

Contributions of Basal and Postprandial Hyperglycemia Over a Wide Range of A1C Levels Before and After Treatment Intensification in Type 2 Diabetes

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OBJECTIVE—To determine the relative contributions of basal hyperglycemia (BHG) versus postprandial hyperglycemia (PPHG) before and after treatment intensification in patients with glycated hemoglobin A_{1c} (A1C) >7.0% while on prior oral therapy.

RESEARCH DESIGN AND METHODS—Self-measured, plasma-referenced glucose profiles and A1C values were evaluated from participants in six studies comparing systematically titrated insulin glargine with an alternative regimen (adding basal, premixed, or prandial insulin, or increasing oral agents). Hyperglycemic exposure (>100 mg/dL [5.6 mmol/L]) as a result of BHG versus PPHG was calculated.

RESULTS—On prior oral therapy, 1,699 participants (mean age 59 years, diabetes duration 9 years) had mean fasting plasma glucose (FPG) of 194 mg/dL (10.8 mmol/L), and mean A1C was 8.7%. BHG contributed an average of 76–80% to hyperglycemia over the observed range of baseline A1C levels. Adding basal insulin for 24 or 28 weeks lowered mean FPG to 117 mg/dL (6.5 mmol/L), A1C to 7.0%, and BHG contribution to 32–41%. Alternative regimens reduced FPG to 146 mg/dL (8.1 mmol/L), A1C to 7.1%, and the contribution of BHG to 64–71%. BHG contributions for patients with A1C averaging 7.6–7.7% were 76% at baseline and 34 and 68% after adding basal insulin or other therapies, respectively.

CONCLUSIONS—When A1C is >7.0% despite oral therapy, BHG routinely dominates exposure. Intensified therapy reduces A1C and changes this relationship, but BHG amenable to further intervention still accounts for one-third of total hyperglycemia after basal insulin treatment and two-thirds after alternative methods.

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The importance of controlling hyperglycemia as measured by glycated hemoglobin A_{1c} (A1C) levels to reduce the risk of long-term, diabetes-related complications is well understood. That A1C reflects contributions from both basal (fasting) and postprandial hyperglycemia (PPHG) is also well established. How treatment of basal hyperglycemia

(BHG) versus PPHG should be prioritized in the management of type 2 diabetes is less clear.

In 2003, Monnier et al. (1) published a landmark study describing the relative contributions of BHG and PPHG to overall hyperglycemic exposure at different levels of A1C. This analysis was based on 1-day, four-point daytime

glucose profiles from 290 patients with type 2 diabetes who were treated with diet therapy with or without oral antihyperglycemic drug (OAD) therapy and without insulin. The findings suggested that PPHG accounted for ~70% of overall glycemic exposure above normal levels in patients in the lowest range of A1C (<7.3%), with the contribution from BHG increasing with higher A1C. In the highest A1C range (A1C >10.2%), the contributions were reversed; PPHG contributed ~30% and BHG ~70%. This pattern has been proposed to reflect a fundamental biologic property of type 2 diabetes: a tendency of PPHG to appear early in the natural history of the disorder, with BHG appearing later after further decline of β -cell capacity (2). A potential clinical implication of this view is that when A1C is only moderately elevated therapeutic intervention should target PPHG. Other studies support the importance of PPHG at lower A1C levels and BHG at higher levels (2–8), but features of their designs may influence estimates of the relative contributions of BHG and PPHG. Specifically, the timing of glucose measurements, the level of basal glucose considered above normal, inclusion or exclusion of individuals not receiving antihyperglycemic therapy, and the effects of treatments that affect mainly BHG or PPHG all might influence these relationships.

The purpose of this study was to measure the relative contribution of BHG versus PPHG in a common and specific clinical setting. We evaluated seven-point glucose profiles in a large group of patients with type 2 diabetes with A1C >7.0% on OAD, for whom the relative importance of BHG versus PPHG has direct relevance to further therapy. Because 100 mg/dL (5.6 mmol/L) is considered the upper limit of normal fasting plasma glucose by the American Diabetes Association (9,10), the current analysis defined basal values above this level as elevated. We aimed to determine, using our method of calculation, whether before intensifying therapy these patients showed the A1C-dependent

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patterns of hyperglycemic exposure proposed by the earlier findings and to define how adding basal insulin and other interventions altered the initially observed patterns of hyperglycemia.

RESEARCH DESIGN AND METHODS

Study and patient selection criteria

Data from six similarly designed randomized trials enrolling adult patients with type 2 diabetes with suboptimal glycemic control on oral antihyperglycemic therapy were pooled for analysis (11–16). These studies were selected from a total of 63 supported by the sanofi-aventis development program for insulin glargine by having the following characteristics: prospective, randomized, active-comparator design; insulin glargine given once daily without use of prandial insulin; required use of a systematic insulin-titration algorithm; adherence to good clinical practice guidelines; availability of participant-level data; follow-up of at least 24 weeks; and collection of at least seven-point self-measured glucose profiles. Insulin-dosing decisions were made frequently (daily, every 3 days, or weekly) seeking fasting glucose levels <100 mg/dL (5.5 mmol/L). Entry criteria for all studies specified that A1C be >7.0% at enrollment. In each study, the active comparator treatment (human NPH insulin, insulin lispro, premixed insulin, or OAD intensification) also used a specific algorithm. Details of the studies can be found in Supplementary Table 1 and in the original publications.

Baseline and 24-week participant level data were pooled according to treatment. One study (15) did not have a week 24 visit; week 28 data were used. To be included in the present analysis, participants must have finished 24 to 28 weeks of treatment with complete seven-point glucose profile data at both baseline and week 24 or 28. All glucose profiles included measurement before and 2 h after each meal and at bedtime.

Statistical analysis

Calculation of the relative contributions of glucose. A graphical depiction of the area under the curve (AUC) for normal, basal, and postprandial glycemic exposure is shown in Supplementary Fig. 1. The daily blood glucose (BG) response to meals was estimated by calculating the incremental AUC of daytime BG from the overall glucose profile. The total duration for the seven-point profile was 24 h, with the glucose level at the 24th h imputed by the value at fasting before breakfast. Four areas were calculated geometrically from the seven-point curve as follows: 1) normal glycemic exposure (AUC_N)— $100 \text{ mg/dL} \times 24 \text{ h} = 2,400 \text{ mg/dL per h}$ of exposure; 2) BHG (AUC_B)—the area between 100 mg/dL and a line projected rightward for 24 h from the fasting (before breakfast) glucose value in the profile (the area is taken to represent the daily abnormal glycemic exposure resulting from BHG); 3) PPHG (AUC_P)—the area above the line projected rightward from the fasting sample before breakfast and below the

line connecting the six remaining points, minus any area below the line projected from the basal value, if applicable (this area is considered a reflection of the postprandial glycemic responses to breakfast, lunch, and dinner); and 4) total glucose (AUC_G)—the total area under the glucose curve is the sum of the other three areas [$AUC_G = AUC_N + AUC_B + AUC_P$]. As a result, the relative contributions of postprandial and fasting BG to the total BG increment were calculated, respectively, by using the following equations: $[AUC_P/(AUC_B + AUC_P)] \times 100\%$ for the postprandial contribution and $[AUC_B/(AUC_B + AUC_P)] \times 100\%$ for the basal contribution. Negative values were set to zero.

Outcomes. The outcomes of interest were correlations between A1C and AUC_G , AUC_B , and AUC_P , and the overall basal contribution (percentage) to hyperglycemia at baseline and end point; seven-point glucose profiles at baseline and after 24 or 28 weeks of treatment analyzed by A1C category; and the relative contributions of postprandial and fasting glucose to total hyperglycemia before and after treatment by A1C category, and by different treatment groups (basal insulin vs. other, and insulin glargine vs. NPH insulin). The A1C categories were <8.0, 8.0 to <8.5, 8.5 to <9.0, 9.0 to <9.5, and $\geq 9.5\%$. Hypoglycemic events were also assessed.

Statistical methodology

Pearson correlation analysis was performed between outcomes and predictors.

Table 1—Patient demographics and baseline characteristics

Characteristic	Overall	Insulin glargine	NPH insulin	Basal insulin (total glargine and NPH)	Other (lispro, premix, or OAD)
<i>n</i>	1,699	1,026	235	1,261	438
Age (years)	59.4 (9.4)	59.9 (9.5)	56.8 (8.7)	59.3 (9.4)	59.5 (9.3)
Male (%)	57.7	58.0	53.6	57.2	59.4
White (%)	94.6	95.5	85.4	93.8	96.6
Weight (kg)	87.6 (15.9)	86.7 (15.9)	94.2 (16.1)	88.1 (16.2)	86.4 (15.1)
Duration of diabetes (years)	9.0 (6.0)	9.1 (6.3)	9.0 (5.2)	9.1 (6.1)	8.8 (5.9)
Baseline fasting plasma glucose (mg/dL)	193.5 (47.6)	194.4 (47.1)	200.8 (47.3)	195.6 (47.2)	187.6 (48.3)
Baseline A1C (%)	8.69 (0.94)	8.73 (0.95)	8.62 (0.92)	8.71 (0.95)	8.62 (0.93)
Baseline A1C category, <i>n</i> (%)					
<8.0	422 (24.8)	236 (23.0)	63 (26.8)	299 (23.7)	123 (28.1)
8.0 to <8.5	348 (20.5)	220 (21.4)	44 (18.7)	264 (20.9)	84 (19.2)
8.5 to <9.0	298 (17.5)	173 (16.9)	47 (20.0)	220 (17.4)	78 (17.8)
9.0 to <9.5	245 (14.4)	147 (14.3)	38 (16.2)	185 (14.7)	60 (13.7)
≥ 9.5	386 (22.7)	250 (24.4)	43 (18.3)	293 (23.2)	93 (21.2)

Values are mean (SD) unless otherwise noted.

A regression analysis adjusted to study or other exploratory factors was performed to test the robustness of the correlation analysis. In addition, A1C correlations at week 24 or 28 in patients on basal insulin (insulin glargine or NPH insulin) were compared with those on another therapy (insulin lispro, premixed insulin, or OAD intensification) and in the subgroups of patients taking insulin glargine versus those taking NPH insulin.

Week 24 or 28 outcomes comparisons (basal insulin vs. other, insulin glargine vs. NPH insulin, or other comparisons) were performed with two sample *t* tests with Satterthwaite unequal variance approximation. To consider the A1C effect, the comparisons were also performed using ANOVA models with week 24 or 28 A1C category, study, and comparison category as factors. The comparisons were also repeated using an ANCOVA model with the change in A1C as a covariate and study and comparison category as factors.

Hypoglycemia incidence (*n/N* for each group) was calculated for symptomatic hypoglycemia (all reported events), glucose-confirmed hypoglycemia (symptomatic

events with reported glucose values <50 mg/dL [2.8 mmol/L]), and severe symptomatic hypoglycemic events (any symptomatic hypoglycemic event requiring assistance and a BG of <36 mg/dL [2.0 mmol/L], if available, or with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration). Odds ratios and *P* values were calculated using logistic regression with study and comparison category as factors.

RESULTS

Demographics and baseline characteristics

The demographic and clinical characteristics of the 1,699 study participants are shown in Table 1. Oral therapies used at baseline were mostly limited to metformin alone (5%), a sulfonylurea (45%), or the two together (46%). Fewer than 5% of patients were taking another monotherapy or combination regimen or diet therapy only. Of the 1,261 patients assigned to basal insulin, 1,026 (81%) received insulin glargine and 235 (19%) received human NPH insulin. Of the

438 assigned to other regimens, 32% were treated with premixed insulin, 36% with prandial insulin, and 32% with additional oral therapy. Baseline characteristics of these subgroups were similar.

Glycemic patterns and hyperglycemic exposure by A1C ranges at baseline

The overall mean ± SD BG concentration from baseline glucose profiles was 189 ± 49 mg/dL (10.5 ± 2.7 mmol/L), and total glycemic exposure (AUC_G) correlated very significantly with baseline A1C (*r*² = 0.545; *P* < 0.0001). The mean relative basal contribution to total hyperglycemic exposure at baseline was 78%. Mean seven-point glucose concentration time profiles at baseline for each of the A1C ranges are shown in Fig. 1A. The overnight values imputed by a line between the bedtime value and a next-morning value projected to be the same as the fasting value of that day are not shown in the figure. Figure 1B shows the basal and postprandial contributions computed for each A1C range. The BHG contribution

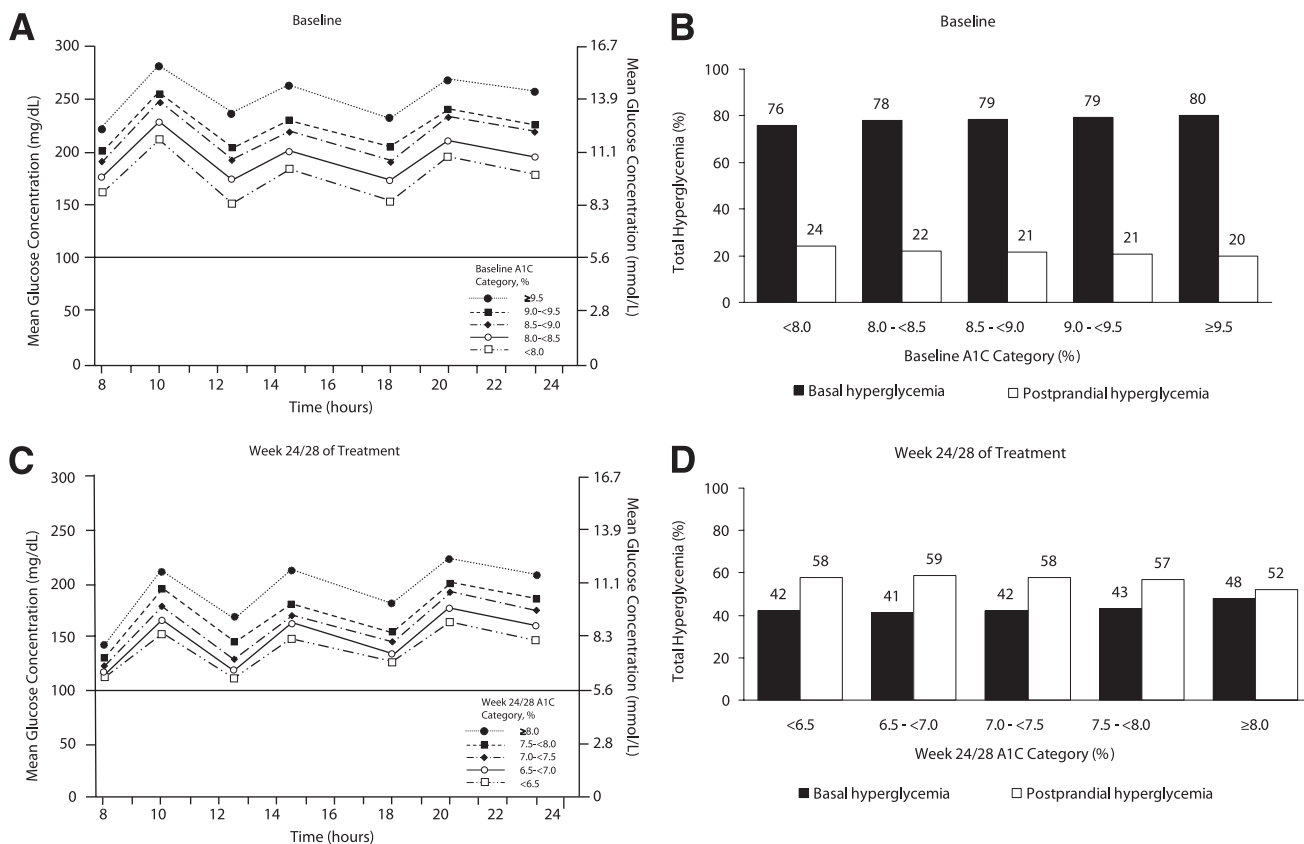


Figure 1—A: Baseline seven-point glucose profiles by A1C category. B: Relative contributions of BHG and PPHG to overall hyperglycemia by A1C category at baseline. C: The seven-point glucose profiles by A1C category at week 24 or 28. D: Relative contributions of BHG and PPHG to overall hyperglycemia by A1C category at week 24 or 28.

ranged from 76 to 80% of hyperglycemic exposure and that from PPHG ranged from 24 to 20% from the lowest (<8.0%, mean A1C 7.6%) to the highest A1C ($\geq 9.5\%$, mean A1C 10.0%) ranges. A tendency toward a greater contribution from PPHG at lower and from BHG at higher ranges of baseline A1C approached but did not reach statistical significance ($P = 0.074$).

Effects of intensification of treatment on A1C and fasting plasma glucose

After 24 or 28 weeks of intensified treatment, mean \pm SD basal glucose from the profiles for the whole population was 121 ± 35 mg/dL (6.7 ± 1.9 mmol/L), and mean week 24 A1C was $7.04 \pm 0.91\%$. Mean seven-point glucose concentration time profiles at week 24 or 28 by end point A1C category are shown in Fig. 1C. After intensification of treatment total glycemic exposure correlated significantly with achieved A1C ($r^2 = 0.471$; $P < 0.0001$). The mean relative basal contribution to total hyperglycemic exposure

after treatment intensification was 43%. Figure 1D shows the BHG and PPHG contributions for each A1C category for week 24 or 28 for all participants. Intensification of therapy reduced the contribution from BHG from 76 to 80% at baseline to 41–48%. A statistically significant increase of the contribution from BHG relative to PPHG from lower to higher ranges of A1C was evident ($P = 0.0155$).

Effects of basal insulin versus other forms of intensified treatment

The 1,261 participants whose treatment was intensified with insulin glargine or NPH insulin and the 438 who used premixed insulin, prandial insulin, or additional oral therapy achieved similar mean levels of A1C (7.02 vs. 7.09%) (Table 2). Mean total glucose levels were also similar for the two means of intensification of treatment ($3,596 \text{ mg} \cdot \text{h} \cdot \text{dL}^{-1}$ [$199.6 \text{ mmol} \cdot \text{h} \cdot \text{L}^{-1}$] vs. $3,437 \text{ mmol} \cdot \text{h} \cdot \text{L}^{-1}$ [$190.8 \text{ mmol} \cdot \text{h} \cdot \text{L}^{-1}$]). However, the mean basal glucose from the profiles for each group differed (115 mg/dL [6.4 mmol/L] vs. 137 mg/dL [7.6 mmol/L] for

basal insulin vs. other treatment; $P < 0.0001$), and the seven-point profiles showed different patterns (Fig. 2A). Treatment with basal insulin reduced the mean relative contribution from BHG to 34%. The other treatment methods resulted in a mean relative BHG contribution of 68%. The contributions from BHG and PPHG after treatment are shown by ranges of achieved A1C for the basal insulin group in Fig. 2B and the group treated in other ways in Fig. 2C. After addition of basal insulin, the BHG contribution ranged between 31 and 41%, with a greater contribution from BHG at the higher ranges of achieved A1C. In a subanalysis, participants treated with insulin glargine or NPH insulin were compared directly; patterns of hyperglycemia were generally alike with the two insulins (Table 2).

Intensification of therapy with premixed or prandial insulin or additional oral agents resulted in a range of contribution from BHG from 63.5 to 71% of overall hyperglycemic exposure. Despite the similarity of achieved A1C levels after treatment intensification with basal insulin

Table 2—Baseline, week 24 or 28, and change in A1C and glucose variables and correlations with change in A1C by treatment category

Characteristic and visit	Overall	Basal insulin	Other treatment	Subanalysis	
				Insulin glargine	NPH insulin
<i>n</i>	1,699	1,261	438	224	235
A1C (%)					
Baseline	8.69 (0.94)	8.71 (0.95)	8.62 (0.93)	8.66 (0.91)	8.62 (0.92)
Week 24/28	7.04 (0.91)	7.02 (0.88)	7.09 (0.98)	7.00 (0.85)	6.90 (0.70)
Change	−1.65 (1.03)	−1.69 (1.00)	−1.53 (1.12)	−1.66 (1.00)	−1.73 (0.89)
AUC _B (mg·h·dL ^{−1})					
Baseline	2,155 (1,176)	2,271 (1,183)	1,821 (1,091)	2,598 (1,220)	2,449 (1,256)
Week 24/28	590 (739)	477 (654)	917 (864)	596 (822)	587 (734)
Change	−1,565 (1,243)	−1,794 (1,204)	−904 (1,112)	−2,003 (1,250)	−1,863 (1,341)
Correlation	0.425*	0.449*	0.371*	0.480*	0.460*
AUC _P (mg·h·dL ^{−1})					
Baseline	560 (592)	573 (611)	521 (533)	603 (681)	628 (681)
Week 24/28	635 (601)	748 (610)	311 (434)	849 (711)	865 (672)
Change	75 (729)	174 (730)	−211 (646)	246 (878)	237 (851)
Correlation	0.155*	0.132*	0.304*	0.179†	0.023‡
Total glucose AUC _G (mg·h·dL ^{−1})					
Baseline	5,003 (1,233)	5,126 (1,241)	4,649 (1,139)	5,425 (1,162)	5,308 (1,239)
Week 24/28	3,555 (786.4)	3,596 (779)	3,437 (798)	3,795 (905)	3,814 (775)
Change	−1,448 (1,213)	−1,530 (1,204)	−1,212 (1,208)	−1,631 (1,269)	−1,494 (1,215)
Correlation	0.543*	0.531*	0.566*	0.589*	0.547*
Basal contribution (%)					
(AUC _B / [AUC _B + AUC _P]) × 100					
Baseline	78.2 (22.1)	79.1 (21.3)	75.6 (24.2)	80.3 (21.2)	78.2 (23.0)
Week 24/28	42.6 (39.3)	33.7 (36.0)	67.9 (37.2)	35.9 (37.5)	35.3 (37.1)
Change	−35.7 (41.9)	−45.4 (38.3)	−7.7 (39.2)	−44.3 (39.3)	−43.0 (40.6)
Correlation	0.121*	0.150*	−0.014‡	0.126‡	0.216†

Values are mean (SD) unless otherwise noted. * $P < 0.0001$. † $P < 0.001$ between change in glucose profile parameter and change in A1C from baseline to end point. ‡ $P > 0.05$.

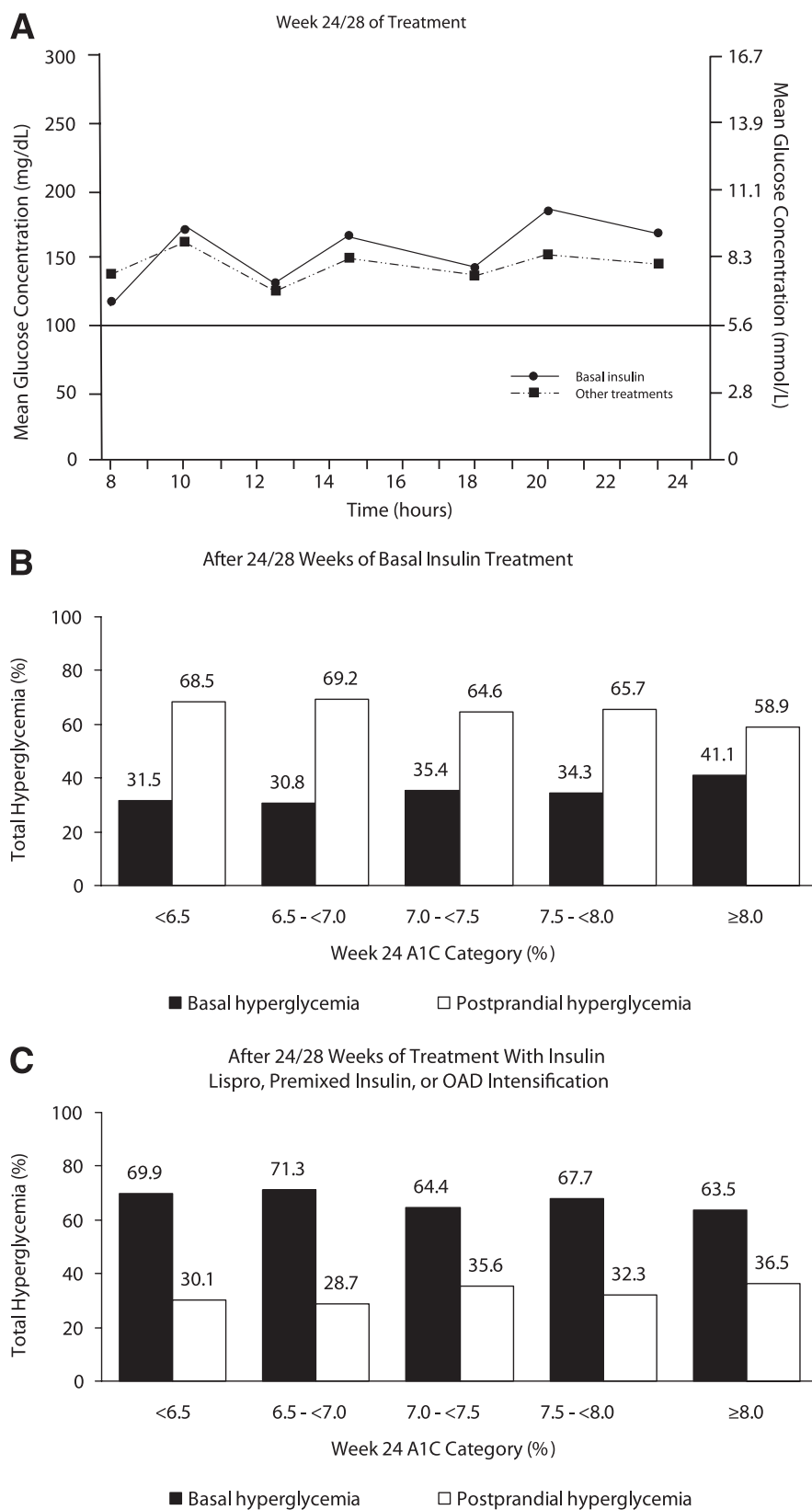


Figure 2—A: The seven-point glucose profiles for patients on basal insulin versus other treatments at week 24 or 28. B: Relative contributions of BHG and PPHG to overall hyperglycemia by A1C category after 24 or 28 weeks of basal insulin treatment. C: Relative contributions of BHG and PPHG to overall hyperglycemia by A1C category after 24 or 28 weeks of treatment with insulin lispro, premixed insulin, or OAD intensification.

compared with the other forms of therapy, the incidences of symptomatic hypoglycemia and glucose confirmed symptomatic hypoglycemia were greater with the other treatments than with basal insulin (65.1 vs. 59.5%, $P = 0.0390$; 42.2 vs. 31.5%, $P < 0.0001$). The incidence of severe symptomatic hypoglycemia was low and not clearly different between methods of intensification (2.5 vs. 1.2%, for other regimens vs. basal insulin, respectively; $P = 0.0589$) (Supplementary Table 2).

CONCLUSIONS—In this population of patients with type 2 diabetes who required intensification of antihyperglycemic therapy, the contribution from BHG to total hyperglycemic exposure was uniformly high (76–80%) across the observed range of A1C levels at baseline. After intensification of treatment leading to lower mean levels of A1C, there was a smaller (but important) contribution from BHG and greater one from PPHG. Alteration of the contributions from BHG and PPHG was especially prominent when basal insulin was used. For all patients treated with basal insulin, an average of 34% contribution from residual BHG was present, in contrast with 68% after treatment intensification with other agents. After addition of basal insulin, a modest tendency toward higher residual BHG with increasing A1C category at end point was found, whereas this pattern did not emerge after treatment with other agents.

These observations suggest the form of treatment used by patients can be a more significant factor affecting the contribution to hyperglycemia from basal versus postprandial glucose elevations than the observed A1C level alone. To illustrate this point, with oral therapies alone at baseline, participants with A1C <8.0% (mean 7.6%) had 76% contribution from BHG. After intensification of treatment with basal insulin, people with A1C 7.5–7.9% (mean 7.7%) had 34% contribution from BHG. After intensification with premixed insulin, prandial insulin, or additional oral therapy individuals with A1C in the same range (mean 7.7%) had 68% contribution from BHG.

Several aspects of the methods we used could have contributed to differences between these findings and earlier ones. The present analysis included a large population studied both before and after additional treatment and used seven-point

glucose profiles to estimate glycemic exposure during a full 24-h interval. Whereas some earlier studies did not include basal values lower than 110 mg/dL (6.1 mmol/L) in calculations of hyperglycemia, in keeping with definitions of fasting hyperglycemia that were then current (17), we considered normal fasting levels to be <100 mg/dL (5.6 mmol/L) (9,10) and elevations above this level to contribute to BHG exposure. The generalizability of our findings is limited by the fact that, at baseline, the study population included neither patients with A1C already <7.0% who might have relatively greater contribution from PPHG, nor individuals whose treatment was limited to lifestyle. Thus, the present findings do not address questions such as whether PPHG usually exceeds BHG early in the course of type 2 diabetes and whether initial pharmacotherapy should target PPHG rather than BHG. Our findings also do not provide insight into the relative effects of BHG versus PPHG on medical outcomes. Finally, use of seven-point self-measured glucose profiles has certain limitations, including lack of direct assessment of glucose levels overnight and variability resulting from day-to-day differences in collection time and eating patterns in individual patients. Therefore, additional studies using continuous glucose monitoring in well-defined populations will be of interest (18).

The present findings have clinical implications. They support the view that for most patients not achieving A1C levels <7.0% with oral therapies, targeting BHG with basal insulin or other methods of treatment (as proposed by current treatment guidelines) (19) is a more desirable first option than targeting PPHG. Moreover, with the methods used in these studies, neither BHG nor PPHG is routinely normalized with a single intervention, so that additional treatment with current or future methods will be helpful for many patients.

In summary, this analysis of 1,699 patients shows that when A1C is higher than 7.0% despite diet and oral therapy, BHG dominates hyperglycemic exposure over a wide range of A1C values. It expands the original concept of Monnier et al. (1,2) by showing that intensification of antihyperglycemic therapy changes the relative contribution of BHG versus PPHG, depending on the main effects of the form of treatment used. When treatment is intensified with basal insulin, BHG is markedly reduced yet still accounts for about one-third of hyperglycemic exposure

when close to A1C targets and potentially may be reduced further. Normalization of glycemic exposure will require attention to both BHG and PPHG.

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M.R., G.U., A.D., R.Z., and J.R. analyzed the data, contributed to discussions, and wrote, reviewed, and edited the manuscript.

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