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Successful Glycemic Control Decreases the Elevated Serum FGF21 Level without Affecting Normal Serum GDF15 Levels in a Patient with Mitochondrial Diabetes

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Mitochondrial diabetes mellitus is a subtype of diabetes linked to mutations in mitochondrial DNA. In patients with mitochondrial diabetes mellitus, the effect of glycemic control on the serum concentrations of fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15) has not been evaluated. FGF21 and GDF15 have been reported to be useful biomarkers for the diagnosis and severity assessment of mitochondrial diseases like mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Recent studies have shown FGF21 acts in an endocrine fashion to regulate glucose and lipid metabolism in type 2 diabetes mellitus, while the exact biological functions of GDF15 remain unknown. Although mitochondrial diabetes mellitus is commonly found in cases with mitochondrial diseases, the comparison of FGF21 and GDF15 levels between those with and without diabetes has not been performed. Here, we report a 24-year-old woman with mitochondrial diabetes mellitus, who showed a high level of serum FGF21, but not serum GDF15, at diagnosis. In our case, liraglutide, a glucagon-like peptide-1 receptor agonist, added to insulin glargine was effective for her glycemic control and showed no adverse effects, including gastrointestinal symptoms and hypoglycemia, during a 14-week observation. The successful glycemic control caused a decrease in the FGF21 level, without affecting the GDF15 level. Thus, we should consider patients' glycemic control levels in using FGF21 values for the diagnosis of mitochondrial diseases. In addition, sustained GDF15 levels during glycemic treatment in our case suggest the usefulness of GDF15 as a marker for clinical severity of muscle-manifested mitochondrial diseases.

Keywords: biomarker; FGF21; GDF15; GLP-1 receptor agonist; mitochondrial diabetes mellitus
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Introduction

Mitochondrial diabetes mellitus is a subtype of diabetes linked to mutations in mitochondrial DNA. The mitochondrial DNA 3243(A-G) mutation is a major cause of mitochondrial diabetes and accounts for 0.5%-2.8% of the general diabetic population (Suzuki et al. 2003). Diabetic patients with this mutation can develop neuromuscular diseases such as mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) (Yatsuga et al. 2012). They show a reduction in insulin secretory ability and early requirement of insulin therapy (Suzuki et al. 2003, Murakami et al. 2016). Thus, insulin therapy is usually used for mitochondrial diabetes mellitus, whereas other diabetic therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists, have been rarely described (Suzuki et al. 2003).

Recently, serum fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15) have been reported to be useful biomarkers for diagnosis and severity assessment of mitochondrial diseases like MELAS (Liang et al. 2014; Yatsuga et al. 2015). FGF21 is a member of the FGF19 subfamily, which acts in an endocrine fashion to regulate glucose and lipid metabolism (Chavez et al. 2009). It is expressed predominantly in liver as well as in adipose tissue and pancreatic beta cells (Kurosu et al. 2007). GDF15, a member of the transforming growth factor beta superfamily, is expressed in almost all tissues, but its exact biological functions remain unknown (Yatsuga et al. 2015). A study demonstrated that the expression and secretion of GDF15 in the cells harboring a MELAS-causing mutation were increased treated with lactate (Fujita et al. 2015).

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These results suggest that GDF15 levels could reflect the disease severity in the MELAS patients.

Although mitochondrial diabetes mellitus is common in other muscle-manifested mitochondrial diseases such as MELAS (Yatsuga et al. 2012), it has not been evaluated whether diabetes mellitus can affect the serum concentrations of FGF21 and GDF15 in previous studies of these diseases (Liang et al. 2014; Yatsuga et al. 2015). Moreover, to the best of our knowledge, the level of FGF21 or GDF15 has been rarely evaluated in mitochondrial diabetes mellitus without evident neuromuscular signs. In addition, it has not been evaluated whether glycemic control levels can affect the serum concentrations of FGF21 and GDF15 in mitochondrial diabetes mellitus, although FGF21 has been recognized as a distinct endocrine factor of glycemic metabolism in type 2 diabetes mellitus (Chen et al. 2011; Iglesias et al. 2012).

Here, we report a case of mitochondrial diabetes mellitus without evident neuromuscular symptoms, which showed the distinct changes in FGF21 levels with maintained GDF15 levels during GLP-1 receptor agonist treatment.

Case Presentation

A 24-year-old woman was referred to our hospital for evaluation of hyperglycemia. She had developed deep vein thrombosis (DVT) and had been treated with edoxaban for 2 weeks. She had taken the pill and had a long flight before developing DVT. Following laboratory tests for DVT evaluation, hyperglycemia (serum glucose: 486 mg/dL; normal range, 60-110 mg/dL) was noted. She denied alcohol consumption and smoking. Her past history was unremarkable except for DVT. Her family history revealed that her brother had MELAS and had died at the age of 23, although her mother reported no significant symptoms. No other family members suffering from diabetes mellitus, deafness, or neuromuscular diseases were known. She was admitted for further workup.

On admission, the patient was alert and oriented. She was 150.1 cm tall and weighed 39.7 kg. Her body mass index was 17.6 kg/cm^2. Although she was mildly dehydrated, her general appearance was good, and physical examination revealed no other significant abnormalities such as obvious muscle weakness and atrophy, tendon reflex disorders, or vibration sensation. Her funduscopic finding was not significant. Laboratory test results are presented in Table 1. They revealed elevated levels of hemoglobin A1c (HbA1c) (14.0%; normal range, 4.7%-6.2%), glycoalbumin (GA) (41.3%; normal range, 11%-16%), fasting plasma glucose (277 mg/dL; normal range, 60-110 mg/dL), and serum C-peptide (0.8 ng/mL; normal range, 0.7-2.5 ng/mL). Daily urine C-peptide excretion was low (41 μg/day; normal range, 30-170 μg/day). The C-peptide levels were relatively low under the high glucose level. The testing for anti-glutamic acid decarboxylase (GAD), anti-insulinoma antigen 2 (IA2), and anti-insulin antibodies was negative. Although blood lactate and pyruvate concentrations were within normal ranges (blood lactate: 13.6 mg/dL, normal range: 3.0-17.0 mg/dL; blood pyruvate: 0.91 mg/dL, normal range: 0.30-0.94 mg/dL; blood lactate-to-pyruvate ratio: 14.9), those of cerebrospinal fluid (CSF) lactate and pyruvate were substantially higher (CSF lactate: 43.7 mg/dL, CSF pyruvate: 1.89 mg/dL, CSF lactate-to-pyruvate ratio: 23.1). Serum FGF21 and GDF15 levels were measured as previously reported (Yatsuga et al. 2015), with results of 421.6 pg/mL (normal range, 0-350.0 pg/mL) and 557.6 pg/mL (normal range, 0-710.0 pg/mL), respectively.

Along with the evaluations for diabetes mellitus, we started insulin intensive therapy and adjusted the insulin dosages. Her glycemic control was improved (pre-meal and bedtime daily average blood glucose level: 137.8 mg/dL) with the daily insulin regimen comprising insulin lispro (12 U before breakfast, 10 U before lunch, and 8 U before supper) and insulin glargin (12 U at bedtime) on the 9th day after admission. The total daily insulin units per kilogram of body weight were 1.06 U/kg. Although a glucagon stimulation test showed a persistent low response of serum C-peptide levels (serum C-peptide: baseline, 0.5 ng/mL and 6 min after glucagon infusion, 0.9 ng/mL; fasting serum glucose: 106 mg/dL), the patient and her family received information about the smaller number of daily injections and lower risk of hypoglycemia with GLP-1 receptor agonists, and enthusiastically requested their use. Thus, after consent was received, confirmation of no gastrointestinal manifestations and a normal result in an acetaminophen absorption test, liraglutide, a GLP-1 receptor agonist, was carefully administered instead of insulin lispro. No gastrointestinal symptoms developed, and hence, the dosage of liraglutide was gradually increased. Consequently, the regimen comprising liraglutide (0.6 mg before breakfast) and insulin glargine (14 U at bedtime) maintained her glycemic control (pre-meal and bedtime daily average blood glucose level: 147.0 mg/dL).

Based on the suspicion of mitochondrial disease as a result of her family history and early-onset diabetes mellitus without obesity, an A3243G mutation in the mitochondrial tRNA$^{Leu(UUR)}$ gene was evaluated in urinary epithelial cells as previously reported (McDonnell et al. 2004), after obtaining written informed consent from the patient. It revealed the presence of an A3243G mutation in 64% of the mitochondrial DNA. Thus, a diagnosis of mitochondrial diabetes mellitus was established.

Further evaluation of other possible affected organs was performed. The mini-mental state examination score was 30, and a Wechsler adult intelligence scale-third edition showed that her intelligence quotient score was 81. The results of auditory tests, brain magnetic resonance imaging, an electrocardiogram, and cardiac ultrasonography were not significant. For a functional test of skeletal muscles, the aerobic forearm exercise test with cycle ergometer (15W for 15 min) was performed. This showed only a mild increase in blood lactate levels from a baseline level of 23.8

Table 1. Laboratory results on admission.

Complete blood count		Reference ranges	FGF21 (pg/mL)	421.6	0-350.0
WBC (/μL)	5,950	3,500-9,400	GDF15 (pg/mL)	557.6	0-710.0
RBC ($\times 10^4/\mu$L)	475	420-570	**Plasma**		
Hb (g/dL)	14.0	13-17.5	HbA1c (%)	14.0	4.7-6.2
Hematocrit (%)	40.4	40-52	Fasting glucose (mg/dL)	277	60-110
Platelet ($\times 10^4/\mu$L)	34.1	15-35	2h post-prandial glucose (mg/dL)	596	
Blood chemistry			**Antibodies**		
CRP (mg/dL)	0.3	0-0.4	Anti-GAD (U/mL)	< 0.3	0-1.4
ALB (g/dL)	4.3	3.7-5.2	Anti-IA2 (U/mL)	< 0.4	0-0.39
T-bil (mg/dL)	0.7	0.2-1.0	Anti-insulin (U/mL)	< 0.4	0-0.3
AST (IU/L)	44	10-40	**Whole blood**		
ALT (IU/L)	33	4-44	Lactate (mg/dL)	13.6	3.0-17.0
CK (IU/L)	32	56-244	Pyruvate (mg/dL)	0.91	0.30-0.94
BUN (mg/dL)	13.8	8-22	**Cerebrospinal fluid**		
Creatinine (mg/dL)	0.53	0.61-1.04	Lactate (mg/dL)	43.7	3.0-17.0
Sodium (mEq/L)	131	135-147	Pyruvate (mg/dL)	1.89	0.30-0.94
Potassium (mEq/L)	4.6	3.5-5.0	**24-hour urine collection**		
Chloride (mEq/L)	94	98-110	Daily urine C-peptide excretion (μg/day)	41	30-170
Amylase (mg/dL)	111	40-115	**Urinalysis**		
TSH (μIU/mL)	0.60	0.541-4.261	Specific gravity	1.010	
Glycoalbumin (%)	41.3	11-16	pH	5.5	
Fasting Insulin (μIU/mL)	0.3	1.84-12.2	Protein	−	
Fasting C-peptide (ng/mL)	0.8	0.7-2.5	Ketones	+/−	
2h post-prandial C-peptide (ng/mL)	2.6				

WBC, white blood cell count; RBC, red blood cell count; ALB, serum albumin; T-bil, total bilirubin; AST, aspartate aminotranferase; ALT, alanine aminotranferase; CK, creatine kinase; BUN, blood urea nitrogen; TSH, thyroid stimulating hormone; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; HbA1c, hemoglobin A1c; anti-GAD, anti-glutamic acid decarboxylase antibody; Anti-IA2, anti-insulinoma antigen 2 antibody.

mg/dL to a peak level of 39.1 mg/dL 10 min after starting exercise, although muscle biopsy was not permitted. To score the severity of the disease, the total scores of section 1 and 2 of the Japanese mitochondrial disease rating scale (JMDRS) (Yatsuga et al. 2012) and the total scores of section I and II of the Newcastle Mitochondrial Disease Adult Scale (NMDAS) (Schaefer et al. 2006) were used. In our case, the former score was 0 and the latter was 5.

After discharge, she developed no signs of myopathy. Neither the JMDRS nor the NMDAS scores changed during the following 14 weeks. She continued the combination therapy at the same dosage of liraglutide and insulin glargine. Her HbA1c and GA levels were gradually improved to 6.4% and 14.1%, respectively, without adverse events 14 weeks after discharge. Laboratory tests (Table 2) also showed a fasting plasma glucose level of 100 mg/dL and serum C-peptide level of 1.0 ng/mL. A glucagon stimulation test showed an improved, but still low, response of serum C-peptide levels (serum C-peptide: baseline, 0.8 ng/mL and 6 min after glucagon infusion, 1.4 ng/mL; fasting serum glucose: 111 mg/dL). Blood lactate and pyruvate concentrations were 11.8 mg/dL and 1.01 mg/dL, respectively. Those of CSF lactate and pyruvate were decreased but still high (CSF lactate: 26.2 mg/dL; CSF pyruvate: 1.19 mg/dL). The serum FGF21 level was substantially decreased to 98.9 pg/mL, whereas the serum GDF15 level was relatively steady (403.9 pg/mL).

Discussion

We reported a patient with mitochondrial diabetes mellitus, who showed high serum FGF21, but normal serum GDF15, at diagnosis. Following improvement in her glycemic control, she had a decreased level of FGF21 and maintained her GDF15 level.

In our case, the high level of FGF21 on admission was over the diagnostic value of mitochondrial diseases (Yatsuga et al. 2015). However, her level of FGF21 after glycemic treatment was significantly decreased to the level under the threshold of a diagnosis of mitochondrial diseases according to a previous study (Yatsuga et al. 2015). As for the influence of glycemic treatment on FGF21 levels in type 2 diabetes patients, FGF21 levels decreased after starting glycemic therapies including insulin (Yang et al. 2011) or exenatide, a GLP-1 receptor agonist (Samson et al. 2011), although no similar studies in mitochondrial diabetes patients were reported. Therefore, the results of FGF21 in

Table 2. Laboratory results and clinical scales fourteen weeks after discharge.

	On admission	14 week	Reference ranges
HbA1c (%)	14.0	6.4	4.7-6.2
Glycoalbumin (%)	41.3	14.1	11-16
Fasting glucose (mg/dL)	277	100	60-110
Fasting C-peptide (ng/mL)	0.8	1.0	0.7-2.5
Fasting C-peptide index	< 0.01	1.0	
2h post-prandial glucose (mg/dL)	596	150	
2h post-prandial C-peptide (ng/mL)	2.6	3.2	
Glucagon stimulation test			
C-peptide 0 min (ng/mL)	0.5	0.8	
C-peptide 6 min (ng/mL)	0.9	1.4	
Blood lactate (mg/dL)	13.6	11.8	3.0-17.0
Blood pyruvate (mg/dL)	0.91	1.01	0.30-0.94
Blood L/P	14.9	11.7	
CSF lactate (mg/dL)	43.7	26.2	3.0-17.0
CSF pyruvate (mg/dL)	1.89	1.19	0.30-0.94
CSF L/P	23.1	22.0	
FGF21 (pg/mL)	421.6	98.9	0-350.0
GDF15 (pg/mL)	557.6	403.9	0-710.0
JMDRS	0	0	
NMDAS	5	5	

HbA1c, hemoglobin A1c; L/P, lactate to pyruvate ratio; CSF, cerebrospinal fluid; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; JMDRS, the total scores of section 1 and 2 of the Japanese mitochondrial disease rating scale; NMDAS, the total scores of section I and II of the Newcastle Mitochondrial Disease Adult Scale.

our case suggest that we should consider glycemic control levels in using FGF21 values for the diagnosis and evaluation of mitochondrial diseases.

Furthermore, the FGF21 concentrations in our case could be influenced by not only hyperglycemia itself but also mitochondrial dysfunctions due to hyperglycemia. Actually, blood and CSF lactate and pyruvate levels also changed following her glycemic control in our case (Table 2). Moreover, a study showed the significantly lower level of FGF21 in patients with type 1 diabetes, which was likely to show reduced insulin secretions and non-obesity, than ones with type 2 diabetes (Xiao et al. 2012). Taken together with reduced insulin secretions and without obesity in our case, the substantially high FGF21 concentrations on admission might come from hyperglycemia-induced mitochondrial dysfunctions.

In addition, the previous history of DVT and the anticoagulant use were less likely to affect FGF levels. The admission of our case was two weeks after edoxaban was started and DVT was in remission at that time. Moreover, edoxaban was continued during her observation period.

On the other hand, in our case, the levels of serum GDF15 were below the diagnostic value of mitochondrial diseases both on admission and under glycemic control (Yatsuga et al. 2015). This discrepancy between FGF21 and GDF15 alterations during glycemic treatment suggests the superiority of GDF15 as a marker for clinical severity of muscle-manifested mitochondrial diseases because our case presented with no evident neuromuscular signs and showed no changes in JMDRS and NMDAS during the 14-week clinical course. This is compatible with the previous observation about the comparison between FGF21 and GDF15 (Yatsuga et al. 2015).

The clinical usefulness of biomarkers like FGF21 and GDF15 has been rarely studied in mitochondrial diabetes without evident neuromuscular signs. A study suggested measuring FGF21 concentrations had little added value in monitoring and predicting the prognosis in carriers of A3243G mutation without evident neuromuscular signs (Koene et al. 2014). However, a prognostic biomarker for monitoring disease progression should be worth pursuing since some patients with mitochondrial diabetes mellitus develop MELAS (Murakami et al. 2016). Thus, further investigations should be needed for clinical biomarkers including FGF21 and GDF15 in mitochondrial diabetes without evident neuromuscular signs.

Finally, in our case, liraglutide added to insulin glargine seemed effective for glycemic control and showed no adverse effects, such as gastrointestinal symptoms and hypoglycemia, although the observation period was relatively short. Because there is a concern about gastrointestinal dysfunctions in the use of GLP-1 receptor agonists in mitochondrial diabetes patients (Sun et al. 2012), careful observation in our case is needed from now on, although we excluded clinical gastrointestinal dysfunction as much as possible before the introduction of liraglutide. Some

previous studies using model cells of mitochondrial diabetes mellitus have reported that GLP-1 and GLP-1 receptor agonists may possibly attenuate mitochondrial damage in pancreatic beta cells (Fan et al. 2010; Mukai et al. 2011; Ogata et al. 2014; Ciregia et al. 2015). Therefore, sustained glycemic control in our case may demonstrate the potential favorable effect of liraglutide on beta cells, although improved glycemic control because of intensive insulin therapy itself largely contributed to the recovery of beta cell functions and glycemic control. Some effects on glucagon secretion caused by liraglutide also could be considerable although plasma glucagon levels in our case were not examined regrettably. Moreover, careful observation of glycemic control and insulin secretion capacity should be offered in cases with GLP-1 receptor agonists like our case since we are afraid that the observation period of our case was relatively short and not enough.

In conclusion, we report a patient with mitochondrial diabetes mellitus without evident neuromuscular signs. The successful glycemic treatment with a GLP-1 receptor agonist caused a decrease in the FGF21 level, without affecting the GDF15 level. Thus, we should recognize the influence of glycemic control levels on FGF21 values in case of using FGF21 for the diagnosis of mitochondrial diseases as well as the possible superiority of GDF15 as a marker for clinical severity of muscle-manifested mitochondrial diseases.

Conflict of Interest

The authors declare no conflict of interest.

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