CASE REPORT

A case of glucocorticoid-induced diabetes in which the efficacy between sitagliptin and metformin was compared

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Abstract To date, promising strategies for treating glucocorticoid (GC)-induced diabetes with antidiabetic drugs have not been established. We herein report the case of a woman with GC-induced diabetes in which we compared the efficacy of two kinds of orally administered antidiabetic drugs sitagliptin and metformin by continuous glucose monitoring (CGM) and meal-challenge test (MCT). As a result, CGM showed that daily fluctuation of blood glucose levels was reduced during administration of metformin but not during administration of sitagliptin. On the other hand, MCT showed that administration of metformin reduced plasma glucose levels accompanied by the decrease of plasma insulin levels and the increase of plasma glucagon levels, whereas administration of sitagliptin had little effects on these parameters. This case is the first report to compare the efficacy between sitagliptin and metformin in glucose homeostasis by CGM and MCT in a patient with GC-induced diabetes.

Keywords Glucocorticoid · Diabetes · Sitagliptin · Metformin · Meal-challenge test

Introduction

At pharmacological concentrations, glucocorticoid (GC) has potent anti-inflammatory, antiallergic, and immunosuppressive effect. Therefore, GC, such as betamethasone, is frequently prescribed to treat a wide variety of diseases, including collagen, allergic, and autoimmune diseases. However, despite its efficacy, chronic use of GC causes many adverse effects, including increased susceptibility to infection, osteoporosis, psychological dysfunction, and metabolic disorders such as hyperglycemia and dyslipidemia [1]. Hyperglycemia occurs even in the absence of known type 2 diabetes mellitus [2]. Patients who received chronic GC treatment have an odds ratio (OR) of 1.36–2.31 for the development of new-onset diabetes [3–6]. The mechanisms responsible for diabetes after chronic GC treatment have been explained by reduced insulin sensitivity, increased hepatic gluconeogenesis, and impaired α - and β -cell functions [7, 8]. However, despite the high prevalence and known mechanisms of GC-induced diabetes, to date, promising strategies for treating GC-induced diabetes using antidiabetic drugs have not been established. We herein present a case of GC-induced diabetes in which we compared the efficacy of two kinds of orally administered antidiabetic drugs sitagliptin and metformin.

Case report

A 62-year-old woman with a family history of type 2 diabetes was referred to our hospital for the treatment of diabetes. She had a history of cholecystectomy for gall stone and colon resection for rectal cancer at the age of 42 and 52 years, respectively. At 55 years of age, she was diagnosed as hypertension and dyslipidemia at her annual

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checkup and started taking antihypertensive and antidyslipidemic drugs. At 58 years of age, she was diagnosed as having eosinophilic sinusitis and started taking Celestamine®, a combination tablet containing 0.25 mg of betamethasone. She had no diabetes before this treatment; indeed, 4 months earlier, her HbA1c level was 6.0 %. After treatment with betamethasone, however, it gradually elevated and reached 7.7 % before admission to our hospital.

On admission, she measured 157 cm in height, 68 kg in weight (body mass index 27.6 kg/m²), and 98 cm in waist circumference. Her body weight increased by 5 kg after treatment with betamethasone. Her blood pressure was 140/78 mmHg, and her heart rate was 72 beats/min under the administration of 5 mg/day of amlodipine and 40 mg/day of telmisartan. A physical examination showed a slightly cushingoid appearance, such as moon-shaped face and thin skin. The levels of fasting plasma glucose, immunoreactive insulin (IRI), C-peptide (CPR), HbA1c, and glycated albumin were 123 mg/dl, 13.4 µU/ml, 2.6 ng/ml, and 6.9 and 16.0 %, respectively. Her glutamic acid decarboxylase antibody level was <0.3 U/ml. Lipid profiles, such as low-density lipoprotein cholesterol (LDL-C), were well controlled under the treatment of 1 mg/day of pitavastatin. Results of other routine laboratory and urine findings were within normal ranges. Endocrine examinations showed that all levels of serum and urinary cortisol and serum adrenocorticotropin (ACTH) were less than lower limits due to treatment with betamethasone. Because of her clinical course, during which her diabetes occurred after treatment initiation with betamethasone, and because of the above laboratory findings, we diagnosed her diabetes as having GC-induced diabetes. Chest radiography and electrocardiography were normal. She had no obvious diabetic complications, except for carotid atherosclerosis. On the other hand, she had low bone mineral density (BMD) of the proximal femoral neck (*T* score −2.2) by dual-energy X-ray absorptiometry.

After admission, she was served an energy-control diet of 1520 kcal/day, and her glycemic control gradually improved without antidiabetic medication. However, although her preprandial blood glucose levels were well controlled, postprandial (2-h) levels, especially after lunch and supper, were not below 200 mg/dl. Therefore, after glycemic stabilization, we performed a glucagon stimulation test (GST) (intravenous injection of 1 mg glucagon) and a 75-g oral glucose tolerance test (OGTT) to evaluate her insulin secretory capacity and insulin resistance and select an appropriate type of antidiabetic drug. GST showed that C-peptide (6 min after glucagon stimulation) and delta C-peptide (0 → 6 min), markers for insulin secretory capacity, were 7.0 ng/ml and 3.9 ng/ml, respectively. On the other hand, OGTT showed that insulinogenic index, a

marker for early-phase insulin secretion, and homeostasis model assessment of insulin resistance (HOMA-R) and Matsuda index, markers for insulin resistance, were 0.25, 2.65, and 2.83, respectively. These results suggest that, although her insulin secretory capacity was preserved, she had slightly blunted early-phase insulin secretion and insulin resistance. Subsequently, we selected sitagliptin and metformin for treating her GC-induced diabetes and evaluated the efficacy of these two kinds of drugs using continuous glucose monitoring (CGM) and meal-challenge test (MCT). CGM was carried out on the day of MCT (Fig. 1). MCT was carried out after overnight fast using a standardized mixed meal (51 % carbohydrates, 34 % fat, 15 % protein, 460 kcal in total, consumed within 15 min) 30 min after administration of betamethasone (0.25 mg) (Fig. 2). Blood samples for determination of levels of plasma glucose, IRI, and immunoreactive glucagon (IRG) were obtained at −30, 0, 15, 30, 60, 90, 120, 180, and 240 min after meal ingestion. MCT was carried out three times: The first MCT was without an antidiabetic drug. The second and third MCTs were with sitagliptin (50 mg) and metformin (500 mg twice a day), respectively. As a result, CGM showed that daily fluctuation of blood glucose levels was reduced during administration of metformin but not during administration of sitagliptin (Fig. 1). On the other hand, MCT showed that administration of metformin reduced plasma glucose level, decreased IRI and HOMA-R (2.65 → 1.31), and increased IRG, whereas administration of sitagliptin had little effects on these parameters (Fig. 2).

Written informed consent was obtained from this patient after a full explanation of this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki, 1964, and later revision.

Discussion

In this report, we present a case of GC-induced diabetes in which the administration of metformin was effective in the control of hyperglycemia. To our best knowledge, this is the first report to compare the efficacy between sitagliptin and metformin in glucose homeostasis, including insulin and glucagon, by CGM and MCT in a patient with GC-induced diabetes.

GC-induced diabetes is a common adverse effect during chronic GC treatment. Although the exact prevalence of diabetes in patients who received chronic GC treatment is unknown, the OR for developing new-onset diabetes has been reported to be from 1.36 to 2.31 [3–6]. All these studies have shown that total GC dose and duration of treatment are strong risk factors for GC-induced diabetes.

Fig. 1 Continuous glucose monitoring (CGM) on the day of meal-challenge test (MCT) without antidiabetic drug (a), with sitagliptin (b), and with metformin (c)

In addition, it was shown that age and high BMI are risk factors for GC-induced diabetes [9]. In this case, although GC dose was not high (betamethasone 0.25 mg/day), our patient had lengthy GC treatment (>4 years), was of relatively high age (58 years), and had a high BMI (25.6 kg/m²) at the beginning of GC treatment. These findings suggest that she was a high-risk patient for GC-induced diabetes. In addition, because she had a family history of diabetes, genetic factors might also have contributed to the onset of her diabetes.

It is well known that the predominant mechanism responsible for GC-induced diabetes is explained by reduced peripheral insulin sensitivity [7, 8]. Pagano et al. [7] reported that administration of prednisolone for 7 days in healthy volunteers showed a 50 % reduction in insulin sensitivity by using the insulin clamp technique. In accordance with this finding, we confirmed that our patient had insulin resistance according to the HOMA-R and Matsuda index. It has been thought that GC-induced reduction in peripheral insulin sensitivity is mainly due to the impairment of insulin-mediated glucose uptake in skeletal muscle by directly interfering with insulin signaling. In addition, GC-induced skeletal muscle atrophy and proteolysis and

lipolysis resulting in elevated circulating amino acid and free fatty acid levels, also reduce insulin sensitivity in skeletal muscle. On the other hand, it has been shown that the increment in hepatic glucose production and impaired α - and β -cell functions are also responsible for GC-induced diabetes through several different mechanisms [8].

To date, promising strategies for treating GC-induced diabetes have not been established. Patients treated with GC often experience the failure of several organs, including liver, kidney, lung, and heart. In such a situation, various orally administered antidiabetic drugs are contraindication. In addition, the effects of GC have a great variability between patients. Therefore, although some limited studies have shown that thiazolidinediones and glucagon-like peptide 1 (GLP-1) receptor agonists are effective in GC-induced hyperglycemia and diabetes [10–13], there have been few studies to evaluate the efficacy of other oral antidiabetic drugs, including biguanide and dipeptidyl-peptidase-4 (DPP-4) inhibitors for GC-induced diabetes. It has been shown that insulin therapy alone is the most promising and flexible option for treating GC-induced diabetes. However, insulin therapy may be less acceptable for patients because of several negative factors, such as the

Fig. 2 Meal-challenge test (MCT) was carried out after overnight fast using a standardized mixed meal (51 % carbohydrates, 34 % fat, 15 % protein, 460 kcal in total, consumed within 15 min) 30 min after administration of betamethasone (0.25 mg) without antidiabetic drug (MCT1), with 50 mg of sitagliptin (MCT2), and with 500 mg of

metformin (MCT3). Plasma glucose, immunoreactive insulin (IRI), and immunoreactive glucagon (IRG) levels without antidiabetic drug (open circle), with 50 mg of sitagliptin (filled square), and with 500 mg of metformin (filled triangle) were measured at -30, 0, 15, 30, 60, 90, 120, 180, and 240 min after meal ingestion

problem of injection, weight gain, and high cost. Therefore, in clinical practice, all currently available oral anti-diabetic drugs are tried to the patients with GC-induced diabetes without therapeutic evidences [9, 14].

In our case, the patient had typical characteristics of GC-induced diabetes. This means that she had insulin resistance and slightly blunted early-phase insulin secretion, which resulted in postprandial hyperglycemia, especially after lunch and supper, but normal fasting plasma glucose levels. From the evidence of treatment for GC-induced diabetes, her above-mentioned clinical characteristics, comorbidities such as obesity and osteopenia, and past history of cholecystectomy and colon resection, we considered that a GLP-1 receptor agonist was a suitable drug for treating her GC-induced diabetes. However, she hesitated to receive GLP-1 receptor agonist because of an injection therapy. We therefore selected sitagliptin and metformin and compared the efficacy between these two drugs.

Sitagliptin is a potent and selective DPP-4 inhibitor and has frequently been prescribed for treating patients with type 2 diabetes. DPP-4 inhibitors lower blood glucose level by enhancing insulin secretion and inhibiting glucagon secretion in a glucose-dependent manner [15]. However, in

our case, treatment with sitagliptin had little effect on plasma insulin and glucagon levels during MCT and failed to ameliorate hyperglycemia. We considered a possible reason for this failure of efficacy: Dose and plasma GLP-1 activity of sitagliptin (50 mg) in this case were not enough to ameliorate hyperglycemia. It has been shown that GC reduces incretin effects of GLP-1 [16, 17]. Previous studies have shown that sitagliptin decreases fasting and postprandial plasma glucose levels in a dose-dependent manner [18, 19]. In addition, GLP-1 receptor agonists, having higher plasma-activated GLP-1 concentrations than those of DPP-4 inhibitors, ameliorate GC-induced hyperglycemia [12, 13]. Plasma-activated GLP-1 concentrations after administration of DPP-4 inhibitors including sitagliptin increase in a dose-dependent manner [20]. These findings suggest that dosage and plasma GLP-1 activity of sitagliptin in our case might not be enough to ameliorate hyperglycemia. In addition, future study is needed to confirm whether GC-induced hyperglycemia in our patient could be improved if she receives sitagliptin at a higher dose than that given during this study.

On the other hand, metformin was effective for treating her GC-induced diabetes. Metformin is the established

first-line therapy for type 2 diabetes and has a low risk of causing hypoglycemia. Metformin lowers blood glucose level by inhibiting hepatic glucose production and causing incremental peripheral glucose uptake by activating adenosine monophosphate (AMP)-activated protein kinase (AMPK) [21]. In addition, a more recent study by Miller et al. [22] showed that metformin suppresses hepatic glucagon signaling by decreasing production of cyclic AMP, independently of AMPK. Considering these functional mechanisms, metformin may be a suitable drug for controlling GC-induced diabetes. However, there are no published trials to estimate the therapeutic effects, because most patients treated with GC have conditions such as hypoxia and renal and liver insufficiency, which are contraindications to the use of metformin. However, in our case, the patient had no contraindicating factors to metformin administration. Instead, her GC-induced diabetes was characterized by postprandial hyperglycemia and insulin resistance, on which metformin likely exerts a potent effect. Indeed, her postprandial hyperglycemia and insulin resistance dramatically improved. In addition, and interestingly, her plasma glucagon level during MCT was increased in spite of the decreased plasma glucose level. These findings were consistent with result of previous studies [23], and we assume that such phenomena are due to the effects of suppression of hepatic glucagon signaling by metformin.

There are several limitations to this report. First, this was single case report comparing efficacy between sitagliptin and metformin in a single patient with GC-induced diabetes. Also, it was not a crossover design, and we thus cannot exclude the possibility that dietary therapy after hospitalization influenced the difference of efficacy between sitagliptin and metformin. Therefore, further study is necessary to conclude which of the two drugs are superior for treating GC-induced diabetes. Second, because this study evaluated very short-term effects of sitagliptin and metformin, long-term effects of these drugs on GC-induced diabetes are unknown.

Conclusion

We presented the first case of GC-induced diabetes comparing the efficacy between sitagliptin and metformin by CGM and MCT. Although both a DPP-4 inhibitor and metformin are often prescribed for treating patients with GC-induced diabetes and type 2 diabetes in clinical practice, there is no therapeutic evidence of the use of these drugs for treating GC-induced diabetes. Therefore, further prospective studies with large number of patients are needed to clarify whether DPP-4 inhibitor and metformin are effective for treating GC-induced diabetes.

Conflict of interests None.

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