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Significant elevation of serum dipeptidyl peptidase-4 activity in young-adult type 1 diabetes

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ABSTRACT

Aims: Currently, inhibition of dipeptidyl peptidase-4 (DPP-4) is widely used in the treatment of type 2 diabetes. Application of this strategy is awaited as a new therapeutic approach for type 1 diabetes, but the scientific basis is still lacking. This report describes the evaluation of serum DPP-4 activity in type 1 diabetes compared with control subjects, and assessment of relationships between DPP-4 activity and diabetic complication markers and metabolic variables in type 1 diabetes.

Methods: We examined serum DPP-4 activity in Japanese young-adult type 1 diabetes ($n = 76$, females 69.7%, age 30.9 ± 6.2 years, duration of diabetes 16.5 ± 11.1 years; mean ± SD) and healthy controls ($n = 22$). Association of the enzymatic activity with diabetic micro- and macro- vascular complication markers and clinical parameters was also assessed.

Results: Subjects with type 1 diabetes displayed significantly higher serum DPP-4 activity than healthy controls (relative value, control: 1.00 ± 0.28, T1D, 1.29 ± 0.38; $p = 0.0011$) independent of other clinical parameters. In type 1 diabetes, DPP-4 activity was positively correlated with duration of diabetes ($r = 0.248$, $p = 0.031$), while not correlated with HbA1c level. In univariate correlation analysis of diabetic complication markers and other metabolic parameters, coefficient of variation of R-R intervals (CVR-R) and gamma (γ)-glutamyltransferase (GGT) levels were correlated with DPP-4 activity. GGT was extracted as an independent variable of DPP-4 activity in multivariate analysis ($\beta = 0.213$, $p = 0.035$).

Conclusions: Serum DPP-4 activity is significantly elevated in Japanese type 1 diabetes, suggesting pathophysiological significance of the enzyme in type 1 diabetes.

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1. Introduction

Dipeptidyl peptidase 4 (DPP-4), also known as CD26, is a multifunctional transmembrane glycoprotein and widely recognized as a critical player in glucose homeostasis [1]. DPP-4 is a serine protease enzyme that inactivates incretin hormones, glucagon-like peptide (GLP)-1, and glucose-dependent insulinotropic peptide (GIP). GLP-1 and GIP are secreted from intestine after ingestion of meals and exert pivotal functions on metabolic homeostasis through enhancement of glucose-dependent insulin secretion from pancreatic β-cells, suppression of excessive glucagon secretion from α-cells, and other various bioactivities. DPP-4 cleaves proline- or alanine-containing peptides, and therefore not only incretin hormones, but also quite a lot of other peptides, including stromal cell-derived factor 1 (SDF-1), substance P, and neuropeptide Y (NPY), are also known to be substrates of DPP-4 [1]. In addition to its peptidase activity, DPP-4 also binds to some proteins and is directly involved in various processes, including immune stimulation, binding to extracellular matrix, and lipid accumulation [2]. According to a report by Lamers et al., DPP-4 itself can function as an adipokine that impairs insulin sensitivity [3], suggesting its wide-ranged pleiotropic bioactivities and significance. DPP-4 is widely expressed on cell surface of many organs, and is also present in blood as a soluble form, thus it is possible to directly assess activity of the enzyme in serum or plasma samples, and also predict its systemic impact.

Given the significance of DPP-4 activity in the metabolic disorders, DPP-4 inhibitors such as sitagliptin, vildagliptin, and saxagliptin have been widely used in the treatment of type 2 diabetes, as this disease manifest relative insulin deficiency by insulin resistance and impaired insulin secretion together with deteriorated incretin effects. DPP-4 inhibitors exert blood glucose-lowering effect without inducing weight gain or increasing risk of hypoglycemia [4]. Furthermore, this class of agents is suggested to have other potential beneficial effects for diabetic microangiopathy independent of its effects on glycemia [5]. These clinical data indicate that therapies targeting DPP-4 are promising for a wide-range of patients with type 2 diabetes.

In type 1 diabetes which manifest absolute insulin deficiency, in contrast to type 2 diabetes, therapy is largely dependent on insulin supplementation. However, glycemic fragility is still a problem in the disease, in spite of recent advancement in insulin treatment regimen, and thus development of new therapeutic approaches is awaited. Considering its pivotal role in energy metabolism, DPP-4 inhibition is expected to be effective in type 1 diabetes. Indeed, a DPP-4 inhibitor is reported to improve glycemic control also in type 1 diabetes [6]. Looking ahead to establishment of DPP-4-targeting therapies in type 1 diabetes, scientific basis for its indication is required.

Several reports describe that serum DPP-4 activity is increased in type 2 diabetes [7,8], and this could be an explanation for the usefulness of the inhibitors. On the other hand, the role of DPP4 activity in type 1 diabetes is still unclear. Until now, to our knowledge, there have only been three reports that assessed the DPP-4 activity in type 1 diabetes, and those were based on small sample sizes. Two studies reported elevated DPP-4 activity in type 1 diabetes compared to healthy controls [9,10], whereas one reported no significant alteration [11], indicating the significance of the enzyme in type 1 diabetes is still not established. In addition, these reports did not investigate the correlation with diabetic complication markers or other biological variables, except only one report describing a relationship with diabetic retinopathy [12]. Also, a possible impact of DPP-4 activity on diabetic macrovascular complications is still unknown, and should be clarified also in type 1 diabetes. Thus, in this study, to establish the scientific basis for the future indication of DPP-4 inhibitors in type 1 diabetes, we conducted a cross-sectional study including (1) evaluation of serum DPP-4 activity in type 1 diabetes in comparison with healthy controls, and (2) assessment of possible relationships between DPP-4 activity and diabetic complication markers or metabolic variables in type 1 diabetes. Here we report that serum DPP-4 activity was significantly elevated in Japanese young-adult type 1 diabetes correlated with disease duration and liver function represented by γ-glutamyltransferase (GGT) level, thus suggesting its pathophysiological implication in type 1 diabetes.

2. Methods

2.1. Study population

Young Japanese type 1 diabetes patients who had undergone annual periodic examinations at Osaka University Medical Hospital or Osaka Police Hospital were recruited in the present study. All patients were diagnosed as type 1 diabetes by diabetes specialists at the time of presenting hyperglycemia and/or ketosis in their clinical history, and since that time all had been under treatment with insulin therapy. The patients with neoplasm, autoimmune diseases, and administration of oral anti-diabetic agents were excluded. In total, 76 type 1 diabetes patients were enrolled as subjects, and 22 healthy volunteers were also recruited as controls. The study was approved by the local ethics committee (Osaka University Hospital; 14001) and was conducted in accordance with the principles of the Helsinki Declaration. All participants provided written informed consent. All data and blood samples were collected in the study period between March 6, 2013 and July 30, 2014.

2.2. Clinical and biochemical assessment

The clinical assessments included a medical history interview, physical examination (height, weight and resting blood pressure), coefficient of variation of R-R intervals (CVR-R), carotid intima-media thickness, ankle-brachial index (ABI), pulse wave velocity (PWV), and eye fundus photography as previously reported [13,14]. Smoking status was classified as having a current smoking habit or not. Venous blood samples were taken, and the laboratory analyses were performed by SRL Inc. (Tokyo, Japan). Methods for biochemical analyses; aspartate transaminase (AST): malate dehydrogenase activity assay, alanine transaminase (ALT): lactate dehydrogenase activity assay, GGT: standard chromogenic assay using l-γ-glutamyl-3-carboxy-4-nitroanilide as substrate, glucose: