

# Effect of Coenzyme Q10 Treatment on Clinical Manifestations in a Young Woman with Mitochondrial Diabetes



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## Abstract

We report the case of a 25-year-old woman with mitochondrial diabetes mellitus (MDM). She was diagnosed with Wolff-Parkinson-White syndrome at 12 years old. She was later diagnosed as diabetes mellitus without autoimmune disorders at 15 years old, and the mitochondrial DNA 3243 mutation was detected by the gene analysis. Neurosensory deafness was identified at 16 years of age, and hypertrophic left ventricular cardiomyopathy was detected at 24 years of age. We started administration of coenzyme Q10 (CQ10), and subsequently her clinical symptoms and glycemic control were improved accompanied by decreasing blood lactate level. We assessed neurological signs of MDM using the Japanese Mitochondrial Disease Rating Scale (JMDRS). The JMDRS was improved from 12/80 points at the start of CQ10 to 5/80 points at 12-month period after starting CQ10. These findings suggest that CQ10 treatment could be effective on clinical symptoms, a lactate level and glycemic control in a patient with MDM.

**Keywords:** Mitochondrial Diabetes Mellitus; Glycemic Control; Endogenous Insulin Secretion; Neuromuscular Symptom; Coenzyme Q10

**Abbreviations:** BMI: Body Mass Index, CPR: C-Peptide Immunoreactivity, CQ10: Coenzyme Q10, FPG: Fasting Plasma Glucose, HbA1c: Hemoglobin A1c, JMDRS: Japanese Mitochondrial Disease Rating Scale, MODY: Maturity Onset Diabetes of the Young, MDM: Mitochondrial Diabetes Mellitus, WPW syndrome: Wolff Parkinson White Syndrome

## Introduction

Mitochondrial disease shows various clinical manifestations such as neuromuscular disorders, including muscle weakness, encephalopathy, mental disorder and neurosensory deafness, cardiomyopathy, short stature and diabetes mellitus. Of these disorders, diabetes mellitus is known as maternal inherited mitochondrial diabetes mellitus (MDM), which is identified in up to 1% of all patients with diabetes mellitus. The mitochondrial DNA 3243A>G mutation is most common genetic abnormality (80-90%), whereas other mutations, such as 8296A>G and 14577T>G, are less frequent [1]. Diabetes mellitus is the most common endocrine disorder in mitochondrial disease, because mitochondrial dysfunction greatly affects pancreatic  $\beta$ -cells, leading to insulin secretion defect [2]. Coenzyme Q10 (CQ10) is well known to act as an electron carrier of the respiratory chain in mitochondria and has been shown to improve the mutation-associated dysfunction of the respiratory chain in mitochondria. Various reports demonstrated that administration of CQ10 had some clinical benefits toward neuromuscular symptoms [3], elevated lactate levels [4], and

neurosensory deafness [5]. On the other hand, there were few reports showing improvement in glycemic control and endogenous insulin secretion when using CQ10 in patients with MDM [5,6]. We encountered a case of MDM with the mitochondrial DNA 3243A>G mutation, and hereby reported changes in glycemic control and other clinical manifestations after administration of CQ10.

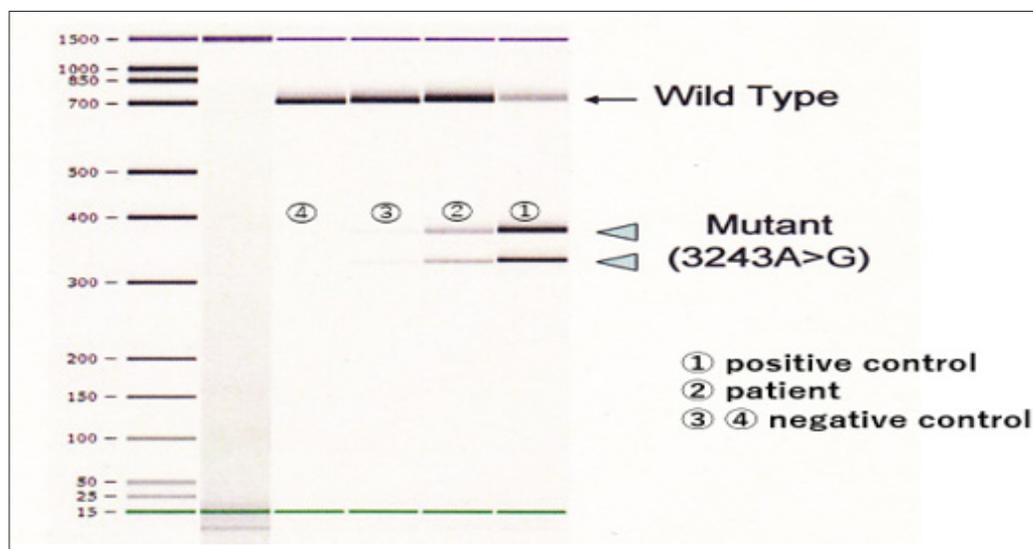
## Case Report

A 25-year-old woman presented to our hospital with leg numbness, malaise, headache and muscle weakness, which had existed for 1-month period. She was already diagnosed with MDM and treated with insulin. Her hemoglobin A1c (HbA1c) levels continued to be 8-9%, despite multiple daily injections of insulin. She was admitted to our hospital for examination of neuromuscular symptoms and improvement of glycemic control.

In the past history, her growth and psychomotor development were normal. She was diagnosed with Wolff-Parkinson-White (WPW) syndrome at 12 years of age. She was found to have

glucosuria through a urine glucose screening at schools at 15 years of age and identified as having diabetes in the detailed examination of the screening program. She was not obese with body mass index (BMI) of 18.8kg/m<sup>2</sup>,  $\beta$ -cell associated antibodies were all negative, and insulin secretion capacity was maintained at the time

of diagnosis. There were no neuromuscular symptoms, including muscle weakness, fatigue and impaired hearing, at that time. Subsequently, maturity-onset diabetes of the young (MODY) genes and mitochondrial DNA genes were analyzed, and the mitochondrial DNA 3243A>G mutation was detected (Figure 1).



**Figure 1:** Analysis of mitochondrial DNA 3243 mutations.

Neurosensory deafness was identified by an audiogram at 16 years of age, and hypertrophic left ventricular cardiomyopathy was detected at 24 years of age. Her 53-year-old mother and 24-year-old younger sister were also identified as the mitochondrial DNA 3243A>G mutation at the same time as this patient. Her mother already had diabetes mellitus, neurosensory deafness and Hashimoto disease. Her sister had no clinical symptom associated with the mitochondrial DNA mutation. Upon hospitalization, the patient's height, body weight, and BMI were 155.4cm (-1.6 SD), 44.5kg and 18.4kg/m<sup>2</sup>, respectively. There was neither muscle weakness nor muscle atrophy in the upper and lower extremities, and her sense of touch and pressure at the extremities was normal. The Achilles tendon reflex and peripheral sensation were diminished; bilateral pure tone was 40-50dB. Fasting plasma glucose (FPG) level was 181 mg/dL, HbA1c level 10.3%, Plasma C-peptide immunoreactivity (CPR) level 0.25ng/dL, and blood lactate level 28.8mg/dL. Electrocardiogram showed WPW syndrome. Computed tomography images showed no calcification, but mild atrophy of the whole brain and cerebellum was detected by magnetic resonance imaging. These findings suggested aggravation of glycemic control and decreasing insulin secretion possibly due to progression of mitochondrial dysfunction. We tried to use CQ10 of 30 mg concomitant with prosultiamine of 225mg, levocarnitine chloride of 300mg, and tocopherol acetate of 100mg daily aimed to rescue the mitochondrial dysfunction proposed by previous studies [3-6].

To evaluate clinical effect of CQ10 treatment on glycemic control and endogenous insulin secretion, we examined HbA1c and plasma CPR levels after administration of CQ 10. We conducted glucagon loading test (CPR levels at 3, 6, 9, and 15 minutes after administration of glucagon of 1mg) to evaluate furthermore endogenous insulin secretion. We also examined blood lactate levels and assessed neurological signs of MDM using the Japanese Mitochondrial Disease Rating Scale (JMDRS). The JMDRS was revised following the European Neuromuscular Center mitochondrial disease rating scale in 2003 [7-9]. The JMDRS is useful for evaluation of clinical symptoms of MDM and has enabled longitudinal analysis of disease progression. Figure 2 shows the clinical course after administration of CQ10. Self-monitored FPG and HbA1c levels were improved from 181mg/dL, 10.3% before using CQ10, 157mg/dL, 8.5% at 2-month period, 130mg/dL, 7.2% at 7-month period and 105mg/dL, 6.8% at 12-month period after using CQ10. Fasting CPR levels before and 2 months, 7 months and 12 months after using CQ10 were 0.21, 0.53, 0.68 and 0.70ng/mL, respectively. There was also improvement in plasma CPR reaction on glucagon loading test as shown in Figure 3. On the other hand, there was no increase in the daily insulin dose. Blood lactate levels decreased from 28.8mg/dL before using CQ10 to below 10 mg/dL during using CQ10. The JMDRS was 12/80 points at the start of CQ10, and decreased to 10/80 points at 2-month period, 9/80 points at 7-month period and 5/80 points at 12-month period after starting CQ10. There was no need to increase the insulin dose. There were no problematic adverse events during use of CQ10.

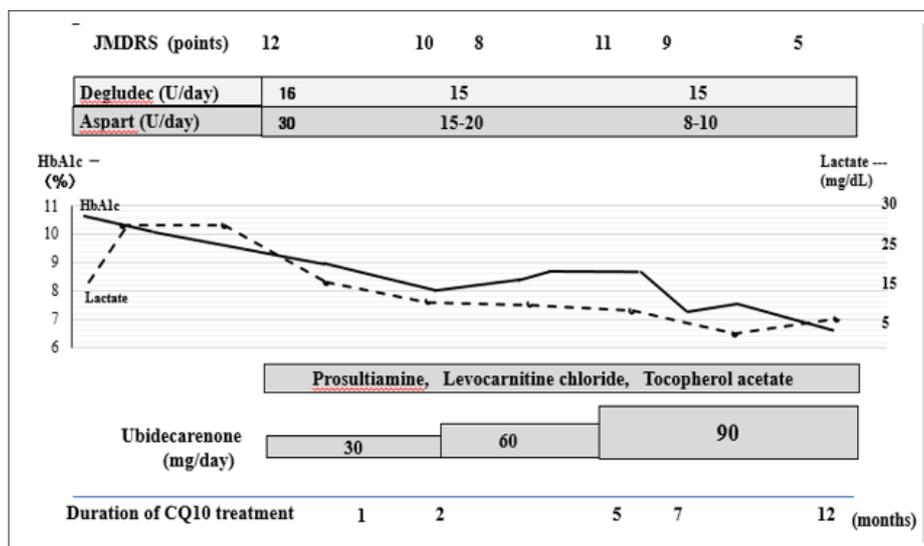


Figure 2: Clinical course of the patient with mitochondrial diabetes mellitus after using CQ10.

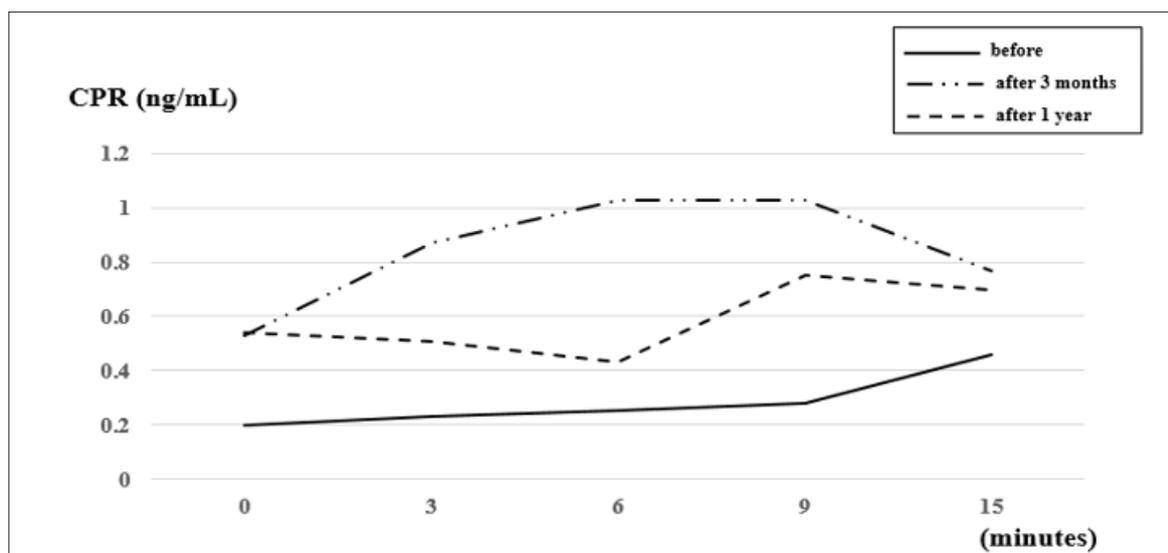


Figure 3: Changes in C-peptide (CPR) levels on glucagon loading test before and after using CQ10.

**Discussion**

CQ10 is an essential electron carrier in the mitochondrial respiratory chain. It acts as an electron carrier in the electron transport chain from complex I - II to complex II - III, and is present in all tissues and cells in the inner mitochondrial membrane [10]. CQ10 is also a lipid-soluble antioxidant and scavenges reactive oxygen species [11]. The mechanisms connecting mitochondrial DNA 3243 mutations and onset of diabetes are thought to be as follows:

- a) Accelerated production of reactive oxygen species and increased oxidative stress,
- b) Reduced oxidative phosphorylation and decreased ATP levels in pancreatic  $\beta$ -cells,

- c) Damaged signal transduction in pancreatic  $\beta$ -cells and reduction in their cell numbers due to apoptosis,
- d) Exhaustion of insulin secretion [12-14].

CQ10 plays a role in stopping step 1), thereby preventing progression to steps 2), 3), and 4). Accordingly, administration of CQ10 might prevent the advance to insulin exhaustion; improving insulin secretion and glycemic control. Richter et al. [15] reported that insulin secretory defects may result from anti-oxidation activities and dysfunction in the mitochondrial respiratory chain. Administration of CQ10 can stop the dysfunction of the mitochondrial respiratory chain and insulin secretion could be improved. The course of the patient described showed important clinical information of possibility of improvement in glycemic

control and endogenous insulin secretion as well as clinical symptoms and a blood lactate level with using CQ10 in MDM. There are some reports showing therapeutic effects on neuromuscular symptoms and a blood lactate level [3-6].

On the other hand, there were few reports showing improvement in glycemic control and endogenous insulin secretion when using CQ10 in patients with MDM [5,6]. Okazaki et al. [6] reported a large dose of CQ10 (60 mg/day) was effective to improve HbA1c levels from 8.5% to 7.5% and to increase glucagon loading CPR levels from 1.8 ng/dL to 2.0 ng/mL at the study of 2-year period. There were some other case reports demonstrating the efficacy of CQ10 on glycemic control for a short period less than 1 year [5,16,17]. Reported more increase in CRR response on glucagon loading test and urinary excretion of CPR among 28 patients with MDM compared with 16 patients without receiving CQ10 treatment for 3-year study period. As compared to the studies conducted by Okazaki et al. [5,6] our study period for 1 year is shorter, and it seems too early to judge the effect of CQ10 on glycemic control and endogenous insulin secretion. Longer-term follow-up should be necessary to evaluate the effect of CQ10 on diabetic control in our case. On the other hand, we started some medication, such as prosultiamine, levocarnitine chloride and tocopherol acetate, other than administration of CQ10. These drugs could play a role to improve mitochondrial function with increasing endogenous insulin secretion and reducing plasma glucose levels. In conclusion, we reported the clinical course with CQ10 treatment in the case of MDM presenting with mitochondrial DNA 3243A>G mutation. CQ10 treatment could be effective on clinical symptoms, a lactate level and glycemic control in a patient with MDM.

## Disclosure

We obtained consent to write this report from the patient, her younger sister, and mother. None of the authors have any potential conflicts of interests to this case report.

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