

Glycemic Response and Attainment of A1C Goals Following Newly Initiated Insulin Therapy for Type 2 Diabetes

GREGORY A. NICHOLS, PHD¹
TERESA M. KIMES, MS¹
JOYCE B. HARP, MD²

TZUYUNG DOUG KOU, PHD²
KIMBERLY G. BRODOVICZ, DRPH²

OBJECTIVE—To identify the characteristics associated with glycemic response to newly initiated insulin therapy.

RESEARCH DESIGN AND METHODS—We identified 1,139 type 2 diabetic patients who initiated insulin therapy between 1 January 2009 and 30 June 2010. Outcomes of interest were the proportion of patients achieving A1C <7% and mean change in A1C within 3–9 months.

RESULTS—Mean A1C at insulin initiation was 8.2 vs. 9.2% among those who did and did not attain A1C <7% ($P < 0.001$). Within a mean of 5 months, 464 (40.7%) patients attained A1C <7%. In multivariable analyses controlling for insulin regimen, dose, and oral agent use, preinsulin A1C was responsible for nearly all the explained variance in A1C change. Each one percentage point of preinsulin A1C reduced the probability of attaining <7% by 26% (odds ratio 0.74 [95% CI 0.68–0.80]).

CONCLUSIONS—Insulin initiation at lower levels of A1C improves goal attainment and independently increases glycemic response.

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Most type 2 diabetic patients require ongoing therapy intensification that eventually includes exogenous insulin administration (1). Despite the theoretical ability of insulin to correct any amount of hyperglycemia, in clinical practice only 30–37% of insulin patients achieved A1C <7% in any given quarter over 7 years of observation (2). Our objective was to examine the characteristics associated with better glycemic response to insulin and achievement of A1C targets.

RESEARCH DESIGN AND METHODS

The data for this observational study were extracted from the pharmacy, laboratory, and electronic medical record systems of Kaiser Permanente Northwest (KPNW). Details of KPNW and its data systems have been recently described (3). For the current observational study, we selected 1,139 KPNW members

who met the following inclusion criteria: 1) entered the diabetes registry prior to 1 January 2008; 2) had no insulin dispensed in 2008; 3) had a new dispense of insulin between 1 January 2009 and 30 June 2010; 4) were aged ≥ 45 years as of the date of dispense; 5) had continuous health plan membership for at least 9 months following the first insulin dispense; 6) had at least one A1C measurement in the year prior to initiating insulin; and 7) had at least one A1C measurement 90–270 days following insulin initiation. The study observation period for each patient began on the date of insulin initiation and ended on the date of the first A1C measured 90–270 days later.

Outcomes of interest were the proportion of patients who achieved A1C <7% within 3–9 months of initiating insulin and mean change (decline) in A1C, calculated by subtracting the value of the

first A1C measure taken 90–270 days following insulin initiation from the A1C value preceding insulin initiation. We identified three insulin regimens: long-acting alone (glargine, detemir, or NPH); short-acting alone (regular or rapid insulins); and combinations of long- and short-acting insulins.

RESULTS—Of 1,139 patients, 464 (40.7%) attained A1C <7% following insulin initiation (Table 1). Patients who attained A1C <7% were older (aged 66.1 vs. 62.6 years; $P < 0.001$), were less likely to be of a nonwhite race (7.1 vs. 12.2%; $P = 0.006$), and had slightly shorter duration of diabetes (8.5 vs. 9.0 years; $P = 0.050$) compared with patients who did not attain A1C <7%. Mean A1C at insulin initiation was 8.2% among those who subsequently attained <7% compared with 9.2% among those who did not ($P < 0.001$). Mean decline in A1C with insulin was greater among patients who attained the 7% goal (1.9 vs. 1.3%; $P < 0.001$). Patients who achieved A1C <7% did so with fewer mean units of insulin per day (47.4 vs. 53.2 units/day; $P < 0.001$) and less use of any oral agent (67.2 vs. 73.0%; $P = 0.035$). The majority of patients used a combination of insulin types (55.6%), whereas 33.3% used only long-acting and 11.2% used only short-acting insulins.

In multivariable analyses, A1C prior to insulin initiation was the dominant factor in goal attainment; each one percentage point of A1C prior to insulin reduced the probability of attaining A1C <7% by 26% (odds ratio 0.74 [95% CI 0.68–0.80]). Although other variables were statistically significant, A1C prior to initiation accounted for 96% of the discriminatory power of the model. Likewise, A1C prior to insulin initiation was responsible for nearly all of the explained variance of change in A1C. Relative to a regimen of long-acting insulin only, short-acting insulin only or combination regimens were significantly associated with goal attainment and glycemic response. Micro- and macrovascular complications and the use of other nondiabetes

From the ¹Kaiser Permanente Center for Health Research, Portland, Oregon; and the ²Department of Epidemiology, Merck Research Laboratories, Rahway, New Jersey.

Corresponding author: Gregory A. Nichols, greg.nichols@kpchr.org.

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Table 1—Bivariate associations and multivariable models of the probability of attaining A1C <7% and change in A1C following insulin initiation

	Bivariate associations		Probability of attaining A1C <7%		Change in A1C		
	Achieved A1C <7% (n = 464)	Did not achieve A1C <7% (n = 675)	P value	Odds ratio (95% CI)	P value	Partial R ²	P value
Insulin regimen (%)			<0.001				
Long-acting insulin only	24.1	39.6		Referent	—	Referent	—
Short-acting insulin only	19.2	5.6		3.13 (1.96–5.01)	<0.001	0.003	0.003
Combination of long- and short-acting insulin	56.7	54.8		2.04 (1.53–2.74)	<0.001	0.005	<0.001
Preinsulin A1C (%)	8.2	9.2	<0.001	0.74 (0.68–0.80)*	<0.001	0.644	<0.001
Diabetes duration (years)	8.5	9.0	0.050	0.96 (0.94–0.99)	0.007	0.005	<0.001
Insulin units per day	47.4	53.2	<0.001	0.99 (0.98–1.00)	0.024	0.002	0.014
Any oral agent use (%)	67.2	73.0	0.035	0.84 (0.63–1.11)	0.208	0.001	0.174
C-statistic or R ²	—	—	—	0.699*	—	0.659	—

*Preinsulin A1C alone produced a c-statistic of 0.671.

medications were not statistically significant covariates in either model.

CONCLUSIONS—With sufficient doses and appropriate lifestyle management, insulin can reduce any level of elevated A1C to the therapeutic goal (4). In our observational study of 1,139 patients in a clinical practice setting, we found that only 41% achieved A1C <7% within a mean of 5 months after initiating insulin. Our findings were remarkably similar to a recent observational study in five European countries (5) and to the Treating To Target in Type 2 Diabetes (4-T) study (6). Thus, even in a rigorous clinical trial setting, A1C goal attainment with insulin therapy is less than optimal.

We examined a wide variety of demographic, clinical, and therapy-related variables in an effort to identify factors that contributed to A1C goal attainment and that were associated with glycemic response to insulin initiation. We found that the level of A1C prior to starting insulin was by far the single most important factor, accounting for 95% of the discriminatory ability to predict the probability of goal attainment and 96% of the explainable variance in A1C change. The recent INSTIGATE (INSulin Titration – Gaining an understanding of the burden of Type 2 diabetes in Europe) observational study also reported that change in A1C over the first 6 months of new insulin therapy was almost entirely dependent on baseline A1C (5), a relationship also noted in studies of oral antihyperglycemic medications (7,8). This is not surprising; achieving any given A1C goal should be easier for the patient who is closer to the

goal when the therapy is initiated. However, although mean A1C among patients who achieved A1C <7% was lower prior to insulin, these patients also had a significantly greater mean change in A1C after starting the therapy, and shorter diabetes duration also was independently associated with A1C and greater A1C reduction. Thus, initiating insulin earlier in the course of oral agent failure seems to improve glycemic goal attainment as well as improve glycemic response.

An important limitation of the current study was that we could not observe insulin titration schedules. We studied glycemic response 3–9 months following insulin initiation, but it is possible that some patients who did not achieve A1C goals in this time frame were being titrated more slowly. If so, the proportion that will ultimately attain A1C goals is likely higher. Another limitation is that we estimated units per day from dispensing records; we could not observe actual units consumed.

In summary, we found that less than one-half of patients newly initiating insulin therapy in a clinical practice setting achieved the recommended A1C goal of <7% within 3–9 months. After considering a large number of demographic and clinical characteristics, it seems that the key to glycemic success with insulin, as with oral agents, is intensifying therapy quickly when current therapies begin to fail.

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