Treatment response in the first Emirati patient with diabetes associated with the A3243G mitochondrial point mutation

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Background: Maternally Inherited Diabetes and Deafness (MIDD) is estimated as the cause of 1% of cases of diabetes. Due to the small patient population, it is not clear which diabetes treatments are most effective in MIDD.

Aims: We discuss the response to different classes of hypoglycaemic agents in the first Emirati patient reported with mitochondrial diabetes.

Method: A 23-year old male presented with hyperglycaemia and features atypical for Type 1 Diabetes including retinal changes at diagnosis. MIDD was confirmed by presence of an A to G point mutation in the *tRNALeu(UUR)* gene at base pair 3243 (A3243G) of the mitochondrial genome using targeted next generation sequencing. We report his management and his clinical features at 3.8 years of follow-up.

Results: At diagnosis, anti-GAD and anti-IA2 antibody titres were not elevated and insulin secretory reserve was maintained, with C-peptide of 0.631nmol/L and simultaneous plasma glucose of 11.6mmol/L. No objective hearing loss was detected at presentation. Microvascular disease was detected at 39 days after onset of diabetes with background retinopathy (R1) and maculopathy (M1), and elevated albumin-creatinine ratio (ACR) (3.7mg/mmoL, with subsequent microalbuminuria of 3.1, 4.1, 3.1, and 5.6mg/mmoL at 12, 14, 17, and 19 months, respectively). Pinhole visual acuity (VA) was 0.8 (left) and 0.7 (right). BMI, HbA1c, and triglycerides were 27.3kg/m2, 8.5%, and 1.34mmol/L, respectively. MIDD was confirmed by genetic analysis in the patient's mother, who had an established diagnosis of diabetes mellitus; his brother declined screening. He was initially managed with insulin and metformin (HbA1c from 8.5% to 6.9%). He was switched to sulphonylurea (gliclazide) after diagnosis of MIDD (HbA1c from 6.9% to 7.7%), with canagliflozin added at 12 weeks (HbA1c from 7.7% to 6.2%, subsequently to 9%) and sitagliptin combined at 48 weeks (HbA1c from 9% to 8.7%). Dulaglutide was added at 73 weeks, leading to a dramatic improvement in his HbA1c from 8.7% to 6.5% and BMI from 28.4 to 25.4kg/m2 within 4 months and cessation of insulin, canagliflozin and sulphonylurea treatment. Dulaglutide was discontinued due to intolerance with subsequent deterioration of glycaemic control (HbA1c 9.4%). At 3.8 years of follow-up, he progressed to pre-proliferative retinopathy (R2, M1); his ACR was 7.0mg/mmoL. Pinhole VA reduced to 0.4 (left) and 0.3 (right). He remained overweight (BMI, 27.6kg/m2). LDL was elevated at 3.5mmol/L, and triglycerides were 1.3mmol/L while taking atorvastatin 20mg.

Discussion: The use of glucagon-like peptide-1 (GLP-1) analogues in patients with MIDD has been shown to effectively improve HbA1c within 6 months in three recent case reports. In this case, a GLP-1 induced a dramatic improvement in HbA1c within 4 months with cessation of several concomitant medications, sustained until the GLP-1 was discontinued due to lack of tolerability, with subsequent deterioration in glycaemic control. Although a full case series is lacking, accumulating evidence from case reports suggests that GLP-1 treatment may be particularly effective in people with MIDD.