Letter

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A case of mitochondrial diabetes mellitus with successful therapeutic response following the initiation of imeglimin

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SUMMARY: Mitochondria are present in cells throughout the body and play a crucial role in energy production. They contain their own DNA, and mutations in this DNA can lead to a reduction in pancreatic beta cells and decreased insulin secretion, contributing to the development of diabetes. Insulin therapy has been considered a rational treatment, as the primary issue is impaired insulin secretion, but it primarily serves as a coping mechanism. Recently, however, imeglimin – a drug believed to influence various mitochondria-mediated processes – has been introduced and is expected to offer therapeutic benefits for mitochondrial diabetes. Here, we report a case of successful glycemic control following the addition of imeglimin in a patient with mitochondrial diabetes mellitus. After starting imeglimin, the patient's blood glucose levels stabilized, and he continues treatment. While the molecular target of imeglimin remains unknown, it is possible that the drug may offer significant benefits for patients with mitochondrial diabetes mellitus.

Keywords: mitochondrial diabetes mellitus, imeglimin, intractable disease

Mitochondria are present in the cells throughout the body and play a crucial role in energy production, among other functions. Mitochondrial diseases refer to a group of disorders caused by mitochondrial dysfunction. In Japan, mitochondrial diseases are classified as designated intractable diseases. Mitochondria have their own DNA, mutations in this DNA can lead to a reduction in pancreatic beta cells and decreased insulin secretion, where they contribute to diabetes (*1*). Mitochondrial diabetes was first reported in 1992 as being associated with the 3243A>G mutation in the mitochondrial gene (*2*). Mitochondrial dysfunction reduces insulin sensitivity, and insulin resistance is thought to contribute to the impaired glucose tolerance observed in mitochondrial diabetes (*3,4*). Pathology is also associated with a high rate of sensorineural hearing loss and increases the risk of complications such as cardiomyopathy and encephalopathy, making early diagnosis and appropriate treatment crucial. Insulin therapy has been considered a reasonable treatment for the disease, as it primarily involves impaired insulin secretion; however, it serves only as a coping therapy. Recently, imeglimin, a drug that reduces the accumulation of dysfunctional mitochondria and may help maintain β-cell function and achieve effective glycemic control in type 2 diabetes, has been introduced (*5*) and is expected to offer therapeutic benefits for mitochondrial diabetes. In this study, we report a case of successful glycemic control in a patient with mitochondrial diabetes mellitus treated with imeglimin.

The patient in this case is a man in his 40s. In his 20s, the patient was diagnosed with diabetes and visited a nearby hospital. He was started on oral diabetes medications but discontinued them on his own without further follow-up. In his mid-30s, his health deteriorated, and he visited the nearby hospital again. At that time, his blood glucose was consistently over 450 mg/dL, and his HbA1c was 12.6%. At the first visit, the prescribed insulin degludec, glimepiride, anagliptin, voglibose, followed by observation. The patient was found to have no neuropathy or diabetic retinopathy and was monitored for approximately 6 months. A slight increase in HbA1c was observed; therefore, empagliflozin was introduced. While HbA1c stabilized, the patient began complaining of hearing loss. Genetic testing confirmed moderate sensorineural hearing loss and the 3243A>G mutation, diagnosing him with mitochondrial diabetes mellitus, which is classified as an intractable disease. A discrepancy between HbA1c and blood glucose levels was observed, prompting a detailed blood glucose evaluation using FreeStyle Libre Pro®. The results indicated that the falsely high HbA1c levels were due to diurnal variations in blood glucose. It was determined that blood glucose levels should be evaluated not only by HbA1c but also by glycoalbumin (GA). Considering the patient's medication adherence and other factors,

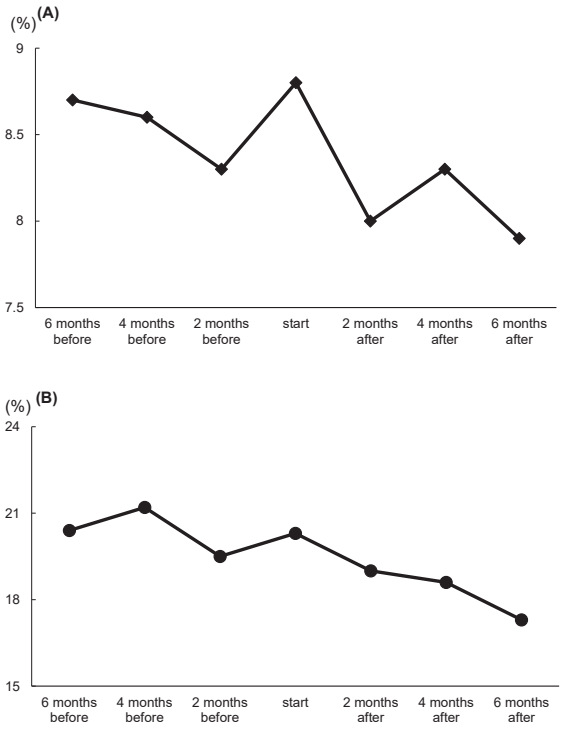

Figure 1. Blood glucose levels were assessed by (A) HbA1c and (B) GA. HbA1c, hemoglobinA1c; GA, glycoalbumin.

insulin degludec was adjusted to units, and sitagliptin, empagliflozin, mitiglinide, and voglibose were prescribed from 9 months prior to starting imeglimin. Despite these adjustments, the patient's blood glucose levels remained unstable and elevated. Therefore, imeglimin 2,000 mg/day was added to the regimen. Figure 1 shows the trends in HbA1c and GA from 6 months before to 6 months after starting imeglimin. Six months after starting imeglimin, HbA1c decreased from 8.8% to 7.9% and GA from 20.3% to 17.3%. Side effects, including nausea and abdominal discomfort, were noted but improved, and the prescription was continued. Consent for reporting was obtained from the patient.

This case involves a patient with mitochondrial diabetes mellitus who was started on imeglimin, resulting in stabilized blood glucose levels and a favorable therapeutic effect. Most patients require insulin therapy owing to a decrease in pancreatic beta cells and insulin secretion. Early initiation of intensive insulin therapy is important to reduce the burden on the remaining pancreatic beta cells. Mitochondrial dysfunction can also lead to lactic acid accumulation, increasing the risk of lactic acidosis. Therefore, strenuous exercise is restricted, and the use of biguanides is generally considered undesirable (*6*), making it challenging to address insulin resistance in mitochondrial diabetes.

Imeglimin is a hypoglycemic agent with both pancreatic and extrapancreatic roles. Although the molecular target of imeglimin is still unknown, various studies have been conducted on its expression. Imeglimin has been reported that enhancing mitochondrial function by increasing basic mitochondrial respiration (*7*). Furthermore, imeglimin may be beneficial for patients with mitochondrial diabetes because of its ability to reduce mitochondrial oxidative stress and increase ATP production (*8*). However, imeglimin is a new drug that was recently approved in 2021 (*7*), and this study did not evaluate the benefit of long-term continuous administration or improvement of symptoms, such as hearing loss, other than glycemic control. Therefore, further investigation is needed to evaluate the usefulness of imeglimin in mitochondrial diabetes mellitus. Finally, as the mechanism of action of imeglimin is still unknown and information about the drug is limited to the package insert and interview form, we hope that this case study provides valuable insights for future interventions by healthcare professionals treating patients with mitochondrial diabetes mellitus.

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References

1. Karaa A, Goldstein A. The spectrum of clinical presentation, diagnosis, and management of mitochondrial forms of diabetes. Pediatr Diabetes. 2015; 16:1-9.
2. van den Ouweland JM, Lemkes HH, Ruitenbeek W, Sandkuijl LA, de Vijlder MF, Struyvenberg PA, van de Kamp JJ, Maassen JA. Mutation in mitochondrial tRNA(Leu)(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. Nat Genet. 1992; 1:368-371.
3. Kanamori A, Tanaka K, Umezawa S, Matoba K, Fujita Y, Iizuka T, Yajima Y. Insulin resistance in mitochondrial gene mutation. Diabetes Care. 1994; 17:778-779.
4. Becker R, Laube H, Linn T, Damian MS. Insulin resistance in patients with the mitochondrial tRNA(Leu(UUR)) gene mutation at position 3243. Exp Clin Endocrinol Diabetes. 2002; 110:291-297.
5. Aoyagi K, Nishiwaki C, Nakamichi Y, Yamashita S, Kanki T, Ohara-Imaizumi M. Imeglimin mitigates the accumulation of dysfunctional mitochondria to restore insulin secretion and suppress apoptosis of pancreatic β-cells from db/db mice. Sci Rep. 2024; 14:6178.
6. Murphy R, Turnbull DM, Walker M, Hattersley AT. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD)

associated with the 3243A>G mitochondrial point mutation. Diabet Med. 2008; 25:383-399.
7. Nagamine J. Pharmacological profile and clinical efficacy of imeglimin hydrochloride (TWYMEEG® Tablets), the orally drug for type 2 diabetes mellitus with the first dual mode of action in the world. Folia Pharmacol. Jpn. 2023; 158:193-202 (in Japanese).
8. Hallakou-Bozec S, Vial G, Kergoat M, Fouqueray P, Bolze S, Borel A, Fontaine E, Moller DE. Mechanism of action of Imeglimin: A novel therapeutic agent for type 2 diabetes. Diabetes Obes Metab. 2021; 23:664-673.

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