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ABOUT COVER

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AIM AND SCOPE

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ORIGINAL ARTICLE

Clinical Trials Study

Prediction of the effect on antihyperglycaemic action of sitagliptin by plasma active form glucagon-like peptide-1

Akifumi Kushiyama, Takako Kikuchi, Kentaro Tanaka, Tazu Tahara, Toshiko Takao, Yukiko Onishi, Yoko Yoshida, Shoji Kawazu, Yasuhiko Iwamoto

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Author contributions: Kushiyama A designed research; Kikuchi T, Tahara T, Takao T, Onishi Y and Yoshida Y performed research; Kushiyama A and Tanaka K analyzed data; Kushiyama A, Kawazu S and Iwamoto Y wrote paper.

Institutional review board statement: The protocol was approved by the Institutional Review Board (IRB) of the Institute for Adult Diseases, Asahi Life Foundation.

Clinical trial registration statement: The study is a prospective, single-arm study and was registered at UMIN-CTR (Registration NO: UMIN000010645).

Informed consent statement: All of the subjects gave written informed consent to be included in this study.

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Data sharing statement: The authors declare no conflicts of interest regarding this manuscript.

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Abstract

AIM: To investigate whether active glucagon-like peptide-1 (GLP-1) is a prediction Factor of Effect of sitagliptin on patients with type 2 diabetes mellitus (GLP-1 FEST: UMIN000010645).

METHODS: Seventy-six patients with type 2 diabetes, who had insufficient glycemic control [Hemoglobin A1c (HbA1c) $\geqslant$ 7%] in spite of treatment with metformin and/or sulfonylurea, were included in the investigation. Patients were divided into three groups by tertiles of fasting plasma active GLP-1 level, before the administration of 50 mg sitagliptin.

RESULTS: At baseline, body mass index, serum UA, insulin and HOMA-IR were higher in the high active GLP-1 group than in the other two groups. The high active GLP-1 group did not show any decline of HbA1c (7.6% ± 1.4% to 7.5% ± 1.5%), whereas the middle and low groups indicated significant decline of HbA1c (7.4 ± 0.7 to 6.8 ± 0.6 and 7.4 ± 1.2 to 6.9 ± 1.3, respectively) during six months. Only the low and middle groups showed a significant increment of active GLP-1, C-peptide level, a decreased log and proinsulin/insulin ratio after administration. In logistic analysis, the low or middle group is a significant

explanatory variable for an HbA1c decrease of ⩾ 0.5%, and its odds ratio is 4.5 (1.40-17.6) (P = 0.01) against the high active GLP-1 group. This remains independent when adjusted for HbA1c level before administration, patients' medical history, medications, insulin secretion and insulin resistance.

CONCLUSION: Plasma fasting active GLP-1 is an independent predictive marker for the efficacy of dipeptidyl peptidase 4 inhibitor sitagliptin.

Key words: Dipeptidyl peptidase-4 inhibitor; Active form glucagon-like peptide-1; Hemoglobin A1c; Regression analysis

Core tip: This clinical trials study revealed novel non-responders for the sitagliptin treatment of patients with type 2 diabetes. The fasting active form of glucagon-like peptide-1 (GLP-1) is related to Hemoglobin A1c (HbA1c) lowering and is independent of the previously reported factors associated with non-responders, such as high body mass index or low baseline HbA1c. These non-responders did not show fasting active GLP-1 elevation after sitagliptin administration, nor following ameliorated beta cell function and insulin secretion. The mechanism of poor responsiveness is still not unveiled, however, measuring active GLP-1 might be a good marker for prognosis, and may help clarifying one aspect of response variation against sitagliptin.

Kushiyama A, Kikuchi T, Tanaka K, Tahara T, Takao T, Onishi Y, Yoshida Y, Kawazu S, Iwamoto Y. Prediction of the effect on antihyperglycaemic action of sitagliptin by plasma active form glucagon-like peptide-1. *World J Diabetes* 2016; 7(11): 230-238 Available from: URL: http://www.wjgnet.com/1948-9358/full/v7/i11/230.htm DOI: http://dx.doi.org/10.4239/wjd.v7.i11.230

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is one of the major metabolic hormones[1], so called incretins, that regulates glucose induced insulin secretion (GSIS)[2-4]. The active form of GLP-1 (active GLP-1) is secreted from intestinal L cells[5], and dipeptidyl peptidase 4 (DPP-4) cuts N-terminal two amino acids of active GLP-1 into its inactive form rapidly in both type 2 diabetic patients and healthy subjects[6,7]. DPP-4 inhibitors retard GLP-1 degradation, raise plasma active GLP-1, and stimulate GSIS[8]. In patients with type 2 diabetes the effects of incretins are impaired, especially postprandially, when biologically intact active GLP-1 level is low[9]. DPP-4 inhibitors ameliorate active GLP-1 shortage, inhibit glucose spiking and help avoid hypoglycemia; therefore DPP-4 inhibitors are now widely used in the treatment of type 2 diabetes.

Sitagliptin[10] is one of the major selective DPP-4 inhibitors that improve glycemic control, both as a monotherapy and combined with other anti-hyperglycemic agents[11-15]. There have still been insufficient reports regarding predictors of the efficacy of DPP-4 inhibitor therapy. DPP-4 inhibitors appear to be more effective in patients with a high baseline HbA1c level[16-18], low body mass index (BMI)[17,18], low activity of plasma DPP-4[19], in elderly patients and in patients displaying adequate compliance with diet/exercise therapy[20]. Therefore identifying the predictors of the therapeutic response to DPP-4 inhibitors would be valuable for its clinical use and help further speculation of the mechanism and pathophysiology of type 2 diabete.

We hypothesized that the plasma level of active GLP-1 could be associated with the efficacy of DPP-4 inhibitors in patients with type 2 diabetes. Therefore we investigated the impact that baseline plasma active GLP-1 level had on HbA1c level after sitagliptin administration.

MATERIALS AND METHODS

Design and patients

This was an interventional single-arm study in patients with type 2 diabetes attending hospital at the Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan. The protocol was approved by the Institutional Review Board (IRB) of the Institute for Adult Diseases, Asahi Life Foundation and was registered as clinical trial UMIN000010645. Patients with diabetes who attended the hospital's outpatient clinic were eligible to participate if they were ⩾ 20 years old and had inadequate glycemic control [hemoglobin A1c (HbA1c) ⩾ 7.0%] despite dietary and exercise therapy and taking metformin and/or a sulfonylurea for at least three months.

Registration period: 24 mo from March 11, 2011. Follow-up period: 6 mo patient of final registration start treatment. The study period: The period plus the follow-up period to the registration period. All of the subjects gave written informed consent to be included in this study.

From these, adult patients (aged ⩾ 20 years) with type 2 diabetes mellitus (n = 78) were selected; and patients with type 1 diabetes, patients who took other DPP-4 inhibitors and/or a GLP-1 analog were excluded. Two patients were also excluded because their HbA1c level was below the lower limit of criteria at administration. Data collection was carried out as previously described[21].

Interventions

All 76 patients were given a 50 mg/d dose of sitagliptin, the standard dose for the treatment of type 2 diabetes in Japan, and were checked up with at monthly intervals for 6 mo, with at least two reviews in the first and third month. The doses of metformin and sulfonylurea were fixed throughout the 6-mo period, with a possible exception for the reduction of sulfonylurea when

avoiding anticipated hypoglycemia by doctors.

Laboratory tests

Serum levels of active GLP-1 were measured with a commercially available enzyme-linked immunosorbent assay kit (#EGLP-36K, Merck Millipore, MA). Data collection of age, sex, disease duration, fasting blood glucose level, HbA1c level, BMI, medication/s taken, blood pressure, levels of biochemical indicators (liver function, renal function, uric acid, lipids) were carried out when starting sitagliptin administration. The estimated glomerular filtration rate (eGFR) was calculated using the estimation formula advocated by the Japanese Society of Nephrology: eGFR (mL/min per 1.73 m^2) = 194 × Cr - 1.094 × age - 0.287 (× 0.739 for women)[22].

The levels of plasma insulin (#SU06T, Fujirebio Inc., Tokyo, Japan), C peptide (#VU06T, Fujirebio Inc.), high sensitive C reactive protein (hsCRP) (#OQIY21, Siemens Healthcare, Erlangen, Germany), glucagon (#RB310, Euro-Diagnostica AB, Sweden) and proinsulin/immunoreactivity insulin ratio (PI/IRI) (#HPI-15K, Merck Millipore) were examined. HsCRP was evaluated as logarithmic. The measurement of HbA1c levels were carried out using HLC-723 GHb G8 analyzer (Tosoh Bioscience, Tokyo, Japan) as previously described[23]. During the third month of the administration period, levels of HbA1c, active GLP-1, insulin, C peptide, hsCRP, glucagon and the PI/IRI were again measured. As an index of efficacy, HbA1c decline (dA1c) was calculated during the 6-mo administration of sitagliptin, and a dA1c of $\geqslant$ 0.5% was considered effective.

Statistical analysis

Subjects were divided into tertiles of high, medium and low active GLP-1 level prior to sitagliptin administration. To assess the statistical significance between groups, Tukey post hoc tests with ANOVA were performed, unless otherwise indicated.

Logistic analysis was used to examine whether active GLP-1, or any other factor, was the predictor of the efficacy of sitaliptin. In addition, using multivariate logistic analysis, we examined whether active GLP-1 is an independent predictor. The analysis was performed by Jmp 12.0.1 (SAS Institute, United States) and the data expressed in mean ± SD. The data is illustrated in the table, boxplots and graphs; and $P < 0.05$ is considered statistically significant.

RESULTS

Patients characteristics at baseline

In this study, 76 patients took 50 mg sitagliptin throughout the 6-mo period. No serious adverse effects, nor any adverse effects requiring a change or stop to medications were observed. Table 1 and Figure 1 indicate a patient profile of the subjects divided into three groups by their fasting active GLP-1 level. Measurements of active GLP-1 in the low active GLP-1 group were $\leqslant$ 2 pmol/L, less than assay sensitivity, and $\geqslant$ 4 pmol/L in the high group.

There was no significant difference when comparing sex, age, disease duration, glycemic control, and other parameters of serum profile between the high, middle and low active GLP-1 groups. However, high BMI and serum UA in the high active GLP-1 group was higher than other two groups. The frequency of Biguanide use rose with the increase of active GLP-1 level ($P < 0.05$ Cochran-Armitage trend test). HOMA-IR and plasma insulin were significantly higher in the high active GLP-1 group compared with the other two groups (Figure 1). The high active GLP-1 group also tended to exhibit higher HOMA-β and lower proinsulin/insulin ratio than two groups. There were no significant changes in hsCRP and plasma glucagon level between three groups.

As a result of sitagliptin administration, the high group did not show any decline of HbA1c (7.6% ± 1.4% to 7.5% ± 1.5%), whereas the middle and low indicated significant decline of HbA1c (7.4 ± 0.7 to 6.8 ± 0.6 and 7.4 ± 1.2 to 6.9 ± 1.3, respectively) during six months (Figure 2A). During the first three months of sitagliptin administration, the active GLP-1 level of the low group rose to detectable levels ($\geqslant$ 2 pmol/L). Likewise, the middle group showed a significant increment of active GLP-1, while the high group did not (Figure 2B).

Figure 3 indicates the changes of insulin, C-pepide, PI/insulin ratio, hsCRP, and glucagon for the low and middle groups against the high group over 3 mo, after the administration of sitagliptin. Insulin, C-peptide and PI/insulin levels in the low and middle groups were slightly increased, but tended to decrease in the high group. The changes of C-peptide and hsCRP during these three months were significant, yet fasting plasma glucagon level did not change between groups.

In logistic analysis, the low or middle active GLP-1 group is a significant explanatory variable for dA1c $\geqslant$ 0.5%, and its odds ratio (OR) is 4.5 (1.40-17.6) ($P = 0.01$) when compared against the high active GLP-1 group (Table 2). High HbA1c, high fasting plasma glucose (FPG), high BMI, use of biguanide, high plasma insulin, high HOMA-β and HOMA-IR at the beginning of administration of sitagliptin were also significant explanatory variables. Long disease duration is somewhat advantageous; while sex, age, use of sulfonylurea (SU), C-peptide level, PI/IRI, glucagon level, and hsCRP level at the beginning of administration were not significant.

To further investigate active GLP-1 level, independent, multivariate logistic analyses were performed (Table 2). Active GLP-1 level remained totally significant when adjusted with high HbA1c (model 1), and with HbA1c and background factors such as age, gender, disease duration and BMI (model 2). This was also observed with variables in model 2 and concomitant diabetes drugs (model 3), with model 2 variables and insulin and glucagon secretion, as well as inflammatory conditions (model 4), and also with variables in model 2 and HOMA-

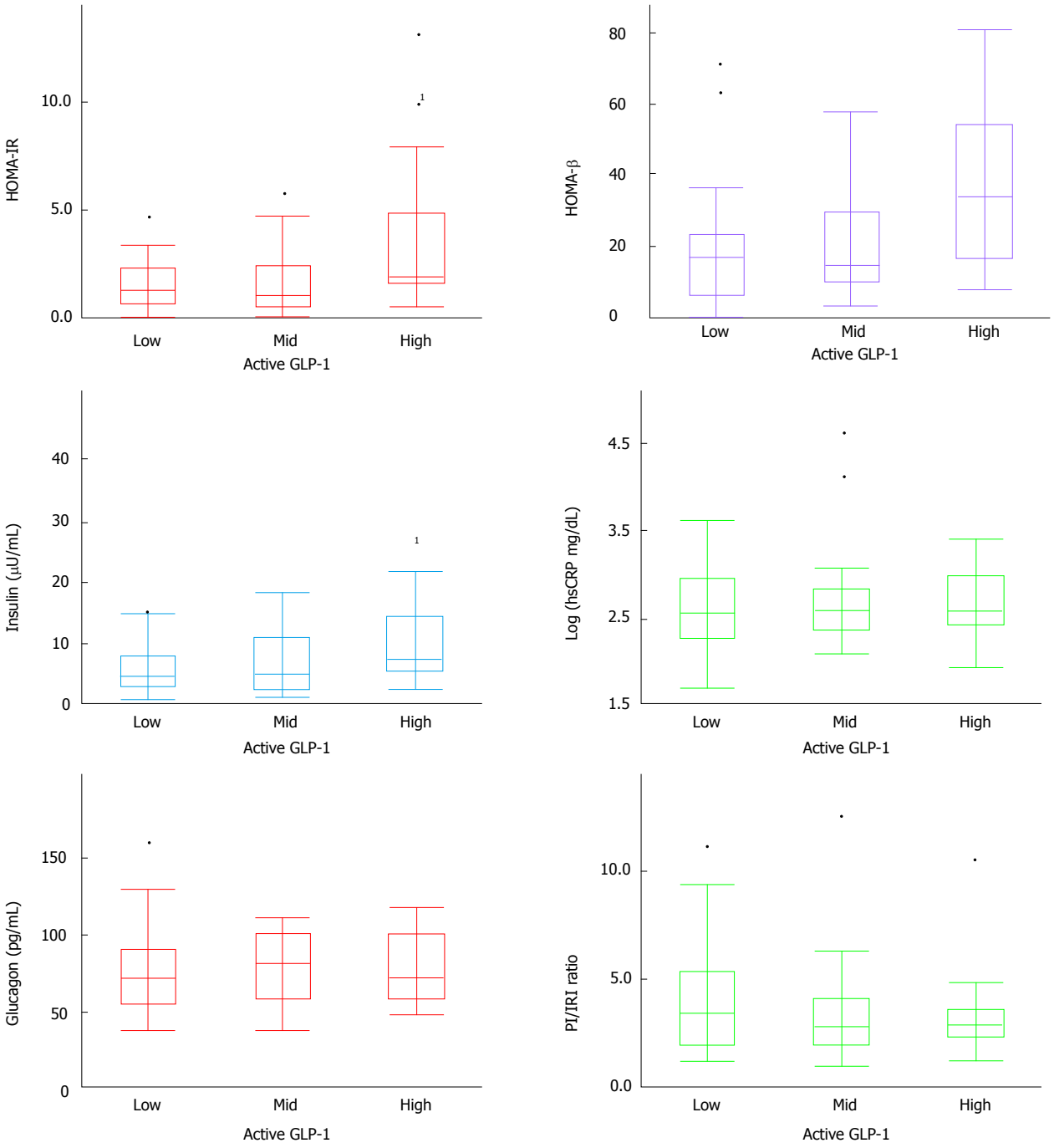

Figure 1 Baseline measurements of homeostasis model assessment of insulin resistance, HOMA-β, insulin, high sensitive C reactive protein, glucagon, and PI/insulin resistance index ratio. Patients' insulin resistance, insulin and glucagon secretion, and hsCRP at baseline is stratified against plasma active GLP-1 level. Data has been presented by boxplot. [1]Mean statistical significance $P < 0.05$. GLP-1: Glucagon-like peptide-1; hsCRP: High sensitive C reactive protein.

IR and HOMA-β (model 5).

DISCUSSION

DPP-4 inhibitors show an indirect effect on glucose lowering through DPP-4 inhibition[24], GLP-1 secretion, and subsequent GSIS and the inhibition of glucagon secretion. Therefore the effect of DPP-4 inhibitors is evaluated primarily by the inhibitory activity of DPP-4, and secondly by the postprandial increase of active GLP-1 concentrations; while significance of the basal active GLP-1 value for the efficacy of DPP-4 inhibitor has been unknown.

In this study, plasma active GLP-1 level of fasting is related to BMI, uric acid, the use of biguanide, HOMA-IR, HOMA-β, insulin level and PI/IRI ratio. The subjects in the high active GLP-1 group are characterized by insulin resistance, hyperinsulinemia and beta cell dysfunction. The high active GLP-1 group presented a decreased responsiveness in glucose lowering effect compared with the other two groups. Glucagon, commonly produced from preproglucagon[25], is not related to active GLP-1

Table 1 Patient characteristics (n = 76)

	Active GLP-1 low (n = 26)	Active GLP-1 mid (n = 25)	Active GLP-1 high (n = 25)	P value
Sex male/female (%)	82	88	88	
Age (yr)	60.5 ± 13.7	63.8 ± 10.8	58.5 ± 15.3	
Disease duration (yr)	16.2 ± 11.2	15.5 ± 10.8	12.7 ± 10.4	
FPG (mg/dL)	161.1 ± 35.4	160.1 ± 41.6	160.7 ± 45.3	
HbA1c (%)	7.43 ± 1.18	7.44 ± 0.66	7.61 ± 1.32	
BMI (kg/m^2)	22.3 ± 5.8	24.1 ± 10.7	26.8 ± 5.6	[1]
Sulfonylurea (%)	54	52	57	
Biguanide (%)	45	52	76	
Systolic BP (mmHg)	126.8 ± 17.5	133.9 ± 15.1	129.2 ± 17.8	
Diastolic BP (mmHg)	74.5 ± 10.8	76.8 ± 13.6	78.0 ± 12.2	
Proteinuria	8	22	21	
γGTP (IU/L)	38.5 ± 34.3	45.9 ± 35.5	43.3 ± 27.5	
AST (IU/L)	28.3 ± 34.0	22.9 ± 8.2	25.0 ± 10.0	
ALT (IU/L)	36.0 ± 60.1	23.9 ± 15.8	32.2 ± 21.3	
TC (mg/dL)	193.3 ± 29.6	214.3 ± 32.0	189.1 ± 26.0	
HDLC (mg/dL)	57.0 ± 16.9	61.6 ± 16.0	51.9 ± 14.3	
TG (mg/dL)	127.1 ± 66.3	133.4 ± 132.0	135.1 ± 68.5	
LDLC (mg/dL)	109.8 ± 26.9	122.4 ± 36.5	110.0 ± 24.5	
UA (mg/dL)	4.87 ± 0.98	5.22 ± 1.09	5.65 ± 1.27	[1]
Cr (mg/dL)	0.83 ± 0.23	0.77 ± 0.15	0.75 ± 0.16	
eGFR (mL/min)	76.7 ± 21.3	78.8 ± 17.7	83.1 ± 19.3	

Data is presented as mean ± SD, or %. [1]Mean statistical significance $P < 0.05$. GLP-1: Glucagon-like peptide-1; HbA1c: Hemoglobin A1c; eGFR: Epidermal growth factor receptor; FPG: Fasting plasma glucose; BMI: Body mass index; GTP: Guanosine triphosphate; HDLC: High density lipoprotein cholesterol; LDLC: Low density lipoprotein cholesterol; AST: Glutamic-oxalacetic transaminase; ALT: Alanine aminotransferase; TG: Thyroglobulin; Cr: Chromium.

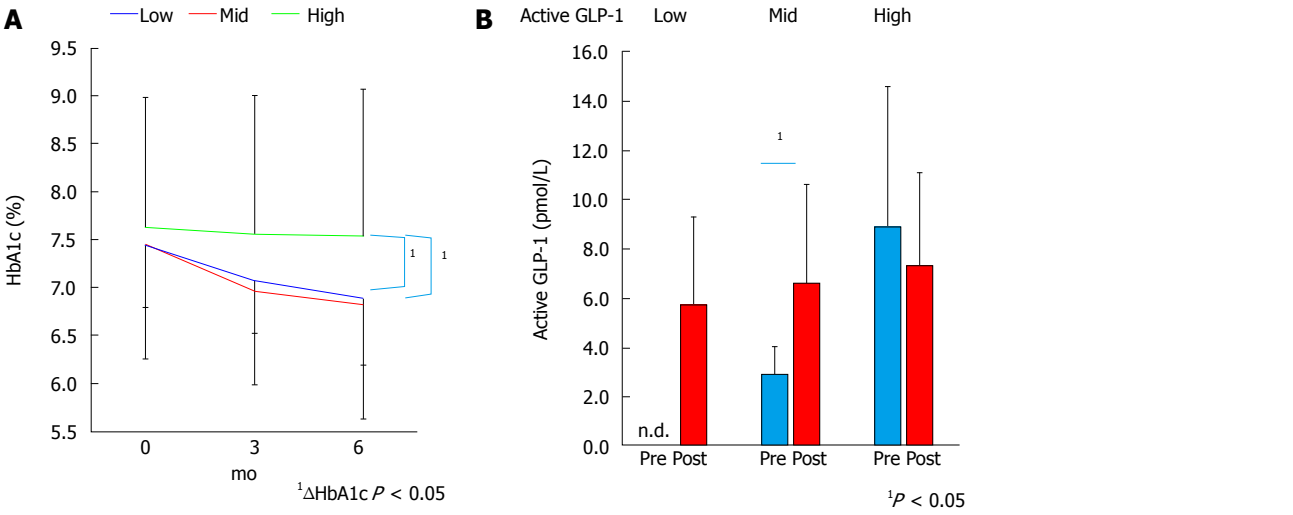

Figure 2 Hemoglobin A1c and active glucagon-like peptide-1 change by sitagliptin administration. A: Change of HbA1c by sitagliptin administration over six months, the data is presented in mean and S.D. [1]Statistical significance of change of HbA1c between the high active GLP-1 group and the low or middle groups; B: Active GLP-1 level before sitagliptin administration and after three months, stratified by plasma active GLP-1 level. Data is presented as the mean and S.D. [1]Mean statistical significance $P < 0.05$. GLP-1: Glucagon-like peptide-1; HbA1c: Hemoglobin A1c.

level. Insulin resistance is related to inflammation, and hsCRP reflects insulin resistance in some cases such as smokers or sufferers of polycystic ovarian syndrome[26,27], however, hsCRP at baseline is not related to active GLP-1 level.

The factors defining plasma active GLP-1 level have not been reported, but are easily speculated as the balance between GLP-1 secretion and inactivation/degradation by DPP-4. If DPP-4 activity is low in insulin sensitive, non-obese subjects, low active GLP-1 level is probably derived from low GLP-1 secretion. In contrast, insulin resistant patients indicated relatively high GLP-1 level in spite of presumably high DPP-4 activity[19]. Therefore, the reason the high baseline active GLP-1 group had the smallest response is probably due to the low contribution of the GLP-1 - DPP-4 system on their insufficient glycemic control or insulin action. The causes of this low contribution of GLP-1 - DPP-4 system should be focused on the fact that sitagliptin cannot raise GLP-1 level in the baseline high active GLP-1 group. One possible speculation is the insufficient inhibition of high DPP-4 activity by sitgliptin. In which

Table 2 Logistic regression analysis to identify the factors associated with the efficacy of sitgliptin (dA1c ⩾ 0.5%)

Variables	Univariate		Model 1		Model 2		Model 3		Model 4		Model 5	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
GLP-1 not high group	4.50 (1.40-17.6)	0.01	5.72 (1.64-25.99)	0.01	4.93 (1.07-32.96)	0.04	7.66 (1.48-57.48)	0.01	8.04 (1.30-75.83)	0.02	5.83 (1.12-45.6)	0.04
HbA1c (%)	1.81 (1.32-2.6)	0.001	1.69 (1.03-3.02)	0.04	2.30 (1.11-5.63)	0.02	2.23 (1.02-5.59)	0.05	2.63 (1.19-6.88)	0.02	2.51 (1.04-7.05)	0.04
FPG (mg/dL)	1.01 (1.00-1.02)	0.003										
Sex (male)	1.85 (0.73-4.65)	0.19			5.69 (0.73-57.54)	0.1	4.39 (0.51-47.1)	0.18	5.53 (0.46-92.72)	0.18	6.97 (0.78-90.5)	0.08
Age (yr)	1.00 (0.97-1.02)	0.77			0.98 (0.91-1.05)	0.53	0.96 (0.88-1.03)	0.26	0.99 (0.92-1.08)	0.89	0.97 (0.90-1.05)	0.48
Duration (yr)	1.03 (1.00-1.07)	0.09			1.01 (0.95-1.09)	0.73	1.01 (0.94-1.09)	0.77	1.03 (0.95-1.13)	0.44		0.67
BMI (kg/m^2)	0.92 (0.83-0.99)	0.05			0.70 (0.50-0.91)	0.003	0.64 (0.43-0.86)	0.001	0.63 (0.39-0.90)	0.01	0.66 (0.43-0.92)	0.01
Sulfonylurea (+)	1.25 (0.63-2.46)	0.53					1.15 (0.22-6.13)	0.87				
Biguanide (+)	2.83 (1.42-5.76)	0.003					0.18 (0.02-1.01)	0.05				
Plasma insulin (μU/mL)	0.9 (0.82-0.98)	0.01							1.25 (0.94-1.69]	0.12		
C peptide (ng/mL)	0.8 (0.55-1.11)	0.19										
PI/IRI	1.33 (0.78-2.6)	0.29							4.94 (0.54-99.3)	0.17		
Glcagon (pg/mL)	0.99 (0.97-1.00)	0.11							0.97 (0.18-4.63)	0.97		
Log (hsCRP) [log (mg/mL)]	1.03 (0.53-1.98)	0.92							0.98 (0.94-1.01)	0.21		
HOMA-β	0.97 (0.95-0.99)	0.01									1.02 (0.94-1.09)	0.67
HOMA-IR	0.83 (0.67-0.99)	0.004									0.98 (0.45-2.15)	0.96

GLP-1: Glucagon-like peptide-1; HbA1c: Hemoglobin A1c; FPG: Fasting plasma glucose; BMI: Body mass index; hsCRP: High sensitive C reactive protein; PI/IRI: Proinsulin/immunoreactivity insulin ratio.

case, GLP-1 overcomes or evades high DPP-4 activity in insulin resistant subject. Activity of plasma DPP-4 correlates with insulin resistance and predicts sitagliptin efficacy[19], however this was not measured. Another speculative cause is the unknown feedback regulation of active GLP-1 level other than DPP-4 activity, such as incretion from L cells. Injection of excessive GLP-1 can cause nausea or vomiting more frequently than administration of DPP-4 inhibitors[28]. Therefore there might be a physiological cap of GLP-1 level caused by unknown factors other than DPP-4, thus avoiding the imbalance of gastrointestinal homeostasis or other catastrophe.

Aside from the result of examination of multiple regression, it is clearly demonstrated that active GLP-1 is statistically independent of other factors, such as HbA1c, disease history, use of medications, the specific hormonal parameters for insulin, glucagon, low-grade inflammation, and HOMA indicators. Active GLP-1 level correlated with insulin resistance but predicts HbA1c improvement independently to insulin resistance. The high active GLP-1 and high DPP-4 activity from insulin resistance might have an additive effect on resistance to sitagliptin treatment.

In accordance with previous reports, our results show the significant predictive capabilities of HbA1c improvement due to sitagliptin treatment, such as high baseline HbA1c, and low BMI[17,18,29]. The positive relationship between baseline HbA1c and the magnitude of HbA1c change by glucose-lowering therapies was irrespective of class or mode of action of therapy category[30]. In addition to BMI, several negative predictive variables are shown; uric acid and high HOMA-IR are pathophysiologically derived from insulin resistance. Hyperinsulinemia and high HOMA-β are also speculated to be subsequent or a compensatory result of insulin resistance, and the use of biguanide is an arbitrary selection of medication for insulin resistant patients. Biguanide itself is reported to increase active GLP-1[31] and is effective[32] in combination with sitagliptin.

Other estimations for long term glycemic management were previously stated, by means of short-term response of change of C-peptide immunoreactivity index[33] or glycated HbA1c[34]. Our data indicated similar findings for insulin secretion and HbA1c change over

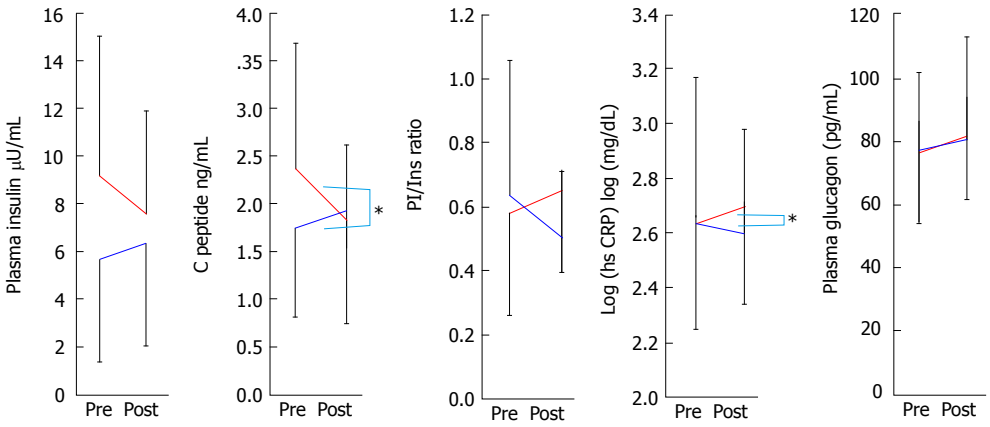

Figure 3 Change in insulin and glucagon secretion, high sensitive C reactive protein during three months of sitagliptin administration stratified against plasma active glucagon-like peptide-1 level at baseline. The data is presented as mean and S.D. *statistical significance of change of HbA1c between the high active GLP-1 group and the low or middle groups. GLP-1: Glucagon-like peptide-1; HbA1c: Hemoglobin A1c.

three months, and furthermore, the change in hsCRP is associated with baseline active GLP-level. It was already documented that a significant inverse correlation was found between changes in GLP-1 and changes in CRP levels[35]. Those predictors seem useful also when anticipating long term effects over a short period, although these changes cannot be predicted before administration. It was also demonstrated that compliance with diet/exercise therapy, weight gain[20], and increased polyunsaturated free fatty acid (eicosapentanoic acid and docosahexanoic acid) level from fish intake[36] predicted the efficacy of sitagliptin. The relevance of the predictors, such as compliance with diet/exercise therapy, weight gain and polyunsaturated fatty acid consumption, in relation to fasting active GLP-1 levels is not clear.

It was reported that GLP-1 levels decreased in Caucasian diabetes patients when compared to non-diabetic subjects[37], GLP-1 levels were much lower in Japanese patients who tend to have lower insulinogenic capabilities compared to Caucasians[38]. This low level of GLP-1 is a risk factor of diabetes onset[39]. Therefore, sitagliptin is probably adequate or effective for low GLP-1 patients and for lower insulinogenic ethnicities such as Japanese. However, our recent report shows young Japanese diabetics tend to be obese and might have higher insulin resistance than previous considered[23], these pathophysiological changes in Japanese patients might decrease the effectiveness of sitagliptin.

This study has several limitations. Firstly, one third of subjects exhibited levels below sensitivity parameters. When assay sensitivity has been improved, they might be further classified. Other limitations are the design, the study of an open-label, single arm trial and the somewhat small spectrum of subjects, and it being a single-ethnicity study, performed in a single health center. In addition, inactive GLP-1, postprandial GLP-1 and DPP-4 activity were not measured, which may have been helpful to resolve the remaining questions from the study.

As announced in TECOS trial[40,41] and in another cohort study[42], sitagliptin is safe in regards to the development of cardiovascular events, and is a useful agent that can significantly reduce HbA1c. However, sitagliptin does not greatly exceed traditional treatments with respect to this HbA1c lowering effect[40]. Thus it is important to avoid applying this treatment to subjects supposed to be non-responders. In spite of the limitations above, this examination was successful in determining whether a patient is to be given sitagliptin or not, using only a single collection of blood. Measuring active GLP-1 in fasting plasma can give another evaluation of the characteristics of patients with type 2 diabete, independent of insulin secretion and insulin resistance. For daily practical use, the examination costs were rather expensive and health insurance does not apply to this in Japan, and a standard test should be confirmed as a worldwide standard.

In conclusion, we discovered a new factor that predicts the efficiency of sitagliptin, fasting active GLP-1.

COMMENTS

Background

Glucagon-like peptide-1 (GLP-1) regulates glucose induced insulin secretion. Dipeptidyl peptidase-4 (DPP-4) inactivates the active form of GLP-1. Therefore DPP-4 inhibitors retard GLP-1 degradation, raise plasma active GLP-1, and stimulate glucose induced insulin secretion (GSIS). DPP-4 inhibitors are now widely used in the treatment of type 2 diabetes. Sitagliptin is one of the major selective DPP-4 inhibitors.

Research frontiers

Sitagliptin is the most frequently used DPP-4 inhibitor, however not enough is known about the predictors of this therapeutic response. Identifying the predictors would be valuable for its clinical use and help further speculation of the mechanism and pathophysiology of type 2 diabetes. The authors hypothesized that the plasma level of active GLP-1 could be associated with the efficacy of DPP-4 inhibitors in patients with type 2 diabetes.

Innovations and breakthroughs

The subjects in the high active GLP-1 group are characterized by insulin resistance. Those subjects are newly founded non-responders for sitagliptin treatment. The active GLP-1 level and insulin secretion of the subjects rose

only in low and middle active GLP-1 groups, while those in high group did not.

Applications

Sitagliptin is probably adequate or effective for low GLP-1 patients and for lower insulinogenic ethnicities such as Japanese. However, the recent report shows young Japanese diabetics tend to be obese and might have higher insulin resistance than previously considered, these pathophysiological changes in Japanese patients might decrease the effectiveness of sitagliptin.

Terminology

GLP-1, glucagon like peptide-1, is one of the major metabolic hormones, so called incretins. GLP-1 regulates glucose induced insulin secretion. The active form of GLP-1 (active GLP-1) is secreted from intestinal L cells, and DPP-4 cuts N-terminal two amino acids of active GLP-1 into its inactive form rapidly. DPP-4 inhibitors retard GLP-1 degradation, raise plasma active GLP-1, and stimulate GSIS. In patients with type 2 diabetes, the effects of incretins are impaired, especially postprandially, when biologically intact active GLP-1 level is low. DPP-4 inhibitors ameliorate active GLP-1 shortages, inhibit glucose spiking and help avoid hypoglycemia.

Peer-review

This was a well conducted study that has clinical implications. Overall, this study makes an important observation regarding the prediction of the efficacy of DPP-4 inhibitor-therapy based on a baseline clinical parameter.

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Blunting post-meal glucose surges in people with diabetes

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Abstract

Worldwide, the morbidity and mortality associated with non-communicable diseases have been climbing steadily - with costs aggressively keeping pace. This letter highlights a decidedly low-cost way to address the challenges posed by diabetes. High levels of postprandial blood glucose are disproportionately linked to much of the microvascular damage which, in the end, leads to macrovascular complications and organ failures. Systematically controlling post-meal glucose surges is a critical element of overall glycemic management in diabetes. Diet, exercise and medications form a triad of variables that individuals engaged in diabetes self-management may manipulate to achieve their targeted glucose levels. As a rule, diabetes patients in developing countries as well as those living in the pockets of poverty in the western world cannot afford special diets, medications, glucometers and supplies, lab tests and office visits. Exercise is the one option that is readily accessible to all. Decades of research in laboratory settings, viewed holistically, have established that light to moderate aerobic exercise for up to 60 min starting 30 min after the first bite into a meal can blunt the ensuing glucose surge effectively. Moderate resistance exercise, moderate endurance exercise or a combination of the two, practiced post-meal has also been found to improve many cardio-metabolic markers: Glucose, high density lipoprotein, triglycerides, and markers of oxidative stress. On the other hand, pre-breakfast exercise and high-intensity exercise in general have been decidedly counterproductive.

Key words: Pre-meal exercise; Post-meal exercise; Exercise timing; Exercise intensity; Glucose surge; Insulin resistance

Core tip: A critical part of diabetes self-management is the systematic blunting of the post-meal glucose surge. The reason for this is that the glucose surge is closely linked to the vascular complications of diabetes and eventual organ damage. Decades of studies have shown that a moderate intensity exercise - aerobic, resistance or combined - starting 30-40 min after the start of the meal can efficiently blunt the glucose peak. Post-meal studies starting at other times have also shown improvements in other metabolic markers including high density lipoprotein, triglycerides and markers of oxidative stress. Promoting post-meal exercise can make a big difference in the daily lives of diabetes patients worldwide.

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TO THE EDITOR

Non-communicable chronic diseases are costly[1]. The public at large foots a sizable chunk of the economic cost while patients are faced with the double whammy of compromised general health and sizable monitory costs. This note highlights a surprisingly low-cost way to address this problem worldwide.

Moderating post-meal glucose surges is a critical part of diabetes management because these surges are directly linked to the microvascular complications that in turn lead to organ damage and increased morbidity and mortality[2]. There are three well recognized approaches to managing post-meal glucose peaks: Diet, exercise and medications. Poverty, however, stands in the way of using food and medications properly to fight post-meal glucose surges. Physical activity is free for all.

People with insulin resistance have difficulty processing carbohydrates. The general recommendation for getting around this problem has been to rely on "appropriate" carbohydrate intake. American Diabetes Association (ADA) recommends individualized meal plans with the right carb count that would offer a postprandial glucose (ppg) value under 180 mg/dL (9.99 mmol/L)[3] with an expected HbA1c of 7.0%. American Association of Clinical Endocrinologists (AACE) is even more cautious: AACE recommends a ppg under 140 mg/dL (7.77 mmol/L) and an expected HbA1c of 6.5%[4]. Since glucose levels peak around 1 h after the start of meals[5] patients who have glucometers should be able to adjust the carb content of meals with the help of the 1-h glucose value following the major meal of the day. Balancing meals with protein, vegetables, fiber and healthy fat decreases the glycemic load of the meal and offers lower glucose peaks[6,7].

Studies featuring moderate exercise after meals consistently show glucose levels going down. It is possible to blunt the post-meal glucose surge substantially by starting the physical activity about 30 min post-meal and continuing it for up to 60 min[8-11]. This enables the body to use up the incoming glucose molecules to do the work involved in the activity - before they get to build up into a big peak. Insulin levels go up following meals, hepatic glucose production is suppressed and the meal-derived glucose gets used up preferentially as fuel[12]. Hypoglycemia is not of concern during this period[8]. Symptomatic exercise-induced hypoglycemia occurs rarely when the activity is performed during the late postprandial period, two hours or more after the meal[13]. Pre-meal exercise, on the other hand, increases postprandial glucose surges[9,14-17] although glucose is fairly steady for the duration of the pre-meal exercise itself[18-20]. The post-exercise glucose elevation is even more pronounced in the case of high-intensity exercise[21-24]. Pre-breakfast exercise is fueled mainly by hepatic glucose and at the end of the exercise bout the excess glucose arriving from the liver accumulates in the blood, resulting in a post-exercise glucose elevation[21-24]. If lowering the post-meal glucose peak is the goal, pre-meal exercise is the wrong thing to do. A brisk walk for 30 min after the start of every major meal is one option. If walking three times a day is too much, one may opt for one major meal, preferably breakfast, along with smaller meals the rest of the day.

Moderate resistance exercise for 45 min at 45 min post-meal also lowered glucose levels, partially blunting the glucose peak[25]. When post-meal resistance exercise was combined with endurance exercise, hyperglycemia was reduced for the subsequent 24 h by 39%[26]. Moderate post-meal exercise, resistance or aerobic or a combination, improved other metabolic markers also: lipids and markers of oxidative stress[25,27-30]. It looks like moderate resistance and aerobic activities decrease glucose levels directly during the exercise by increasing glucose transport out of the bloodstream. Moderate resistance exercise also improves insulin sensitivity for 24 h or more after the exercise bout.

Taken together, the available data point to 30 min post-meal as the optimal point to start the exercise activity. The mode of exercise can be resistance, aerobic or a combination at moderate intensity. The guidelines recommend resistance exercise 3 times a week[3,4]. There are also other health benefits -mainly physical fitness and body composition - to be had by doing resistance before endurance to minimize the interference effect[31]. The aerobic activity can include a brisk walk, treadmill, elliptical, rowing, stationary bike, dancing or swimming. Resistance exercise can be a 10 min workout using free weights involving major muscle groups. It is important to keep the intensity below 80% VO_{2max}. People under free living conditions have at least three ways to keep the right intensity. They may exercise at a pace that causes a slight shortness of breath. They may also keep HR_{max} at 60%-70%. The maximum heart rate, HR_{max}, is calculated as 220-age (For example, the HR_{max} for a 40-year-old is 180 beats/min; the corresponding pulse rate during the physical activity should be 104-126 beats/min). Those who have glucometers may also check glucose at the end of the workout and adjust the intensity accordingly for the next session.

When it comes to medications, various classes of drugs are available today specifically to manage post-meal glucose surges. These include glinides, short-acting insulins, gliptins, DPP-4 inhibitors and miglitol.

These three approaches to post-meal glucose control would work and complement one another nicely for people who have the resources to afford them. In developing countries and in the pockets of poverty in the Western world, high carb food is the norm. The vast

majority of these diabetes sufferers simply cannot afford the out-of-pocket expenses of office visits, lab tests, glucometers and medications. The one thing universally affordable for the rich and the poor alike is a timely moderate post-meal exercise. It is free, hypoglycemia is not an issue and the patient is in charge. Diabetes patients adopting this approach won't be violating any current guidelines, which encourage any-time exercise.

On the basis of elementary physiology and at least three decades of data, one initiative that could make a difference in the lives of current and future diabetes patients worldwide is to promote post-meal walks (or comparable physical activities) after the major meal of the day. The science is there. It is now up to the public and private agencies in the field and health care providers to make a concerted effort to promote timely post-meal exercise as a self-management tool for diabetes people with diabetes everywhere.

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