Predicting efficacy of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: Association of glycated hemoglobin reduction with serum eicosapentaenoic acid and docosahexaenoic acid levels

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ABSTRACT

This study was initiated to identify clinical and dietary parameters that predict efficacy of dipeptidyl peptidase-4 inhibitors. A total of 72 untreated Japanese patients with type 2 diabetes who received DPP-4 inhibitors (sitagliptin, alogliptin or vildagliptin) for 4 months were examined for changes of glycated hemoglobin (HbA_{1c}) and body mass index (BMI), and self-administered 3-day food records, as well as serum levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DPP-4 inhibitors significantly reduced HbA_{1c} (before initiation of DPP-4 inhibitors 7.2 ± 0.7%, 4 months after initiation of DPP-4 inhibitors 6.7 ± 0.6% [paired *t*-test, $P < 0.01$ vs before]). Multiple regression analysis showed that changes of HbA_{1c} were significantly correlated with baseline HbA_{1c}, as well as estimated intake of fish. Furthermore, changes of HbA_{1c} were significantly correlated with serum levels of EPA ($r = -0.624$, $P < 0.01$) and DHA ($r = -0.577$, $P < 0.01$). HbA_{1c} reduction by DPP-4 inhibitors is significantly correlated with estimated intake of fish and serum levels of EPA and DHA. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00214.x, 2012)

KEY WORDS: Dipeptidyl peptidase-4 inhibitor, n-3 Polyunsaturated fatty acid, Type 2 diabetes

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors improve glycemic control in patients with type 2 diabetes by preventing degradation of two incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), that are secreted from the intestine on ingestion of various nutrients[1,2]. Recent studies have shown associations of DPP-4 inhibitors' efficacy with age and fasting plasma glucose levels, as well as baseline glycated hemoglobin (HbA_{1c}) and body mass index (BMI)[3–5], but clinical parameters that predict the efficacy of DPP-4 inhibitors are largely unknown. The present study showed that alterations in HbA_{1c} level on administration of DPP-4 inhibitors as monotherapy are associated with estimated intake of fish, estimated intake of dietary n-3 polyunsaturated fatty acid (PUFA), and serum levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

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MATERIALS AND METHODS

The protocol was approved by the ethics committee of Kansai Electric Power Hospital, and carried out in accordance with the principles of the Declaration of Helsinki. A total of 72 untreated Japanese patients with type 2 diabetes (the Japan Diabetes Society criteria of 2010[6]; age 64.6 ± 11.3 years; duration of diabetes 9.0 ± 8.9 years; baseline HbA_{1c} 7.2 ± 0.7%; BMI 24.5 ± 4.3 kg/m^2) who had been on diet and exercise therapies participated in the current study. DPP-4 inhibitors (sitagliptin, alogliptin or vildagliptin) were given for 4 months and no other antidiabetic drugs were used during the period. A total of 59 patients received sitagliptin, 12 received alogliptin and one received vildagliptin. HbA_{1c} levels were determined before the initiation of DPP-4 inhibitors and 4 months after the initiation of DPP-4 inhibitors, and were shown in National Glycohemoglobin Standardization Program values, as recommended by the Japan Diabetes Society[6]. Fasting serum levels of DHA, EPA and arachidonic acid (AA) were determined based on fatty acid composition of total lipids including phospholipids, triglycerides and cholesteryl esters in the serum of 20 patients (age 63.1 ± 11.7 years; duration of diabetes 6.7 ± 5.7 years; baseline HbA_{1c} 7.0 ± 0.8%; BMI 24.2 ± 3.1 kg/m^2) before initiation of DPP-4 inhibitors.

Self-administered 3-day food records, which were recorded during the 4-month period, were analyzed for estimated intake of various nutrients using Healthy Maker Pro 501 (Mushroomsoft Co., Ltd., Okayama, Japan). All statistical calculations were carried out using PASW Statistics 18 (SAS Institute Inc., Cary, NC, USA), including linear regression analyses of the associations between changes in HbA_{1c} levels and various parameters. Multiple linear regression analyses were carried out to identify the parameters potentially associated with HbA_{1c} reduction, and simple regression analyses were carried out to evaluate their contributions. A *P*-value of <0.05 was taken to show significant difference. Values are shown as mean ± SD.

RESULTS

In the present study, DPP-4 inhibitors, similarly to previous reports[1], significantly reduced HbA_{1c} levels, but not bodyweight (before initiation of DPP-4 inhibitors 7.2 ± 0.7%; 4 months after initiation of DPP-4 inhibitors 6.7 ± 0.6% [paired *t*-test, $P < 0.01$ vs before]). Multiple regression analysis of HbA_{1c} reduction (ΔHbA_{1c}) taking into account sex, age, duration of diabetes, BMI, baseline HbA_{1c} and estimated intake of various food categories in 3-day food records showed that ΔHbA_{1c} was well correlated with baseline HbA_{1c}, but not with BMI (Table 1). ΔHbA_{1c} also showed a significant association with estimated intake of fish and seafood in the food records (Figure 1a and Table 1). Among fish and seafood, estimated intake of fish, but not shellfish and other seafood, showed a significant association with ΔHbA_{1c} (Table S1). The beneficial effects of fish on human health have been partly attributed to PUFA, such as EPA and DHA[7]. We therefore investigated the association of ΔHbA_{1c} with estimated intake of PUFA. ΔHbA_{1c} was significantly correlated with estimated intake of EPA and DHA, along with baseline HbA_{1c} (Figure 1b and Table S2). As serum EPA and DHA levels might serve as markers for intake of corresponding fatty acids[8] (Figure S1), we analyzed associations of ΔHbA_{1c} with serum EPA and DHA levels. Serum levels of EPA and DHA, but not n-6 PUFA arachidonic acid, were well correlated with ΔHbA_{1c} (Figure 1c). Although ΔHbA_{1c} reduction showed a significant association with estimated intake of milk products (Table 1), we were unable to find nutrients in milk products, including saturated fatty acids, that were responsible for the association.

DISCUSSION

We find that changes of HbA_{1c} levels on administration of DPP-4 inhibitors are associated with estimated intake of fish and estimated intake of dietary n-3 PUFA, as well as serum EPA and DHA levels. Despite being a retrospective cohort study with a limited sample size, these findings are clinically important in two respects: (i) the efficacy of DPP-4 inhibitors can

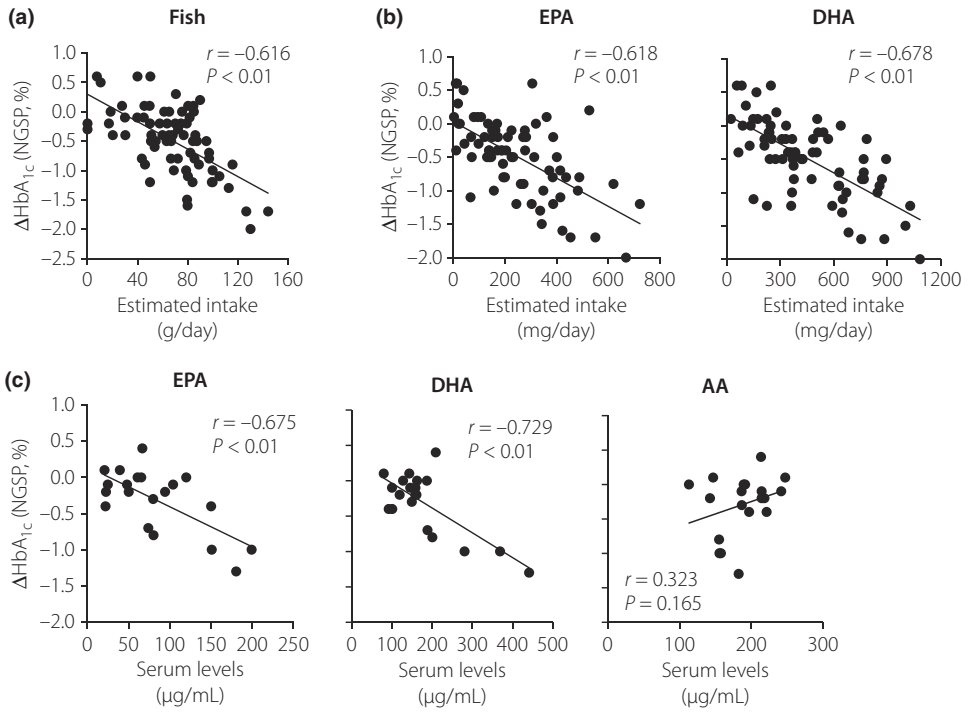

Figure 1 | (a) Correlation between estimated intake of fish and seafood with glycated hemoglobin (HbA_{1c}) reduction (National Glycohemoglobin Standardization Program [NGSP], %) 4 months after initiation of dipeptidyl peptidase-4 inhibitors (ΔHbA_{1c}; $n = 72$). (b) Correlation between estimated intake of eicosapentaenoic acid (EPA), docosahexaenoic (DHA) with ΔHbA_{1c} ($n = 72$). (c) Correlation between serum levels of EPA, DHA and arachidonic acid (AA) with ΔHbA_{1c} ($n = 20$). Linear regression analyses were carried out to calculate the correlation coefficient (*r*) and *P*-values.

Table 1 | Association of glycated hemoglobin reduction and estimated intake of various food categories

	B	SE	β	*P*
Sex	0.065	0.130	0.065	0.621
Age (years)	0.005	0.010	0.103	0.583
Duration of diabetes (years)	0.007	0.009	0.119	0.402
Baseline HbA_{1c} (NGSP)	−0.375	0.120	−0.451	0.005
BMI	0.013	0.018	0.100	0.474
Cereals	0.001	0.001	0.132	0.328
Potatoes and starchy flours	0.002	0.003	0.077	0.592
Sugar and sweeteners	0.013	0.016	0.109	0.414
Beans	0.002	0.001	0.262	0.075
Nuts and seeds	−0.010	0.025	−0.067	0.694
Vegetables	0.000	0.000	0.160	0.391
Fruits	0.000	0.001	0.014	0.940
Mushrooms	0.005	0.007	0.109	0.476
Seaweeds	−0.005	0.024	−0.031	0.842
Fish and seafood	−0.006	0.002	−0.475	0.003
Meats	−0.004	0.002	−0.297	0.077
Eggs	0.001	0.003	0.057	0.720
Milk products	−0.002	0.001	−0.343	0.042
Lipids	0.000	0.016	−0.002	0.990
Snacks	0.004	0.002	0.230	0.104
Beverages	0.000	0.000	−0.120	0.393

Multiple regression analysis regarding changes of glycated hemoglobin (HbA_{1c}) levels (ΔHbA_{1c}) by taking into account sex, age, duration of diabetes, body mass index (BMI), baseline HbA_{1c} (National Glycohemoglobin Standardization Program [NGSP]) and estimated intake of various food categories in 3-day food records in 72 patients with type 2 diabetes. Statistical calculation was carried out using PASW Statistics 18 (SAS Institute Inc.). B and β denote non-standardized and standardized regression coefficients, respectively. For analysis of changes of HbA_{1c} levels, the correlation coefficient squared (R^2) was 0.550 and the *F*-value with 15 degrees of freedom was 3.499 for a *P*-value of 0.003.

be predicted by serum EPA and DHA levels; and (ii) consuming more fish with diet therapy can enhance the efficacy of DPP-4 inhibitors. Furthermore, the current findings suggest that the differing efficacies of DPP-4 inhibitors found among different ethnicities[2] might be partly a result of differences in fish consumption.

Although many studies have shown the beneficial effects of dietary n-3 PUFA from fish[7], the mechanisms involving dietary n-3 PUFA in DPP-4 inhibitor efficacy have not yet been investigated. Although EPA and DHA have been shown to prevent excessive adiposity, thereby ameliorating insulin resistance in animal models, the effects of n-3 PUFA on glycemic control in type 2 diabetes itself are somewhat controversial[9]. Interestingly, it has been found that EPA and DHA enhance GLP-1 secretion, possibly through free fatty acid receptors, such as GPR120, in GLP-1-secreting cells and mice[10,11]. It is thus possible that dietary n-3 PUFA and DPP-4 inhibitors synergistically increase biologically-active GLP-1 levels to facilitate maintenance of glycemic control, but it remains to be determined whether EPA and DHA enhance GLP-1 secretion in patients with type 2 diabetes. In addition, whether the present findings hold true for DPP-4 inhibitors in general is not known, as most of the patients in the current study received sitagliptin or alogliptin, and vildagliptin patients were limited.

We find that the reduction of HbA_{1c} by DPP-4 inhibitors significantly correlates with estimated intake of fish, estimated intake of EPA and DHA, and serum levels of EPA and DHA.

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REFERENCES

1. Dicker D. DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors. *Diabetes Care* 2011; 34(Suppl 2): S276–S278.
2. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the Two Incretin Hormones: Similarities and Differences. *J Diabetes Invest* 2010; 1: 9–23.
3. Maeda H, Kubota A, Tanaka Y, *et al.* The safety, efficacy and predictors for HbA1c reduction of sitagliptin in the treatment of Japanese type 2 diabetes. *Diabetes Res Clin Pract* 2012; 95: e20–e22.
4. Monami M, Cremasco F, Lamanna C, *et al.* Predictors of response to dipeptidyl peptidase-4 inhibitors: evidence from randomized clinical trials. *Diabetes Metab Res Rev* 2011; 27: 362–372.
5. Nomiyama T, Akehi Y, Takenoshita H, *et al.* Contributing factors related to efficacy of the dipeptidyl peptidase-4 inhibitor sitagliptin in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract* 2012; 95: e27–e28.
6. Seino Y, Nanjo K, Tajima N, *et al.* Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. *J Diabetes Invest* 2010; 1: 212–228.
7. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA* 2006; 296: 1885–1899.
8. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. *Am J Clin Nutr* 2006; 83: 1467S–1476S.

9. Fedor D, Kelley DS. Prevention of insulin resistance by n-3 polyunsaturated fatty acids. *Curr Opin Clin Nutr Metab Care* 2009; 12: 138–146.
10. Hirasawa A, Tsumaya K, Awaji T, *et al*. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat Med* 2005; 11: 90–94.
11. Morishita M, Tanaka T, Shida T, *et al*. Usefulness of colon targeted DHA and EPA as novel diabetes medications that promote intrinsic GLP-1 secretion. *J Control Release* 2008; 132: 99–104.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Correlation between estimated intakes and serum concentrations of eicosapentaenoic acid (EPA) and docosahexaenoic (DHA; $n = 16$).

Table S1 | Association of glycated hemoglobin (HbA_{1c}) reduction and estimated intake of fish, shellfish and other seafood

Table S2 | Association of glycated hemoglobin (HbA_{1c}) reduction and estimated intake of polyunsaturated fatty acids

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