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Remission of Diabetes Mellitus in Two Patients with Maturity-Onset Diabetes of the Young After Bariatric Surgery

"Maturity-Onset Diabetes of the Young" Tanılı İki Hastada Bariyatrik Cerrahi Sonrasında Diabetes Mellitusun Remisyonu

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Abstract

We present two cases with "Maturity-onset diabetes of the young" (MODY) undergoing bariatric surgery. Case 1: a 19-year-old woman using intensive insulin for type 1 diabetes mellitus (DM) was diagnosed with obesity. Body mass index (BMI) was 39.17 kg/m^2, fasting blood glucose (FBG) was 199 mg/dL, postprandial blood glucose (PPBG) was 239 mg/dL, glycated hemoglobin (HbA1c) was 11.1%, C-peptide (Cp) was 1.53 ng/mL, and antiGAD and ICA (islet cell autoantibody) were negative. Genetic analysis revealed a heterozygous mutation in HNF1A (MODY 3). We performed Roux-n-Y gastric bypass (RYGB). She discontinued insulin. Case 2: A 33-year-old woman using intensive insulin because of type 2 DM was diagnosed with obesity. BMI was 44.4 kg/m^2. FBG was 195 mg/dL, PPBG was 269 mg/dL, HbA1c was 9.4%, Cp was 1.89 ng/mL, and ICA and AntiGAD were negative. Genetic analysis revealed heterozygous mutation in KCNJ11 (MODY 13). RYGB was performed with an indication of morbid obesity. She discontinued insulin. RYGB was performed first in our cases for MODY. Improvement in glycemic regulation was higher than expected. A decision on bariatric surgery in patients with MODY should be made on the basis of the degree of obesity and glycemic status.

Keywords: Maturity-onset diabetes of the young type 3; bariatric surgery; gastric bypass; diabetes mellitus

Özet

Bariyatrik cerrahi uygulanan "Maturity-onset diabetes of the young" (MODY) tanılı 2 olguyu sunuyoruz. Olgu 1: Tip 1 diabetes mellitus (DM) tanısıyla intensif insülin kullanan 19 yaşında kadın hastaya obezite tanısı koyuldu. Beden kitle indeksi (BKİ): 39,17 kg/m^2, açlık kan şekeri (AKŞ): 199 mg/dL, tokluk kan şekeri (TKŞ): 239 mg/dL, HbA1c: %11,1, C-peptid (Cp): 1,53 ng/mL, AntiGAD ve adacık hücre otoantikoru [islet cell autoantibody (ICA)] negatif saptandı. Genetik analizde HNF1A geninde heterozigot mutasyon saptandı (MODY 3). Roux-n-Y gastrik bypass (RYGB) uygulandı. Hasta insülin kullanımını bıraktı. Olgu 2: Tip 2 DM nedeniyle intensif insülin kullanan 33 yaşında kadın hastaya obezite tanısı koyuldu. BKİ: 44,4 kg/m^2, AKŞ: 195 mg/dL, TKŞ: 269 mg/dL, HbA1c: %9,4, Cp: 1,89 ng/mL, ICA ve AntiGAD negatif saptandı. Genetik analizde KCNJ11 geninde heterozigot mutasyon saptandı (MODY13). Morbid obezite endikasyonuyla RYGB uygulandı. Hasta insülin kullanımını bıraktı. Olgularımız, MODY'de RYGB uygulanan ilk olgulardır. Hastalarımızda glisemik regülasyondaki iyileşme beklediğimizden daha fazlaydı. MODY tanılı hastalarda, bariyatrik cerrahi kararı verilirken obezite derecesi ve glisemik durum birlikte değerlendirilmelidir.

Anahtar kelimeler: Maturity-onset diabetes of the young tip 3; bariyatrik cerahi; gastrik baypas; diabetes mellitus

Introduction

Bariatric surgery is indicated in patients with body mass index (BMI) of ≥40 kg/m^2 or in those with BMI of 35-40 kg/m^2 and type 2 diabetes mellitus (T2DM), severe joint disease, or obesity-related psychological problems (1). Autoantibody-positive diabetes is a contraindication for bariatric surgery. The effectiveness of bariatric surgery on glycemic regulation in patients with maturity-onset

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diabetes of the young (MODY) is unknown. MODY may be caused by mutations in one of the 14 genes, causing an insulin secretion defect (2, 3). In MODY, the insulin secretion defect is independent of autoantibody positivity. However, theoretically, one of the mutations in MODY-related genes may be present in a patient with type 1 diabetes mellitus (T1DM). Moreover, the insulin secretion defect in MODY is not caused by insulin resistance or pathogenetic mechanisms, which may be observed in T2DM. We may believe that bariatric surgery does not improve glycemic regulation in patients with MODY. However, if obesity and MODY are present simultaneously in a patient, bariatric surgery may be used for insulin resistance. By improving insulin resistance, bariatric surgery may have a potential role in treating hyperglycemia after surgery in patients with MODY and obesity. Therefore, the net effect of bariatric surgery on glycemic status in any type of MODY cannot be predicted. There is no report, guideline, or consensus about the applicability of bariatric surgery in patients with MODY.

We present two patients with MODY, one with MODY 3 and the other with MODY 13, and obesity who underwent bariatric surgery.

Case Report

Case 1

Informed consent was obtained from the patient. A 19-year-old woman was referred to our clinic with a complaint of obesity. She had obesity for 10 years. She did not use any antiobesity medication before. She made lifestyle changes such as physical exercise and dietary modifications several times. Her compliance was low for dietary changes. She did not lose weight consistently; lifestyle modifications failed each time. She had a diagnosis of DM such as T1DM and polycystic ovary syndrome (PCOS) for six years. Metformin was given in the first year. She had been taking insulin aspart 3 × 22 IU and detemir 1 × 40 IU subcutaneously for five years and oral contraceptive (drospirenone + ethinylestradiol) for the last year. Her mother had a history of T2DM. There was no paternal history of DM. No family history of DM was observed in her relatives, such as grandmothers or grandfathers.

The physical examination was unremarkable with the exception of obesity and hirsutism (body height: 164 cm, weight: 105 kg, BMI: 39.17 kg/m^2, Ferriman-Gallwey score: 21). Fasting blood glucose (FBG) was 199 mg/dL, postprandial blood glucose (PPBG) was 239 mg/dL, glycated hemoglobin (HbA1c) was 11.1%, fasting C-peptide (Cp) was 1.53 ng/mL, creatinine was 0.68 mg/dL, alanine transaminase was 14 U/L, Na was 140 mmol/L, K was 4.34 mmol/L, thyroid-stimulating hormone was 1.29 mIU/L, fT4 was 1.22 ng/dL, fT3 was 3.36 pg/mL, triglyceride was 90 mg/dL, total cholesterol was 200 mg/dL, low-density lipoprotein was 143.1 mg/dL, high-density lipoprotein was 38.9 mg/dL, 25 (OH)D3 was 5.06 ng/mL, and glucosuria was 4+. Ketonuria, AntiGAD, and ICA were negative (Table 1).

Diagnosis at a younger age, positive family history, adequate Cp, and negative autoantibodies increased the possibility of MODY diagnosis. The presence of obesity and

Table 1. Baseline laboratory findings of the cases.

Parameters	Case 1	Case 2	Normal range
Creatinine (mg/dL)	0.68	0.66	0.6-1.2
ALT (U/L)	14	37	10-40
Na (mmol/L)	140	139	138-142
K (mmol/L)	4.34	4.5	3.5-5
B12 (pg/mL)	245	363	180-800
Folate (ng/mL)	12.3	8.75	5-20
TSH (mIU/L)	1.29	2.26	0.5-4.5
fT4 (ng/dL)	1.22	1.18	0.8-1.6
Triglyceride (mg/dL)	90	173	50-150
Total cholesterol (mg/dL)	200	193	100-200
LDL (mg/dL)	143.1	121.6	<100 (in the patients with diabetes mellitus)
HDL (mg/dL)	38.9	36.8	40-60
25(OH)D3 (ng/mL)	5.06	13.8	40-60
WBC (/mm3)	11300	8440	4000-10000
Hb (g/dL)	14	12.6	12.5-16
Platelet (/mm3)	260000	320000	150000-450000
Glucosuria	4+	2+	Negative
Ketonuria	Negative	Negative	Negative

ALT: Alanine transaminase; TSH: Thyroid-stimulating hormone; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; WBC: White blood cell.

PCOS, history of metformin, and negative autoantibodies decreased the possibility of T1DM. Genetic analysis revealed a heterozygous mutation in HNF1A at c.942C>T (variant of unknown significance). MODY 3 was diagnosed. The patient wanted to undergo bariatric surgery. The patient had four points on an ABCD scoring system (age, BMI, Cp, and diabetes duration). Laparoscopic Roux-n-Y gastric bypass (RYGB) surgery was performed after discussion with the multidisciplinary obesity council. She lost 20 kg in three months and discontinued insulin, and metformin 2 × 1000 mg peroral and gliclazide 1 × 30 mg peroral were given after RYGB. HbA1c was 5.5% at the sixth month, and oral antidiabetic drugs were discontinued after the sixth month of surgery (Table 2).

Case 2

Informed consent was obtained from the patient.

A 33-year-old woman was referred to our clinic with a complaint of obesity. She had obesity for approximately five to six years. She made lifestyle changes such as physical exercise and dietary modifications several times. Her compliance was low for dietary changes. She used orlistat for a few months but discontinued it because of side effects. She did not lose weight consistently; lifestyle modifications failed each time. She had a history of T2DM for seven years. She was given metformin and glimepiride in the first month and then insulin therapy. She had been taking insulin aspart 3 × 12 IU and detemir 1 × 24 IU subcutaneously. Her mother had a history of T2DM. Her father did not have a history of DM. The family history of DM was negative in her relatives, such as grandmothers or grandfathers. The physical examination was unremarkable with the exception of obesity (body height: 158 cm, weight: 110.9 kg, BMI: 4^4.4 kg/m2). FBG was 195 mg/dL, PPBG was 269 mg/dL, HbA1c was 9.4%, Cp was 1.89 ng/mL, creatinine was 0.66 mg/dL, alanine transaminase was 37 U/L, Na was 139 mmol/L, K was 4.5 mmol/L, thyroid-stimulating hormone was 2.26 mIU/L, fT4 was 1.18 ng/dL, fT3 was 3 pg/mL, triglyceride was 173 mg/dL, total cholesterol was 193 mg/dL, low-density lipoprotein was 121.6 mg/dL, high-density lipoprotein was 36.8 mg/dL, 25(OH)D3 was 13.8 ng/mL, and glucosuria was 2+. Ketonuria, ICA, and Anti-GAD were negative (Table 1). Negative autoantibodies, diagnosis at a younger age, response to sulfonylurea, adequate Cp, positive family history increased the likelihood of MODY diagnosis, whereas obesity and requirement of intensive insulin decreased its likelihood.

We performed genetic analysis and found heterozygous missense mutation in KCNJ11 (c.527G>A) (variant of unknown significance). MODY 13 was diagnosed. The patient had five points on an ABCD scoring system. Laparoscopic RYGB surgery was decided by our council. The patient discontinued insulin and lost 21.8 kg in three months. No antidiabetic regimen was necessary, and HbA1c was 5.5% at the sixth month of surgery (Table 3).

Table 2. Clinical follow-up of Case 1 after laparoscopic Roux-n-Y gastric bypass surgery.

Parameters	Preoperative	1st month	3rd month	6th month	12th month
Case 1					
Weight (kg)	105	95	85	76	70
BMI (kg/m^2)	39.17	35.32	31.60	28.25	26.02
Treatment	Intensive insulin	Metformin+gliclazide	Metformin	Metformin	Nothing
Menstruation	Oligomenorrhea	Regular	Regular	Regular	Regular
Glucose (mg/dL)	199		87	94	
HbA1c (%)	11.1		6.2	5.5	
C peptide (ng/mL)	1.53		2.09		
Insulin (U/mL)			7.99		

BMI: Body mass index.

Table 3. Clinical follow-up of Case 2 after laparoscopic Roux-n-Y gastric bypass surgery.

Parameters	Preoperative	1st month	3rd month	6th month	12th month
Case 2					
Weight (kg)	110.9	100	89.1	74.7	65
BMI (kg/m^2)	44.4	40.05	35.69	29.92	26.03
Treatment	Intensive insulin	Nothing	Nothing	Olmesartan/hctz	Olmesartan/hctz
Glucose (mg/dL)	195	99	116	89	105
HbA1c (%)	9.4	7.4	6	5.5	5.5
C peptide					
(ng/mL)	1.89	2.14			
Insulin (U/mL)		20		6	12.9

BMI: Body mass index.

Discussion

To the best of our knowledge, RYGB was first performed in our cases for MODY. Our patients discontinued insulin postoperatively and had a great weight loss. After 12 months of surgery, they did not need any antidiabetic regimen.

In a case report, a boy with T1DM diagnosis was reported to be treated in the neonatal period (4). Then, KCNJ11 mutation was defined, and sulfonylurea was replaced with insulin treatment. The type of DM that was diagnosed previously was different from MODY in both cases. In the presence of appropriate clinical and laboratory features, MODY can be diagnosed in such patients even several years after the emergence of hyperglycemia. We should suspect MODY in patients with diabetes with a history of early-onset diabetes in adolescence/young adulthood (<35 years old), mild fasting hyperglycemia not requiring treatment, sensitivity to sulfonylurea, accompanying hepatic findings, renal anomalies, nondiabetic renal disease, nonhyperglycemic (<180 mg/dL) glucosuria, history of neonatal diabetes or neonatal hypoglycemia, or strong family history (≥2 generations), indicating autosomal dominant inheritance (5-8). If there is an atypical feature, such as lack of autoantibodies, prolonged "honeymoon period" (three to five years), and measurable C peptide (>0.6 ng/mL), in a patient with a known history of T1DM, we should investigate the presence of MODY. Moreover, if there is an atypical feature, such as a presentation at a younger age, lack of significant obesity, or insulin resistance stigmata, in a patient with a known history of T2DM, a possible diagnosis of MODY should be considered (9-11). As described in previous studies, diagnosis at a younger age, positive family history, adequate Cp, negative autoantibodies, and response to sulfonylurea reveal the possibility of MODY in our patients (9). Mutations in HNF1A or KCNJ11 genes cause an insulin secretion defect (2). HNF1A-related MODY is the most frequent subtype and characterized by decreased renal threshold for glucosuria and well-response to sulfonylurea (6). KCNJ11-related MODY is the least frequent subtype of MODY, causing dysfunction of ATP-sensitive K channel and thus responds well to sulfonylurea (2, 6). Our case 2 had a history of response to glimepiride in the first month of the diagnosis of diabetes. In addition, several single-nucleotide polymorphisms regarding KCNJ11 contributed to the development of DM (12).

Because of the long-term use of sulfonylurea or insulin, obesity may develop in HNF1A- or KCNJ11-related MODY. Glucagon-like peptide 1 receptor agonist may be the first choice for patients with MODY 3 (13, 14). Bariatric surgery may be an option for these patients; however, no report, consensus, or guideline exists on its usage in treating MODY. On the basis of the clinical background and patient's willingness, we selected RYGB for our patients. RYGB is a procedure that causes malabsorption and restriction and provides high metabolic improvement (15-17).

The American Diabetes Association workgroup suggested some definitions such as

partial remission (HbA1c<6.5% and FBG: 100-125 mg/dL) and complete remission (HbA1c<6.5% and FBG<100 mg/dL) of DM to be maintained for at least one year without the need of antidiabetic medication after bariatric surgery (18). In a meta-analysis, including seven randomized controlled trials investigating the efficacy of RYGB, partial remission for two years was observed in 42%-75% of the patients, and in 31%-42% of the patients, remission was prolonged up to five years (19). In the meta-analysis, complete remission rates were lower and found to be 25%-60% for one to two years after RYGB. No report exists regarding the glycemic efficacy of RYGB in patients with MODY. Therefore, it is uncertain to expect these criteria to be appropriate in patients with MODY after bariatric surgery. Bariatric surgery cannot correct a beta-cell secretion defect that occurred by a mutation in HNF1A or KCNJ11; therefore, RYGB cannot correct the main pathophysiology of hyperglycemia in patients with MODY. By causing weight loss, RYGB may correct "insulin resistance component." Therefore, improvement in glycemic regulation was much higher than we expected in our patients. No antidiabetic regimen was necessary after surgery in the second patient and in the first patient after a few months of surgery.

Therefore, when deciding on bariatric surgery in a patient with MODY type 3 or 13, degree of obesity, glycemic status, normal levels of C peptide, negative autoantibody status, and patient preference should be considered. The type of bariatric surgery should be decided by a multidisciplinary council. If bariatric surgery is selected, RYGB seems to be the most appropriate procedure because of higher metabolic efficacy. Our cases discontinued insulin postoperatively, and after six months of surgery, no antidiabetic medication was prescribed in both cases. However, glycemic regulation should not be the only indication for patients with MODY.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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