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BRIEF REPORT

Hypoglycemia Abrogates the Vascular Endothelial Protective Effect of Exenatide in Type 2 Diabetes Mellitus

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) receptor agonists improve postprandial glucose, lipid metabolism, and vascular endothelial function. However, little is known about the effect of hypoglycemia on vascular endothelial function in patients on GLP-1 receptor agonist therapy. The aim of the present study was to determine the effect of hypoglycemia on vascular endothelial function in patients with type 2 diabetes mellitus (T2DM) treated with exenatide. Seventeen patients with T2DM underwent a meal tolerance test to examine the changes in vascular endothelial function and in glucose metabolism, both without exenatide and after a single subcutaneous injection of 10 μg exenatide. Vascular endothelial function was evaluated using reactive hyperemia index (RHI) measured by peripheral arterial tonometry before and 120 min after the meal loading test. The primary endpoint was the difference in changes in postprandial vascular endothelial function between the baseline and exenatide test. The results were analyzed in relation to the presence of absence of hypoglycemia. The natural logarithmically scaled RHI (L_RHI) was significantly lower after the baseline meal test but not in the exenatide test. Administration of exenatide caused symptomatic hypoglycemia in two patients during the meal tolerance test. The difference in the change in L_RHI was 0.125 ± 0.085 in the non-hypoglycemic group, whereas it was lower, -0.487 ± 0.061, in the hypoglycemic group. The results of this study also suggest that the presence of hypoglycemia induces vascular endothelial dysfunction even during GLP-1 receptor agonist therapy.
Trial registration: UMIN000015699.

Keywords: Glucagon-like peptide-1 receptor agonist; Hypoglycemia; Vascular endothelial function

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INTRODUCTION

Vascular endothelial dysfunction in patients with type 2 diabetes mellitus (T2DM) develops early in the disease and is therefore already

present by the time the patient reaches the stage of impaired glucose tolerance [1]. This contributes to the occurrence and progression of macroangiopathy [1]. The presence of vascular endothelial dysfunction increases cardiovascular events and can therefore be regarded as a surrogate marker of arteriosclerotic disease. Clinical and experimental evidence suggests that vascular endothelial dysfunction is induced by hypoglycemia and fluctuations in glucose levels, in addition to postprandial hyperglycemia [2–4].

Glucagon-like peptide-1 (GLP-1) receptors are expressed in various organs, including β cells of the pancreas, and have multifaceted effects [5]. GLP-1 receptors are also expressed in vascular endothelial cells, where GLP-1 receptor agonists can directly increase the production of nitric oxide (NO) and inhibit the expression of endothelial cell adhesion factor. In the clinical setting, GLP-1 receptor agonists improve postprandial glucose, lipid metabolism, and vascular endothelial function [6, 7]. However, little is known about the effect of hypoglycemia on vascular endothelial function in patients on GLP-1 receptor agonist therapy. The aim of the present study was to determine the effect of hypoglycemia on vascular endothelial function in patients treated with exenatide. For this purpose, we used data from our previous study [7] on the effect of exenatide on postprandial vascular endothelial dysfunction in patients with T2DM.

METHODS

Study Subjects

This study included 17 patients with T2DM who were admitted to the University of Occupational and Environmental Health Hospital (UOEH) or Wakamatsu Hospital of UOEH between June 2011 and February 2014 and who met the following inclusion criteria: (1) age 20 to less than 80 years; (2) no change in treatment with oral glucose-lowering agents, lipid-lowering agents, and antihypertensive agents during the 12 weeks preceding enrollment; and (3) ongoing treatment by diet regimen alone or by therapy with sulfonylurea, sulfonylurea plus biguanide, or sulfonylurea plus thiazolidine derivatives. Patients who met any of the following criteria were excluded from the study: (1) treatment of diabetes with insulin; (2) experience of episodes of diabetic ketoacidosis, nonketotic hyperosmolar coma, infection, or acute coronary syndrome; (3) pregnancy or possible pregnancy; (4) history of stroke or ischemic heart disease within the preceding 6 months; (5) history of pancreatitis; and (6) cardiac arrhythmia.

This study was approved by the ethics committee of the UOEH, and the subjects received written information about the study and gave consent to participate in the study.

Study Design

Patients with T2DM who were admitted to our hospital underwent meal tolerance tests to determine the changes in vascular endothelial function and in glucose metabolism before and after meal loading. In this test, exenatide was not used on day 1. Instead, it was injected subcutaneously in a bolus dose of 10 μg (Byetta®, AstraZeneca K.K., Osaka, Japan) before meal loading on day 2. Test meal A was used for the meal tolerance test (based on a recipe proposed by the working group of the Japan Diabetes Society. Test meal A consisted of a bowl of cream of chicken soup, five crackers, and pudding, which included a total of 450 kcal; carbohydrate 51.4%, fat 33.3%, protein 15.3%) [8], and blood tests were performed before and 30, 60, 120, and 240 min after meal loading to evaluate changes in glucose metabolism. Vascular endothelial function was evaluated by peripheral arterial tonometry (EndoPAT2000, Itamar Medical, Caesarea, Israel) before and 120 min after meal loading. The primary outcome measure was the difference between changes in vascular endothelial function at 0 and 120 min after meal loading without any dose of exenatide and with a single dose of exenatide. The results were analyzed in relation to the presence or absence of hypoglycemia. This study was registered as UMIN000015699 (Table 1).

Table 1 Baseline characteristics

	Non-hypoglycemic group (n = 15)	Hypoglycemic group (n = 2)
Age (years)	53.2 ± 2.6	51.5 ± 16.5
Gender (male/female)	13:2	2:0
Body mass index (kg/m^2)	27.1 ± 1.5	26.3 ± 0.6
Duration of diabetes (years)	7.0 ± 1.0	3.0 ± 2.0
Diabetes complication		
Neuropathy	9 (60.0)	1 (50.0)
Retinopathy	2 (13.3)	0 (0.0)
Nephropathy	0 (0.0)	0 (0.0)
Diabetes therapy		
Diet only	2 (13.3)	0 (0.0)
Sulfonylurea	12 (80.0)	2 (100.0)
Pioglitazone	0 (0.0)	0 (0.0)
Metformin	3 (20.0)	0 (0.0)
Other treatments		
Lipid-lowering drugs	4 (26.7)	0 (0.0)
Antihypertensive drugs	5 (48.8)	1 (50.0)
Current smokers	9 (60.0)	2 (100.0)
Cardiovascular disease	2 (13.3)	0 (0.0)
Systolic blood pressure (mmHg)	127.4 ± 4.3	116.0 ± 23.0
Diastolic blood pressure (mmHg)	80.6 ± 3.3	65.5 ± 13.5
HbA1c (%)	9.5 ± 0.4	11.4 ± 2.0
Fasting plasma glucose (mg/dL)	153.0 ± 9.5	152.0 ± 19.0
Immunoreactive insulin (μU/mL)	7.4 ± 1.1	5.4 ± 0.1
HOMA-IR	2.8 ± 0.5	2.0 ± 0.2
HOMA-β	32.2 ± 5.7	23.0 ± 5.3
L_RHI	0.54 ± 0.04	0.63 ± 0.40

Data are mean ± SE, n, or n (%)
HbA1c hemoglobin A1c, *HOMA-IR* homeostasis model assessment as an index of insulin resistance, *HOMA-β* homeostasis model assessment beta cell function, *L_RHI* the natural logarithmic scaled reactive hyperemia index

All procedures performed in studies involving human participants were in accordance with the ethics committee of the UOEH and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

RESULTS

The subjects were 17 diabetics (15 men and 2 women) with a mean age of 53.0 ± 2.7 years. The subject population was mildly obese, with a mean BMI of 27.0 ± 1.3 kg/m^2. The mean duration of diabetes mellitus was 6.5 ± 1.0 years. The mean fasting plasma glucose was 152.9 ± 8.5 mg/dL, HbA1c was 9.7 ± 0.4%. Fifteen of them were on oral hypoglycemic drug therapy, comprising metformin alone in one patient, metformin combined with sulfonylurea in two, and sulfonylurea alone in 12. The natural logarithmically scaled reactive hyperemia index (L_RHI) was 0.55 ± 0.05, and there was no significant sex-related difference in L_RHI. Administration of exenatide caused symptomatic hypoglycemia in two patients during the meal tolerance test, which was corrected with an oral dose of glucose. In patients who did not develop hypoglycemia (non-hypoglycemic group), L_RHI after meal loading was significantly decreased (before 0.54, after 0.46; $p = 0.029$) without exenatide administration, whereas such decrease was abrogated by exenatide (before 0.56; after 0.58; $p = 0.699$). In patients who developed hypoglycemia (hypoglycemic group), exenatide had no effect on the index (before 0.64, after 0.39). The difference in the change in L_RHI (ΔL-RHI) was 0.125 ± 0.085 in the non-hypoglycemic group, whereas it was significantly lower, − 0.487 ± 0.061, in the hypoglycemic group (Fig. 1).

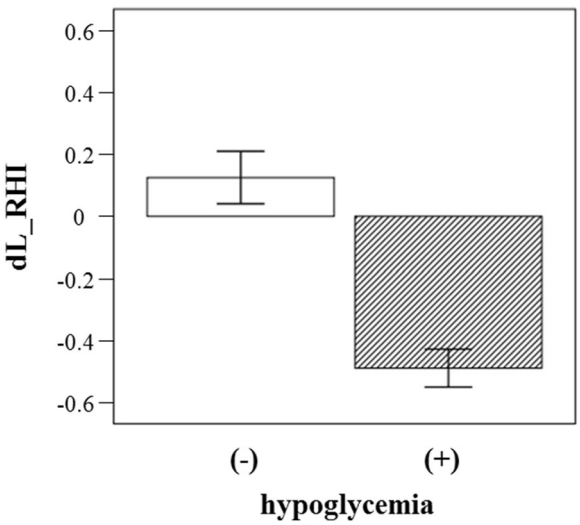

Fig. 1 Changes in natural logarithmically scaled reactive hyperemia index on exenatide meal tolerance test in patients with type 2 diabetic with or without hypoglycemia. A barplot representing mean. Error bars represent standard error (SE) of the mean

DISCUSSION

The above results demonstrated for the first time that the vascular endothelial protective effect of GLP-1 receptor agonist exenatide is attenuated in the presence of hypoglycemia in patients with T2DM.

It has been reported that exenatide improves vascular endothelial function directly by correcting postprandial abnormal glucose and lipid metabolism. It has been reported that GLP-1 receptors are expressed in vascular endothelial cells [9] and that GLP-1 increased NO production to cause improvement in the vasodilatory response in animal experiments [10]. In addition, GLP-1 is reported to inhibit the enhancement of hyperglycemia-induced vascular cell adhesion molecule-1 expression in vascular endothelial cells [11], indicating that this substance exerts a direct and short-term effect on improve vascular endothelial function via vasodilatory and anti-inflammatory actions. Other studies have also shown that GLP-1 receptor agonists improve postprandial glucose and lipid metabolism, as well as vascular endothelial function [6, 7]. The present study also showed that postprandial glucose was improved in all patients. In patients with hypoglycemia, vascular endothelial function decreased despite the improvement in postprandial hyperglycemia and fluctuations in glucose levels (data not shown). It is speculated that hypoglycemia induces NO production by vascular endothelial cells, leading to marked increase in active oxygen from the mitochondria. The effect of hypoglycemia on vascular endothelial cells is also thought to involve adrenaline and noradrenaline, which are known insulin antagonist hormones. Hypoglycemia enhanced monocyte adhesion to endothelial cells through enhanced adrenaline activity and that the latter stimulated

intracellular c-AMP, leading to nuclear translocation of NF-κB [12]. Hypoglycemia is associated with increased proinflammatory cytokines (TNF-alpha, IL-1beta, IL-6, and IL-8) and reactive oxygen species (ROS). Elevations of norepinephrine, epinephrine, and cortisol in hypoglycemia are associated with the elevation of proinflammatory cytokines [13].

At this time, there are five published cardiovascular safety outcome trials [14–18] for the GLP-1 receptor agonists, and it has been clarified that GLP-1 receptor agonists would reduce the incidence of CV outcomes under certain conditions [19]. The results of this study suggest that the presence of hypoglycemia attenuates the vascular endothelial protective effect of GLP-1 receptor agonist exenatide. So, it is necessary to avoid hypoglycemia for possible CV benefits of GLP-1 therapy.

The present study has certain limitations. First, it was an open-label study covering a small sample size with possible selectin bias. Because the number of subjects in the present study was small, we could not evaluate by adjusting for age or sex, etc. Second, only two subjects experienced hypoglycemia in this study, so it was difficult to prove statistically the difference between the two groups.

CONCLUSION

However, the direct effect of hypoglycemia on vascular endothelial function has not been studied previously in a clinical setting. The results of this study also suggest that the presence of hypoglycemia induces vascular endothelial dysfunction even during GLP-1 receptor agonist therapy.

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Author Contributions. KT collected the data, wrote the manuscript, and performed the statistical analysis. YO designed the study and reviewed the manuscript. YT reviewed the manuscript and edited the manuscript.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethics committee of the UOEH and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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