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Early Glycemic Response Predicts Achievement of Subsequent Treatment Targets in the Treatment of Type 2 Diabetes: A Post Hoc Analysis

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Abbreviations

ADA	=American Diabetes Association
FBG	=Fasting Blood Glucose
GBM	=Gradient Boosting Method
HbA_{1c}	=Glycated Hemoglobin
NPV	=Negative Predictive Value
PPV	=Positive Predictive Value
T2DM	=Type 2 Diabetes Mellitus
Met	=Metformin
SU	=Sulfonylurea
Glargine	=Insulin Glargine

Introduction

- ADA consensus guidelines emphasize individualized treatment in the management of T2DM.
- Early glycemic response is a clinical marker that may predict longer-term efficacy for individual patients and provide a clinical tool to enhance personalized treatment.
- This analysis assessed the predictive power of early response for subsequent response across 3 commonly prescribed glucose-lowering medications: metformin, sulfonylurea, and insulin glargine.
- We hypothesized that glycemic response at week 12 (early response) predicts subsequent glycemic responses at week 24 (the primary outcome) and week 52 (the secondary outcome) in the treatment of patients with T2DM.

Methods

- Three previously published randomized clinical trials that included large sample sizes and individual patient data were used for this study.
- Metformin data (*n*=597) [1], sulfonylurea data (*n*=626) [2], insulin glargine data (*n*=1046) [3].
- The GBM was used to identify predictors of subsequent response; predictive accuracy was represented by sensitivity, specificity, PPV, and NPV.
- Treatment success at weeks 24 and 52 was assessed for each patient and defined as achieving an HbA_{1c} level of <7.0% or a reduction from baseline of ≥1.0%.

[1]Schernthaner G, Matthews DR, Charbonnel B, et al. J Clin Endocrinol Metab. 2004;89:6068–76.
[2]Charbonnel BH, Matthews DR, Schernthaner G, et al. Diabet Med. 2004;22:399–405.
[3]Buse JB, Wolffenbuttel BH, Herman WH, et al. Diabetes Care. 2011;34:249–55. doi: 10.2337/dc10-1701.

Results

- For each medication, the optimal early response variable was equal or close to a reduction in HbA_{1c} level of ≥1.0%, which is considered to be clinically meaningful. Therefore, we chose a single, unified early-response measure (a reduction in HbA_{1c} level of ≥1.0%) for all 3 medications.

- The GBM did not select an HbA_{1c} level of <7.0% as an optimal early-response variable in any case. However, since an HbA_{1c} level of <7.0% is clinically meaningful, it was combined with a reduction in HbA_{1c} of ≥1.0% for a composite unified measure in assessing predictive parameters.

Results

- The predictive parameters for improvements in HbA_{1c} at week 24 and week 52, based on the composite unified early-response measure can be seen in Table 1.

Table 1-Predictive parameters for improvements in HbA_{1c} at 24 and 52 weeks based on HbA_{1c} levels at 12 weeks.

Early Response Measure	Subsequent Response	Agent	Sensitivity	Specificity	PPV	NPV
Composite unified	24 weeks	Met	0.83	0.81	0.44	0.96
		SU	0.79	0.94	0.71	0.96
		Glargine	0.67	0.89	0.65	0.90
	52 weeks	Met	0.73	0.84	0.56	0.92
		SU	0.45	0.94	0.74	0.82
Unified	24 weeks	Met	0.90	0.74	0.38	0.98
		SU	0.85	0.88	0.57	0.97
		Glargine	0.74	0.83	0.56	0.92
	52 weeks	Met	0.82	0.78	0.50	0.94
		SU	0.52	0.88	0.62	0.83
Optimal	24 weeks	Met	0.82	0.81	0.44	0.96
		SU	0.85	0.88	0.57	0.97
		Glargine	0.74	0.83	0.56	0.92
	52 weeks	Met	0.56	0.92	0.67	0.88
		SU	0.52	0.88	0.62	0.83

- The predictive parameters assessed by using the optimal early-response measure and the unified measure were consistent with those of the composite unified measure and are shown in Table 1. Across all therapies and early-response measures and at both time points, the NPV remained consistently high (range, 0.82–0.98) (Table 1).

Conclusion

- The high predictive values identified in this analysis support our hypothesis that lack of early glycemic response is a reliable clinical marker for identifying a lack of treatment success at 24 and 52 weeks.

- The high NPV (lack of early glycemic response) appears to be an effective indicator of the likely need for a change in (or intensification of) therapy and could become valuable in clinical practice.

- The study findings support the current treatment recommendations for T2DM, which advise clinicians to evaluate therapeutic response to pharmacologic interventions with metformin, sulfonylureas, or insulin glargine as early as 12 weeks.

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- All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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