Role of Noninsulin Therapies Alone or in Combination in Chromosome 6q24-Related Transient Neonatal Diabetes: Sulfonylurea Improves but Does Not Always Normalize Insulin Secretion

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Chromosome 6q24-related transient neonatal diabetes (6q24-TND) is a rare form of diabetes caused by an overexpression of *PLAGL1* and *HYMAI* (1). After remitting in infancy, diabetes recurs in most patients later in life. While the best treatment remains unknown, many patients are managed with insulin (1). We sought to characterize β-cell function and glucose homeostasis in patients with 6q24-TND and assess their response to sulfonylurea (SU) therapy.

Adults with 6q24-TND and recurrence of hyperglycemia requiring insulin therapy later in life were identified through The University of Chicago Monogenic Diabetes Registry (http://monogenicdiabetes.uchicago.edu/registry) and invited to participate in a trial of SU therapy. Four patients with insulin doses of 0.41–0.76 units/kg/day attempted the trial. Three were available for a mixed-meal test (MMT) and arginine stimulation test (AST) on day one and day five of SU treatment. All insulin products were withheld on the morning of day one. Subjects ingested 7 mL/kg (maximal 360 mL) of BOOST High Protein (http://www.boost.com) within 5 min. Glucose and C-peptide were obtained at 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, and 180 min. At 185 min, 5 g of arginine hydrochloride was infused over 30 s, with samples collected at 184, 187, 188, 189, 190, 192, and 195 min. Glyburide was then initiated and increased daily, while insulin was steadily withdrawn as tolerated to maintain euglycemia using a modified published protocol used for those with mutations affecting the ATP-sensitive potassium channel (2).

Subjects were discharged on glyburide monotherapy with supplemental insulin only if required. Additional oral agents were subsequently added if needed to achieve complete insulin independence. Repeated-measures ANOVA was used to identify differences in metabolic variables between treatment conditions. When comparing MMT and AST before SU with those after a 5-day course of SU, there was no difference in the serum glucose, but C-peptide values were significantly higher in subjects following a course of SU ($P < 0.05$) (Table 1).

All four subjects remained on SU and off insulin therapy with good glycemic control at reevaluation at least 5 months after transition. One subject also required metformin, while two subjects required a combination of metformin and sitagliptin (Table 1).

SU therapy has been used safely and effectively in other forms of diabetes for decades (e.g., type 2, *KCNJ11*, and *HNF1A* diabetes). SU therapy in type 2 diabetes has raised concerns in terms of hastening of β-cell failure (3); however, our data and other reports (4,5) would suggest that insulin therapy may not be required for many years after relapse of diabetes in these patients. We, for the first time, demonstrate that insulin secretion in subjects with 6q24-TND improves in response to SU and provide further evidence that noninsulin-based therapies should be considered for the treatment of 6q24-TND.

Any history of neonatal hyperglycemia is important to note when assessing patients with diabetes as it may suggest an underlying genetic cause and can have a significant impact on clinical management and therapeutic strategies.

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Table 1—Subjects' clinical details

	UC90A	UC153A	UC277A	UC702A
Genetic defect	UPD6	UPD6	UPD6	UPD6
Sex	Female	Male	Female	Female
Gestational age (weeks)	33	34	40	38
Birth weight (g)	1,280	2,470	2,240	1,810
Age at initial diabetes diagnosis (days)	1	1	1	1
Age at diabetes remission (months)	4	7	6	3
Age at diabetes recurrence (years)	13	12	27	12
Age at cessation of insulin (years)	20	23	29	28
BMI at cessation of insulin (kg/m^2)	26.28	31.38	21.66	29.44
Insulin dose at transition (units/kg)	0.59	0.73	0.41	0.76
MMT C-peptide AUC (nmol/L)				
Day 1	83.1	87.9	188.5	—
Day 5	128.9	141.6	307.4	—
AST C-peptide AUC (nmol/L)				
Day 1	8.1	6.1	12.2	—
Day 5	9.6	9.8	23.4	—
Medications at reassessment				
Glyburide (mg/kg)	0.59	0.53	0.13	0.23
Sitagliptin (mg)	100	100	—	—
Metformin (g)	2	2	—	1.5
HbA_{1c} at cessation of insulin (%)	8.2	7.8	7.2	9.9
HbA_{1c} at reassessment (%)	7.1	6.6	7.3	7.5
Months off insulin therapy	5	8	17	6

AUC, area under the curve (calculated by trapezoidal rule); UPD6, uniparental disomy of chromosome 6.

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