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LETTER TO THE EDITOR

Reductions in A1C with Pump Therapy in Type 2 Diabetes Are Independent of C-Peptide and Anti-Glutamic Acid Decarboxylase Antibody Concentrations

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Dear Editor:

INSULIN THERAPY IS OFTEN necessary for patients with type 2 diabetes mellitus (T2DM) to achieve good glycemic control. However, insulin initiation is often delayed, and patients may spend 8 or more years with worsening glycosylated hemoglobin (A1C) values as they progress through treatment regimens including diet and exercise, metformin, and combinations of oral agents.[1] Fear of injections, hypoglycemia, and weight gain, along with the perception that insulin will add to the burden of managing diabetes, all contribute to clinical inertia prior to initiation of insulin therapy.[2,3] Although many T2DM patients reach A1C targets with the addition of basal insulin therapy,[4,5] others require therapy intensification to a multiple daily injection (MDI) regimen. However, even with MDI, about 30% of T2DM patients do not meet A1C targets.[6] These T2DM patients are potential candidates for insulin pump treatment, which offers several advantages compared with MDI. These advantages include adjustable basal rates, fewer needle insertion procedures, ability to deliver precise and convenient boluses, and reductions in both glycemic variability and severe hypoglycemia.[7] Moreover, the ability to download and display information stored in the pump allows tracking of insulin use and assessment of adherence. Some evidence suggests that prompt initiation of pump therapy in T2DM preserves β-cell function[8]; however, the therapeutic value of pump therapy in terms of A1C reduction has been poorly evaluated in T2DM until recently. Whether favorable glycemic response to pump therapy is restricted to the more severe insulin-deficient T2DM patients or to the late-onset autoimmune diabetes subset of T2DM-like patients remains questionable.

The recently completed OpT2mise trial (registered at ClinicalTrials.gov with clinical trial registration number NCT01182493) established that in poorly controlled T2DM patients on optimized MDI regimens, intensification to insulin pump treatment resulted in significant reductions in A1C values. The study population included patients with a wide age range (30–75 years), using MDI regimens and high insulin doses (0.5–1.8 U/kg/day) titrated during a 2-month run-in phase. All oral diabetes medications were stopped except for metformin. Patients were randomized if their A1C value was in the 8–12% range[9] to either pump therapy ($n = 168$) or to remain on MDI ($n = 163$). At the end of the 6-month study phase, glucose control improved more in the pump group (A1C dropped from 9% to 7.9%), with a between-group A1C difference of 0.7% in favor of pump therapy ($P < 0.001$). Moreover, the total insulin daily dose was reduced by 20% with pump compared with MDI, suggesting an increase in insulin sensitivity driven by its continuous subcutaneous infusion.[10]

Investigational centers were required to collect plasma from fasting subjects for C-peptide and anti-glutamic acid decarboxylase (anti-GAD) antibody (Ab) determinations as part of each subject's baseline (before randomization) and end-of-study (6-month) assessments; assays were carried out at a central laboratory (Covance, Inc. [corporate headquarters, Princeton, NJ]). C-peptide level was measured via direct chemiluminescence (Siemens Healthcare Diagnostics, Tarrytown, NY), and anti-GAD Ab level was measured via radioimmunoassay (Kronus, Boise, ID). Subjects were retrospectively grouped according to anti-GAD and C-peptide concentrations to explore associations between these biomarkers and baseline A1C values, A1C changes, or A1C changes attributable to treatment group assignment. Significance tests comparing between- and within-group A1C changes were performed using an analysis of covariance that used treatment group assignment, analyte concentration category, and baseline A1C as covariates.

Baseline A1C values and changes in A1C at 6 months for patients who were categorized according to baseline anti-GAD Ab levels (< 1 or ≥ 1 U/mL) or according to baseline C-peptide levels chosen such that the population was stratified into quartiles (< 156 pmol/L [< 0.47 ng/mL], ≥ 156 to

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Table 1. Baseline and 6-Month Changes in Glycosylated Hemoglobin Values According to Treatment Group, Anti-Glutamic Acid Decarboxylase Antibody Concentration, and C-Peptide Concentration

	Pump treatment			*MDI treatment*			*Comparing treatment groups*
Analyte, concentration range	n	*A1C (baseline) (%)*	*ΔA1C (%)*	n	*A1C (baseline) (%)*	*ΔA1C (%)*	
Anti-GAD Ab							
< 1 U/mL	135	9.0 ± 0.76	−1.07 ± 1.19	129	9.0 ± 0.80	−0.44 ± 1.13	$P < 0.0001$
≥ 1 U/mL	27	8.9 ± 0.67	−1.00 ± 1.28	30	8.8 ± 0.57	−0.24 ± 0.86	$P = 0.01$
Comparing anti-GAD groups			$P = 0.90$			$P = 0.46$	
C-peptide							
< 156 pmol/L (< 0.47 ng/mL)	43	9.0 ± 0.61	−0.96 ± 1.14	35	8.8 ± 0.62	−0.10 ± 0.97	$P = 0.002$
≥ 156 to < 309 pmol/L (≥ 0.47 to < 0.93 ng/mL)	33	8.7 ± 0.61	−0.94 ± 1.11	48	8.9 ± 0.67	−0.53 ± 1.08	$P = 0.035$
≥ 310 to < 569 pmol/L (≥ 0.93 to < 1.72 ng/mL)	40	9.0 ± 0.92	−1.22 ± 1.14	40	9.1 ± 0.90	−0.63 ± 1.06	$P = 0.012$
≥ 569 pmol/L (≥ 1.72 ng/mL)	45	9.1 ± 0.68	−1.07 ± 1.41	35	9.1 ± 0.81	−0.24 ± 1.17	$P = 0.006$
Comparing C-peptide quartiles			$P = 0.74$			$P = 0.14$	

ΔA1C, change in glycosylated hemoglobin (A1C) from baseline to 6 months; Anti-GAD Ab, anti-glutamic acid decarboxylase antibody; MDI, multiple daily injection.

< 309 pmol/L [≥ 0.47 to < 0.93 ng/mL], ≥ 309 to < 569 pmol/L [≥ 0.93 to < 1.72 ng/mL], or ≥ 569 pmol/L [≥ 1.72 ng/mL]) are shown in Table 1. Eighteen percent of patients were positive for the detection of anti-GAD Ab, a somewhat high prevalence compared with that reported in previous studies of T2DM cohorts.[11] This relatively high rate of anti-GAD Ab positivity may represent an unexpectedly high prevalence of T2DM-like subjects with late-onset autoimmune diabetes in our study population, a high false-positive rate in the assay used for determining anti-GAD Ab concentrations, a relatively low cutoff value for establishing anti-GAD Ab positivity, or some combination of these. Baseline A1C values were not correlated with either anti-GAD Ab or C-peptide concentrations. The largest difference between the pump and MDI groups was seen in subjects with low or undetectable C-peptide levels <156 pmol/L (< 0.47 ng/mL). There was no significant difference in A1C drop between patients with or without anti-GAD Ab in both pump ($P = 0.90$) and MDI ($P = 0.46$) groups. Similarly, there was no association between A1C drop and C-peptide concentration in both pump ($P = 0.74$) and MDI ($P = 0.14$) groups. Regardless of treatment assignment (pump or MDI), the mean A1C value decreased equally in each anti-GAD category and in each C-peptide quartile, and the magnitude of A1C decrease was always larger in those assigned to pump therapy compared with MDI.

The OpT2mise study has demonstrated that patients with clinically diagnosed T2DM and poor glycemic control assigned to pump therapy achieve a larger A1C reduction than patients assigned to remain on MDI. The benefits of pump treatment were not dependent on either anti-GAD Ab detection or C-peptide concentrations at baseline. Therefore, the presence or absence of these biomarkers should not be used as a criterion for insulin pump therapy in T2DM patients unable to achieve glycemic control on MDI.

Author Disclosure Statement

Y.R. declares no competing financial interests exist. S.H. is an employee of Medtronic.

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