OBSERVATIONS

Sitagliptin Successfully Ameliorates Glycemic Control in Werner Syndrome With Diabetes

Werner syndrome (WS) is an autosomal recessive disorder caused by a mutation in the *WRN* gene, and it is considered to be a representative type of progeroid syndrome (1). Patients with WS often exhibit insulin resistance, which is associated with the accumulation of visceral fat and disadipocytokinemia. We and others have previously reported that pioglitazone, a peroxisome proliferator–activated receptor γ ligand, improved glycemic control and insulin sensitivity with normalization of disadipocytokine levels in patients with WS (2,3).

Here we describe a diabetic subject with WS that had good glycemic control with pioglitazone initially but worsened because of abdominal obesity and increasing visceral fat area. Sitagliptin, an inhibitor of dipeptidyl peptidase-4, was then administered, which resulted in successful improvement of glycemic control.

A 58-year-old Japanese woman with WS was admitted to our hospital with poor glycemic control. At the first visit to our hospital at 46 years of age, she exhibited graying and loss of hair, short stature, a hoarse voice, refractory skin ulcers, bilateral juvenile cataracts, dyslipidemia, and diabetes. The diagnosis of WS was confirmed by genomic DNA analysis. At that time, her height was 1.46 m, weight was 36 kg, and BMI was 15.1 kg/m^2. Her visceral fat area was 111 cm^2 (normal range, $<$100 cm^2 for Japanese). She was prescribed 15 mg pioglitazone daily, which resulted in stable glycemic control. Her glycated hemoglobin (HbA_{1c}) level was maintained at ~6.9% for 12 years. However, she gradually gained weight and visceral fat area (191 cm^2), which worsened her glycemic control. At the present admission, continuous glucose monitoring system (CGMS) was performed, and postprandial hyperglycemia was observed. Therefore, a 50-mg daily dose of sitagliptin was added to the pioglitazone regimen. Her laboratory parameters before and after sitagliptin administration for 6 months were as follows: fasting glucose, 122 and 110 mg/dL; 2-h postprandial glucose, 162 and 129 mg/dL; fasting C-peptide, 2.81 and 3.32 mg/dL; 2-h postprandial C-peptide, 13.99 and 11.5 mg/dL; HbA_{1c}, 7.5 and 6.5%; and mean ± SD of glucose levels detected by CGMS, 163.2 ± 32.0 and 117.1 ± 20.6 mg/dL, respectively. CGMS confirmed that sitagliptin effectively suppressed postprandial hyperglycemia.

Although patients with WS are insulin resistant, it was suggested that only those who have impaired insulin secretion develop overt diabetes (4). We were unable to observe an improvement in 2-h postprandial C-peptide levels after sitagliptin administration; nevertheless, sitaglipitin may have improved early insulin secretion in response to meals. Furthermore, sitagliptin reportedly suppresses glucagon secretion. Because hyperglucagonemia has been observed in patients with WS (5), sitagliptin may ameliorate glycemic controls at least in part via correction of dysglucagonemia.

In conclusion, we demonstrated that a single dose of sitagliptin was well tolerated in a patient with WS and diabetes, resulting in a significant improvement in glycemic control. Sitagliptin may represent an alternative choice for treatment of diabetes in patients with WS. Further studies on the use of dipeptidyl peptidase-4 inhibitor in WS with diabetes will confirm our findings.

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References

1. Epstein CJ, Martin GM, Schultz AL, Motulsky AG. Werner's syndrome a review of its symptomatology, natural history, pathologic features, genetics and relationship to the natural aging process. Medicine (Baltimore) 1966;45:177–221
2. Yokote K, Hara K, Mori S, Kadowaki T, Saito Y, Goto M. Dysadipocytokinemia in Werner syndrome and its recovery by treatment with pioglitazone. Diabetes Care 2004;27:2562–2563
3. Hattori S, Kasai M, Namatame T, Hattori Y, Kasai K. Pioglitazone treatment of insulin resistance in a patient with Werner's syndrome. Diabetes Care 2004;27:3021–3022
4. Yamada K, Ikegami H, Yoneda H, Miki T, Ogihara T. All patients with Werner's syndrome are insulin resistant, but only those who also have impaired insulin secretion develop overt diabetes. Diabetes Care 1999;22:2094–2095
5. Brown DW. Werner syndrome and genetic obesity: speculation. Med Hypotheses 1995;45:91–93