ min}$) × 90/2 + ($insulin_{120\ min}$ + $insulin_{180\ min}$) × 60/2; AUC for active GLP-1 (AUCGLP-1)= ($GLP\text{-}1_{0\ min}$ + $GLP\text{-}1_{30\ min}$) × 30/2 + ($GLP\text{-}1_{30\ min}$ + $GLP\text{-}1_{120\ min}$) × 90/2 + ($GLP\text{-}1_{120\ min}$ + $GLP\text{-}1_{180\ min}$) × 60/2.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 software (SPSS Inc., Chicago, IL). Normally distributed variables are expressed as the mean and standard deviation, and the 2-tailed independent-sample *t* test was used to compare the parameters between patients with microalbuminuria and normal albuminuria. The Kruskal-Wallis test and the chi-squared test were used to compare variables between the two groups. Pearson's correlation analysis was performed to identify the correlation between hormone levels and UACR. Then, multivariable linear regression analyses were used to detect the mean differences [B; 95% confidence interval (CI)] in LnUACR between patients with different quartiles of postprandial plasma GLP-1 levels, with the first quartile (Q1) set as the reference, to display the degree of influence of post plasma GLP-1 secretion on UACR. We performed multivariate logistic regression analyses to analyze the impact of postprandial GLP-1 levels on the risk of microalbuminuria, shown as the odds ratios [ORs (95%CIs)] for microalbuminuria in different postprandial GLP-1 levels. Confounding variables were adjusted in different models. *P*-values < 0.05 indicated statistically significant differences.

RESULTS

Baseline characteristics of participants categorized by UACR

There were 595 participants with a UACR of less than 30 mg/g (78.3%) and 165 with a UACR of 30 mg/g or higher (21.7%). There were no significant differences in age, sex, BMI, waist circumference, HbA1c, TG, HDL-C, LDL-c, estimated GFR (eGFR) or HOMA-β between participants with normal albuminuria and microalbuminuria. SBP and DBP were higher in the microalbuminuria group than in the normal albuminuria group. The calculated HOMA-IR was also higher in the microalbuminuria group (Table 1).

Glucose and hormone levels during the standard meal test

Glucose and hormone responses are shown in Figure 1 and Supplementary Table 1. Fasting and 180 min glucose levels were slightly increased in the microalbuminuria group compared with the normal albuminuria group (8.6 ± 1.4 mmol/L *vs* 8.3 ± 1.5 mmol/L, $P = 0.004$; 11.7 ± 2.9 mmol/L *vs* 11.1 ± 3.1 mmol/L, $P = 0.026$). Fasting insulin, GLP-1 and glucagon were not different between the microalbuminuria group and the normal albuminuria group. For postprandial insulin, the 120 min and 180 min insulin levels were higher in the microalbuminuria group than in the normal albuminuria group (38.0 ± 20.2 *vs* 33.6 ± 17.9, $P = 0.016$; 31.5 ± 17.2 μIU/mL *vs* 28.2 ± 16.5 μIU/mL, $P = 0.027$). For postprandial GLP-1, the 30 min and 120 min GLP-1 levels were lower in the microalbuminuria group than in the normal albuminuria group (16.7 ± 13.3 pmol *vs* 19.9 ± 15.6 pmol, $P = 0.007$; 16.0 ± 14.1 *vs* 18.4 ± 13.8, $P = 0.037$). Glucagon levels showed no significant difference at any time point during a standard meal test between the two groups. The $AUC_{glucose}$ was slightly higher in the microalbuminuria group than in the normal albuminuria group (2110, 1852 to 2405 *vs* 2027, 1767 to 2345 mmol/L × min, $P = 0.036$), while the AUCGLP-1 was lower in the microalbuminuria group (2257, 1585 to 3506 *vs* 2896, 1763 to 4726 pmol × min, $P = 0.003$).

Pearson's correlation of postprandial GLP-1 levels with UACR

Figure 2 shows the correlations between postprandial GLP-1 levels and UACR, as analyzed by Pearson's correlation test. Ln30 min GLP-1, Ln120 min GLP-1 and the corresponding LnAUCGLP-1 were negatively correlated with LnUACR: Ln30 min GLP-1 ($r = -0.132$, $P < 0.001$), Ln120 min GLP-1 ($r = -0.159$, $P < 0.001$) and LnAUCGLP-1 ($r = -0.206$, $P < 0.001$). There was no correlation between postprandial insulin or glucagon levels and UACR.

The influence of postprandial GLP-1 Levels on UACR in all newly diagnosed T2DM patients

The UACR of the patients in Q4 of postprandial GLP-1 levels was significantly higher than the UACR of the patients in Q1. Since other clinical risk factors were adjusted, the adjusted mean change in the LnUACR of the patients in Q4 *vs* Q1 of 30 min plasma GLP-1 was -0.708 (95%CI: -1.017 to -0.399). The adjusted mean change in the LnUACR of the patients in Q4 *vs* Q1 of 120 min plasma GLP-1 was -0.431 (95%CI: -0.744 to -0.119), and the corresponding mean change in the LnUACR of the patients in Q4 *vs* Q1 of AUCGLP-1 was -0.860 (95%CI: -1.169 to -0.552) (Table 2).

Association of postprandial GLP-1 with microalbuminuria

As shown in Table 3, the prevalence of microalbuminuria in these newly diagnosed T2DM patients was 21.7%, and the prevalence was 27.4%, 25.3%, 18.9% and 15.8% in Q1, Q2, Q3 and Q4 of AUCGLP-1, respectively ($P < 0.05$). Compared with the patients in Q1 of AUCGLP-1, those in Q4 presented a lower risk of microalbuminuria (OR = 0.498, 95%CI: 0.301-0.823, $P < 0.01$). In logistic regression analysis adjusted for sex, age, HbA1c, BMI, SBP, eGFR, HOMA-IR, $AUC_{glucose}$ and $AUC_{glucagon}$, the OR for microalbuminuria of patients in Q4 *vs* those in Q1 of AUCGLP-1 was 0.547 (95%CI: 325-0.920, $P = 0.01$). A consistent association was also found between 30 min GLP-1 or 120 min GLP-1 and microalbuminuria (Table 3).

DISCUSSION

In this study, we identified an association between microalbuminuria and GLP-1 response after a standard meal load in newly diagnosed Chinese T2DM patients. Increased GLP-1 levels at 30 min and 120 min and AUCGLP-1 levels in a standard meal test are correlated with decreased UACR. The prevalence of microalbuminuria in patients with newly diagnosed T2DM was 21.7%, which showed a decreasing trend with increasing quartiles of the levels of GLP-1 at 30 min and 120 min and AUCGLP-1 Levels. Logistic regression analysis revealed that after adjustment for other confounders, patients in Q4 of postprandial GLP-1 levels exhibited a decreased risk of microalbuminuria compared with those in Q1 by up to approximately 50%. The adjusted microalbuminuria risk for patients from Q4 of 30 min GLP-1 levels was 0.534-fold (95%CI: 0.315-0.905). This risk for patients from Q4 of 120 min GLP-1 levels was 0.592-fold (95%CI: 0.355-0.988), and this risk for patients from Q4 of AUCGLP-1 levels was 0.547-fold (95%CI: 0.325-0.920). In summary, postprandial GLP-1 levels were associated with a decreased risk of microalbuminuria in T2DM patients independent of metabolic indexes, including glucose metabolic status and blood pressure levels. The highlights of our study are that the patients were newly diagnosed, which excluded the influence of glucose-lowering therapies. Furthermore, we assessed the fasting and postprandial GLP-1 levels in response to a standard meal, not oral glucose. Third, the GLP-1 determined in our study was active GLP-1, not total GLP-1.

Evidence has revealed the relationship between GLP-1 and diabetic microvascular complications. Acute (5-d) or early-onset diabetes induces an overexpression of GLP-1, which is believed to be an antioxidant and transiently preserves retinal function in the early stage of diabetes progression[14]. Endogenously increased GLP-1 levels in dipeptidyl peptidase 4-deficient rats attenuated diabetic nephropathy[15]. In our study, a lower postprandial GLP-1 response to a standard meal was associated with a higher microalbuminuria risk. Renoprotective mechanisms of GLP-1 are likely complicated. In animal models, GLP-1 may attenuate renal tubular injury by inhibiting endoplasmic reticulum stress and apoptosis, dampening inflammatory reactions, regulating advanced glycation end product formation and other mechanisms[15-17]. GLP-1 secretion

is impaired in patients with abnormal glucose metabolism and body weight gain. In adults and adolescents, impaired GLP-1 secretion may occur early in diabetes development. Compared with that in individuals with nasogastric tube (NGT), the GLP-1 response to an oral glucose tolerance test was lower in patients with prediabetes or T2DM, and this was more pronounced in women[18]. Reduced 120-min GLP-1 concentrations were independent of BMI and age[18]. Adolescents with obesity, IGT and T2DM had lower fasting GLP-1 and glientin 1 levels than those with NGT[19]. The overall GLP-1 response is also reduced in pregnant women with gestational diabetes mellitus[20]. Lower postprandial GLP-1 levels were independently and significantly associated with liver lipid content[21]. Moreover, the incretin effect, including β-cell responses to GLP-1 and the inhibition of glucagon secretion, was also significantly decreased in T2DM patients. The response of insulin to physiological concentrations of GLP-1 was decreased significantly and even absent in people with impaired oral glucose tolerance, hyperglycemia, and diabetes compared with that in healthy volunteers[22,23]. A decrease in the incretin effect and gastrointestinal-mediated glucose disposal were also observed in women with prior gestational diabetes mellitus and prediabetes. Our study indicated that impaired postprandial GLP-1 secretion may be one of the mechanisms that contributes to microalbuminuria.

Lifestyle intervention is the first step in preventing diabetes and its complications. Compared to the use of GLP-1 agonists, the modification of eating habits has lower costs and fewer adverse reactions, so it is more easily accepted by people at high risk of diabetes or patients with early diabetes. Studies have shown that nutrients enhance GLP-1 secretion, thereby contributing to the prevention and progression of diabetes. Researchers have found that dietary proteins play a key role in triggering the postprandial GLP-1 response in the distal intestine[24]. It was reported that fiber-free feeding for 3 wk markedly reduced the total GLP-1 level by 37% in the ileum and 55% in the colon. It is believed that dietary fiber is necessary to preserve the secretion of incretins by intestinal L cells in mice[25]. Dietary resistant starch intake (4 wk of 40 g/d) significantly increased GLP-1 levels as well as early-phase insulin levels and reduced

the intra-abdominal and subcutaneous fat mass. Dietary eriodyctiol modulated the production and release of GLP-1[26]. An increase in plasma GLP-1 levels induced by dietary furocoumarin imperatorin was also found in type 1-like diabetic rats[27]. The speed and sequence of eating also affect GLP-1 secretion. The dietary approach that slows digestion, including the addition of viscous dietary fiber and enzyme inhibitors of phytochemicals into the designed overall food matrix or encapsulation of nutrients, sustains the secretion of GLP-1 after a meal[28]. Intake of protein or glutamine before a carbohydrate or mixed meal can enhance GLP-1 and insulin secretion, delay gastric emptying and improve postprandial blood glucose elevation[29-31]. Mechanisms related to dietary changes in GLP-1 secretion are not very clear. Changing the abundance of intestinal short-chain fatty acids (SCFAs) is probably one of the mechanisms by which diet enhances GLP-1 secretion[32,33]. SCFAs maintain mucosal integrity in the colon, induce L cell numbers and promote the differentiation of L cells, which increase the production of GLP-1[34,35]. This is thought to be mediated through SCFA binding to the free fatty acid receptors 2 and 3 (GPR41 and GPR43) located on L-cells[35]. A dietary fiber-rich diet not only provides raw materials for SCFA production but also improves the ratio of SCFA-producing microbiota.

This study has several limitations. First, it was a cross-sectional study; thus, prospective studies are warranted to confirm that measures that increase postprandial GLP-1 levels, including dietary strategies involving adjusting diet structure and meal sequence, are beneficial for preventing and alleviating diabetic nephropathy by increasing GLP-1 secretion. Second, a mixed meal containing a variety of nutrients may be more likely to mimic the GLP-1 secretion pattern induced by daily diet, but a standard meal test was competent to illustrate the association between postprandial GLP-1 levels and UACR.

CONCLUSION

In conclusion, our study showed that higher postprandial GLP-1 levels after a standard meal were independently associated with microalbuminuria in newly diagnosed T2DM

patients. This finding adds clinical evidence for the renoprotective effect of GLP-1 in newly diagnosed T2DM patients.

ARTICLE HIGHLIGHTS

Research background

The increase in urinary albumin excretion appeared in the early stage of type 2 diabetes mellitus (T2DM) independent of blood glucose and diabetic duration, which suggests that there may be other mechanisms involved in glomerular basement membrane damage during the progression of abnormal glucose metabolism. Identifying related factors and understanding the underlying mechanisms are helpful for the prevention of diabetic nephropathy.

Research motivation

Metabolic hormones have been confirmed to play an important role in the development of diabetes. Evidence that metabolic hormones also have renoprotective effects is needed to develop prevention measures.

Research objectives

To investigate the association between glucagon-like peptide 1 (GLP-1) and microalbuminuria in newly diagnosed T2DM patients.

Research methods

Newly diagnosed T2DM patients were recruited for this cross-sectional study. The urinary albumin-creatinine ratio (UACR) and active GLP-1 levels at 0 min, 30 min, 120 min and 180 min during a standard meal test were determined. We used multivariable linear regression analyses to detect the mean differences [B; 95% confidence interval (CI)] in LnUACR between patients with different quartiles of postprandial plasma GLP-1 levels, with the first quartile (Q1) set as the reference, to display the degree of influence of post plasma GLP-1 secretion on UACR. Multivariate logistic regression

analyses were performed to analyze the impact of postprandial GLP-1 levels on the risk of microalbuminuria, which is shown as the odds rations (95%CIs) for microalbuminuria in different postprandial GLP-1 levels.

Research results

Ln30 min GLP-1, Ln120 min GLP-1 and the corresponding Ln [area under the curve for active GLP-1 (AUCGLP-1)] were negatively correlated with LnUACR. The UACR of the patients in Q4 of postprandial GLP-1 levels was significantly higher than the UACR of the patients in Q1. The prevalence of microalbuminuria decreased with increasing quartiles of 30 min and 120 min and AUCGLP-1 levels. Logistic regression analysis revealed that after adjustment for other confounders, patients in Q4 of postprandial GLP-1 levels exhibited a decreased risk of microalbuminuria compared with those in Q1 by up to approximately 50%. The adjusted microalbuminuria risk for patients from Q4 of AUCGLP-1 levels was 0.547-fold (95%CI: 0.325-0.920).

Research conclusions

Our study showed for the first time that higher postprandial GLP-1 levels after a standard meal were negatively associated with microalbuminuria in newly diagnosed T2DM patients independent of metabolic status. This finding adds clinical evidence for the renoprotective effect of GLP-1 in newly diagnosed T2DM patients.

Research perspectives

Prospective studies should clarify the effect of measures that increase postprandial GLP-1 levels, including dietary strategies involving adjusting diet structure and meal sequence, on preventing and alleviating diabetic nephropathy in the early stage of diabetes.

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