

Abstract citation ID: bvac150.613

Diabetes & Glucose Metabolism
ODP158

***A Pilot Trial on the Efficacy of 5-Aminolevulinic Acid
on Glucose Tolerance in Patients with Maternally
Inherited Diabetes and Deafness***

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Objective: Maternally inherited diabetes and deafness (MIDD) is characterized by progressive insulin secretory disorder caused by impairment of mitochondrial adenosine triphosphate (ATP) production in pancreatic beta-cells. The amino acid 5-aminolevulinic acid (5-ALA) is the first heme biosynthetic precursor and the administration of 5-ALA combined with sodium ferrous citrate (SFC) enhance heme production, leading to improvement of mitochondrial function and ATP production. Several studies showed that the treatment with 5-ALA/SFC improved glycemic tolerance in both patients with prediabetes and those with type 2 diabetes. However, no previous studies investigated the efficacy of 5-ALA in patients with MIDD. We carried out the pilot trial to investigate whether the administration of 5-ALA/SFC can improve insulin secretion and glucose tolerance in patients with MIDD. **Methods:** We enrolled five patients with MIDD receiving multiple daily injections of insulin. The patients were administered 5-ALA/SFC 100 mg twice a day (200 mg per day) for 24 weeks as adjunctive to insulin treatment. The patients underwent a 75-g oral glucose tolerance test (OGTT) twice before (1 st -OGTT) and 24 weeks after the initiation of 5-ALA/SFC (2 nd -OGTT). We measured levels of plasma glucose, insulin, and glucagon at fasting (0 min), and 30, 60 and 120 min after glucose load (Study protocol: Nakamura Y et al. *Medicine (Baltimore)*. 2021; 100: e25100). **Results:** The mean levels of HbA1c tended to decrease from 8.3% to 7.9% ($p = 0.36$) even though total insulin doses had not changed during the 24 weeks of 5-ALA/SFC administration. In the 2nd -OGTT comparing to the 1 st -OGTT, four of the five patients showed a tendency of improvement in glucose levels with a certain degree of insulin increase, but one patient did not show any improvement. The means of area under the curve (AUC) of serum insulin from fasting to 120 min during 2nd -OGTT was 30% larger but not significant compared to that during 1st -OGTT ($p = 0.077$). The late phase of glucose excursion during OGTT determined by AUC of plasma glucose from 60 to 120 min during 2nd -OGTT showed 10% reduction compared to that during 1st -OGTT ($p = 0.041$). The glucagon levels during OGTT were comparable between before and after 5-ALA/SFC administration. The indexes of insulin sensitivity calculated by the homeostasis model assessment of insulin resistance or Matsuda index were not significantly changed between before and after 5-ALA/SFC administration. None of the patients experienced any adverse events during the study. **Conclusions:** The administration of 5-ALA/SFC as adjunctive to insulin therapy might be a novel effective treatment for MIDD that improves insulin secretion via amelioration of mitochondrial function.

Presentation: No date and time listed