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Sitagliptin but not alpha glucosidase inhibitor reduced the serum soluble CD163, a marker for activated macrophage, in individuals with type 2 diabetes mellitus

Akiko Hattori [a,b], *Minoru Takemoto* [a,b,*], *Hirotake Tokuyama* [a,c], *Masaya Koshizaka* [a,b], *Koutaro Yokote* [a,b]

[a] *Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8670, Japan*

[b] *Department of Medicine, Division of Diabetes, Metabolism and Endocrinology, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8670, Japan*

[c] *Yu-karigaoka Tokuyama Clinic, Chiba 285-0850, Japan*

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ABSTRACT

Aims: Dipeptidyl peptidase-4 inhibitor (DPP-4i) is commonly used worldwide for the treatment of type 2 diabetes mellitus. In addition to its hypoglycemic activity, DPP-4i might have anti-inflammatory effects. In this study we examined the effects of DPP-4i on the serum levels of soluble CD163 (sCD163), a marker for activated macrophages, in individuals with type 2 diabetes mellitus. We compared these anti-inflammatory effects with those of α glucosidase inhibitor (αGI).

Methods: Japanese patients with type 2 diabetes mellitus who were stably maintained on ≤2 mg/day glimepiride alone were recruited and randomly assigned to receive additional sitagliptin ($n = 37$) or αGI ($n = 37$). Levels of sCD163 were measured before the addition and after a 24-week treatment period.

Results: Addition of sitagliptin significantly reduced the serum sCD163 (632 vs. 575 ng/mL, $p < 0.05$), while αGI did not display this effect (624 vs. 607 ng/mL). The changes in levels of sCD163 were not related to changes in either HbA1c or body mass index (BMI).

Conclusions: Our results suggested that DPP-4i might exert anti-inflammatory effects in individuals with type 2 diabetes mellitus, which are independent of its effects on glycemia and BMI.

1. Introduction

Chronic inflammation is reportedly related not only to the development and progression of type 2 diabetes [1], especially in obese individuals [2,3], but also to later stage vascular complications [4]. Macrophages play a pivotal role in chronic inflammation and the CD163 molecule has reportedly been expressed in both monocyte and macrophage activation.

* Corresponding author at: Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8670, Japan. Fax: +81 43 226 2095.
E-mail address: minoru.takemoto@faculty.chiba-u.jp (M. Takemoto).

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During macrophage activation the metalloproteinase TNF- α converting enzyme (TACE) cleaved CD163 from the cell membrane and released the molecule into the blood stream [5]. Therefore, it has been reported that soluble CD163 (sCD163) can been used as a marker for activated macrophages [6]. Serum levels of sCD163 have been demonstrated to increase in individuals with insulin resistance related obesity [7] and/or type 2 diabetes mellitus [8].

Dipeptidyl peptidase-4 inhibitor (DPP-4i) has been adopted as a therapeutic agent worldwide. It has been reported that DPP4i does not only improve glucose metabolism but also has various other actions such as anti-atherosclerotic effects [9], along with other beneficial effects on diabetic microvascular complications [10]. Several preclinical and in vitro studies have indicated that DPP4i can reduce both oxidative stress and inflammation [11,12].

Therefore, we also examined the anti-inflammatory effects of sitagliptin and compared these with α glucosidase inhibitor (α GI), a postprandial hypoglycemic agent, by monitoring serum levels of sCD163.

2. Methods

2.1. Subjects

This multicenter, comparative, parallel-group, actively controlled, randomized, open-label and non-inferiority trial was undertaken at 37 sites in Chiba prefecture, Japan [13]. The study was approved by the ethics committees for each center and subsequently registered (UMIN-ID: UMIN 000004674; http://www.umin.ac.jp/ctr/). Eligible study participants were aged 20–79 years, had type 2 diabetes mellitus (T2DM), had been receiving ≤2 mg/day glimepiride alone for ≥2 months, and had a hemoglobin A1c (HbA1c) of 6.9–8.8%. All patients provided written informed consent before participation, and were randomly assigned to either 24 weeks of treatment with sitagliptin (50 mg once a day) or α GI (0.2 mg voglibose or 50 mg miglitol three times a day), in addition to glimepiride (dose unchanged throughout the study). This study was feasible because the efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin compared to α -glucosidase inhibitor in patients with type 2 diabetes inadequately controlled on sulfonylurea alone (SUCCESS-2) and has been already reported [13]. Since it has been reported that serum sCD163 are affected not only by reduction in body weight [14] but also by blood glucose levels [15], we aimed to exclude these effects as much as possible. Therefore, we selected patients whose rate of variability of HbA1c and body mass index (BMI) during the SUCCESS-2 study were maintained within a confidence interval of 95%.

2.2. Clinical parameters of blood samples

Venous blood samples were collected at baseline and at the end of the 24-week treatment period in the morning after a 12-h fast. sCD163 levels were measured via Enzyme-Linked Immuno Sorbent Assay (DC1630, R&D systems, USA).

The standard value for sCD163 in this ELISA kit was 472 ± 186 ng/mL.

2.3. Statistical analysis

For the baseline variables and changes in clinical parameters, summary statistics were constructed using frequencies and proportions for categorical data, and means and standard deviations for continuous data. We used Welch's *t*-test for parametric data, Wilcoxon rank sum test for non-parametric data, Pearson's chi-squared test for categorical variables such as sex, anti-hypertension drugs, and lipid-lowering agents, to compare between two groups, as appropriate. In the primary analysis, we analyzed the changes of sCD163 level from baseline to 24-weeks in each group by paired *t*-test. We used Pearson's correlation coefficient for parametric data and Spearman's rank correlation coefficient for nonparametric data to evaluate the statistical association between other parameters and sCD163. All comparisons were planned and all *p* values were two sided. *P* values of <0.05 were considered statistically significant. All statistical analyses were performed using the JMP pro12 (SAS Institute Japan, Tokyo, Japan).

3. Results

Serum sCD163 level was significantly reduced by sitagliptin independent of changes in HbA1c and BMI.

Table 1 shows the characteristics of the individuals in each group. Individuals assigned to sitagliptin were slightly and higher BMI compared with those assigned to α GI. Levels of sCD163 measured at the start of the study did not differ between the groups. While evaluating the association between serum sCD163 and clinical parameters among all participants, age was positively associated whereas total and high-density lipoprotein (HDL) cholesterol were negatively associated with serum sCD163 (Table 2).

After the addition of sitagliptin or α GI for 24 weeks, body weight and BMI had significantly decreased in individuals who received α GI, while levels of HbA1c had slightly decreased in individuals who received sitagliptin (Table 3). No severe hypoglycemic events were recorded during our study. Three minor hypoglycemic events (one in the sitagliptin group and two in the α GI group) were noted, but the frequency of hypoglycemic events between both groups were not statistically significant.

Levels of sCD163 had significantly decreased in individuals who received sitagliptin but not in those who received α GI, as shown in Fig. 1, while there were no changes in CRP levels in both groups, as shown in Table 3. It has been reported that serum sCD163 levels are affected by metabolic parameters such as blood glucose concentration and body weight. Therefore we then examined any association between the reduction in cCD163 and changes in HbA1c, Glycoalbumin (GA), BMI and total cholesterol (T-CHO) in individuals who received sitagliptin. No such association was found (Fig. 2), indicating that sitagliptin possesses anti-inflammatory effects which are independent from its ability to lower blood glucose and BMI.