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A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients

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ABSTRACT

Aims/hypothesis. Glucagon-like peptide-1 (GLP-1) exerts beneficial effects on the cardiovascular system. Here, we examined the effect of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, on systemic inflammation and pro-inflammatory (M1)/anti-inflammatory (M2)-like phenotypes of peripheral blood monocytes in diabetic patients.

Methods. Forty-eight type 2 diabetic patients were divided into the following two groups: sitagliptin-treatment (50 mg daily for 3 months) (n=24) and untreated control (n=24) groups. Measurements were undertaken to assess changes in glucose-lipid metabolism, serum levels of inflammatory cytokines such as serum amyloid A-LDL (SAA-LDL), C-reactive protein (CRP), interleukin-6 (IL-6), IL-10 and tumor necrosis factor-α (TNF-α). Furthermore, the effects of sitagliptin treatment on M1/M2-like phenotypes in peripheral blood monocytes were examined.

Results. Treatment with sitagliptin significantly decreased fasting plasma glucose, hemoglobin A1c (HbA1c), serum levels of inflammatory markers, such as SAA-LDL, CRP, and TNF-α. In contrast, sitagliptin increased serum IL-10, an anti-inflammatory cytokine, as well as plasma GLP-1. In addition, sitagliptin increased monocyte IL-10 expression and decreased monocyte TNF-α expression. Multivariate regression analysis revealed that the sitagliptin treatment was the only factor independently associated with an increase in monocyte IL-10 (β=0.499; R^2=0.293, P<0.05). However, other factors including the improvement of glucose metabolism were not associated with the increase.

Conclusions/interpretation. This study is the first to show that a DPP-4 inhibitor, sitagliptin, reduces inflammatory cytokines and improves the unfavorable M1/M2-like phenotypes of peripheral blood monocytes in Japanese type 2 diabetic patients.

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10; TNF-α, tumor necrosis factor-α.

Clinical Trial Registration number: UMIN R000006517.

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1. Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors improve glucose metabolism through the elevation of glucagon-like peptide-1 (GLP-1) receptor signaling, which induces insulin secretion and suppresses glucagon secretion in the pancreas [1]. Several studies have shown the beneficial effects of GLP-1 on the cardiovascular system [2]. Experimental studies have demonstrated that DPP-4 inhibitors, as well as GLP-1 receptor agonists, reduce monocytes/macrophages accumulation in the arterial wall by inhibiting the inflammatory response in monocytes/macrophages, thereby contributing to the attenuation of atherosclerotic lesions in apolipoprotein E-knockout mice, a murine atherosclerotic model [2–6]. However, the effect of DPP-4 inhibitors on atherogenesis in humans is unknown. The monocyte–macrophage system, which plays a key role in the pathogenesis of inflammation and atherosclerosis, shows at least two distinct phenotypes of differentiation: pro-inflammatory (M1) and anti-inflammatory (M2) [7,8]. Therefore, this study was designed to assess the potential effects of sitagliptin, a DPP-4 inhibitor, on cardiovascular risk markers, such as oxidatively modified low-density lipoprotein (LDL), inflammatory cytokines, and M1/M2-like phenotypes of peripheral blood monocytes in type 2 diabetic patients.

2. Methods

A total of 48 Japanese diabetic outpatients (25 men and 23 women; mean age, 60.0±1.7 years) were recruited in our clinic during the period from January 2011 to December 2011. Diabetic subjects were defined as those with hemoglobin A1c (HbA1c) of≥6.5% (according to the National Glycohemoglobin Standardization Program [NGSP]). This study is a part of the Japan Diabetes & Obesity Study, which has undergone clinical trial registration in the University Hospital Medical Information Network (UMIN) system (UMIN Study ID: UMIN R000006517). The study protocol was approved by the Ethics Committee for Human Research at Kyoto Medical Center. Written informed consent was obtained from all participants. This study was a prospective, randomized, open-label, blinded endpoint design, employing simple randomization. Forty-eight patients were assigned to a sitagliptin-treated group, in which sitagliptin (50 mg daily) was administered for 3 months, or an untreated control group. Patients taking insulin-sensitizing agents or insulin therapy were excluded from the study. All other medications were continued and remained unchanged during the study protocol.

At the beginning and end of the study, we measured the body mass index (BMI), systolic and diastolic blood pressures (SBP and DBP, respectively), HbA1c [NGSP], plasma levels of fasting glucose (FPG) and GLP-1, serum levels of immunoreactive insulin (IRI), homeostasis model assessment of insulin resistance (HOMA-IR), LDL-cholesterol (LDL-C), serum amyloid A-LDL (SAA-LDL), C-reactive protein (CRP), interleukin-6 (IL-6), IL-10, and tumor necrosis factor-α (TNF-α) as previously described [8–11]. The expressions of TNFα, IL-6, and IL-10 mRNA in monocytes were examined as previously described [8,12,13].

The sample size was calculated with a type I error of 5%, a statistical power of 80%, and a standardized effect size of 0.65, so as to demonstrate a sitagliptin-induced change of 1.0 pg/ml of serum IL-10 as being significant using the paired *t*-test. Data are presented as the mean±SE, and $P<0.05$ was considered significant. Student's *t*-test was used for comparisons of the means between the two groups. If the data were not normally distributed, the Wilcoxon test was used. A paired *t*-test was applied to evaluate changes from the baseline to post-treatment [9]. Repeated measures ANOVA was used to assess the effects of sitagliptin on the measured variables. Multivariate regression analysis was performed to elucidate the factors related to the changes of anti-inflammatory cytokines. The independent variables were gender, age, sitagliptin treatment, initial value of dependent variables, and changes of variables that were significantly altered by the sitagliptin treatment. In addition, the variables showing high collinearity with other variables were excluded from independent variables.

3. Results

There were no significant differences between the control and sitagliptin groups for all measured variables at the baseline (Table 1). Treatment with sitagliptin for 3 months caused a significant reduction of serum levels of FPG, and HbA1c in type 2 diabetic patients ($P<0.05$), despite no changes in BMI, SBP, DBP, IRI, HOMA-IR, and LDL-C after the treatment. FPG and HbA1c were significantly decreased from the baseline to 1.5 months (FPG: 9.2±0.5 → 8.0±0.4 mmol/l, $P<0.05$; HbA1c: 8.2±0.2 → 7.5±0.2 %, $P<0.01$), and from 1.5 months to 3 months after sitagliptin treatment (FPG: 8.0±0.4 → 7.7±0.4 mmol/l, $P<0.01$; HbA1c: 7.5±0.2 → 7.2±0.1 %, $P<0.01$), while there was no significant decrease in the control group. Sitagliptin treatment led to a significant decrease in the serum levels of SAA-LDL, CRP, and TNF-α ($P<0.05$), as well as significant increases in plasma GLP-1 ($P<0.05$) and serum IL-10 in these patients (from 9.8±0.8 to 12.8±1.1, $P<0.01$). In addition, after sitagliptin treatment, the expression of IL-10 was significantly increased (from 0.9±0.1 to 1.1±0.1, $P<0.05$) and TNF-α was significantly decreased (from 3.3±0.6 to 1.9±0.2, $P<0.05$) in peripheral blood monocytes from these diabetic patients (Table 1). Serum IL-6 and monocyte IL-6 expression tended to be decreased by the sitagliptin treatment. However, such changes did not occur in patients treated without sitagliptin. Multivariate regression analysis revealed that the factors that were independently associated with an increase of serum IL-10 were the initial value of IL-10 and the sitagliptin treatment (initial value of IL-10, $\beta=-0.320$; the sitagliptin treatment, $\beta=0.521$; $R^2=0.324$, $P<0.05$). However, age, gender, and the changes of HbA1c, GLP-1, SAA-LDL, and CRP by the treatment with sitagliptin did not have a significant influence on the change of IL-10 (Table 2). Regarding an increase of IL-10 expression in monocytes, multivariate regression analysis revealed that the only factor that was independently associated with the increase was the sitagliptin treatment ($\beta=0.499$; $R^2=0.293$, $P<0.05$). However, age, gender, initial value of IL-10