Glucose Measurements at Various Time Points During the OGTT and Their Role in Capturing Glucose Response Patterns

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Intermediate time points during the oral glucose tolerance test (OGTT) have received more attention recently (1), with some researchers even suggesting to use 1-h glucose when screening for prediabetes (2). We demonstrated that characterization of glucose response patterns from OGTTs with five time points provides useful insights into the heterogeneity of type 2 diabetes development (3). Although such analyses are feasible in small pathophysiological investigations, they are not common in large epidemiological studies where the number of glucose measurements during an OGTT is often limited. Therefore, we aimed to study how well different combinations of fewer than five time points during an OGTT approximate glucose response patterns based on five time points.

We analyzed data from the Relationship between Insulin Sensitivity and Cardiovascular disease (RISC) study, which we previously used to develop a glucose pattern classification model (3). The Tübingen Family Study (TUEF) cohort was used for external validation (4). Both studies included five-point OGTTs with glucose measurements at 0, 30, 60, 90, and 120 min. We excluded participants with self-reported diabetes or screen-detected diabetes (fasting plasma glucose $\geq$7.0 mmol/L or 2-h postload plasma glucose $\geq$11.1 mmol/L), participants taking glucose-lowering medication, and those with missing measurements at any of the five time points.

We previously identified four glucose response patterns using latent class trajectory modeling, and the final model was implemented as an online application (3). We used this application to estimate glucose response class membership probabilities based on eight more commonly occurring combinations of time points in both cohorts. This resulted in eight sets of class membership probabilities for each individual, including the reference probabilities based on all five time points.

In the first analysis, we assigned each individual to the class with the highest probability (hard assignment) in each of the eight scenarios. Class memberships from the scenarios based on fewer than five time points were cross-tabulated with the reference classification based on all available data. Agreements were characterized by the Cohen κ statistic. As the hard assignment does not take the uncertainty in the classification into account, we also calculated the relative entropy, a measure of adequate separation between classes (5), for all eight scenarios. All analyses were done separately in the RISC and TUEF cohorts. The psych (version 1.8.4) and LCTMtools (version 0.1.1) R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria) packages were used to calculate κ and relative entropy, respectively.

The final samples included 1,443 participants (644 men and 799 women) from the RISC study and 3,214 participants (1,158 men and 2,056 women) from the TUEF study. Participants from the RISC cohort had a median (interquartile range) age of 44 years (37–50) and

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BMI of 25.1 kg/m^2 (22.8–27.9). Twenty-eight percent of them had a family history of diabetes. In the TUEF study there were more women than men (64%), and in comparison with the RISC study, participants were of similar age but were slightly heavier with a BMI of 28.5 kg/m^2 (24.2–34.9) and a higher percentage had a family history of diabetes (41%).

κ coefficients ranged between 0.41 and 0.85 in the development cohort and between 0.34 and 0.84 in the external validation cohort (Table 1). Of the combinations with two time points, the 0–60 combination provided the strongest agreement, even stronger than the 0–30–120 combination including three measurements. The 0–60–120 combination provided the best agreement among combinations with three time points. The 0–30–60–120 combination outperformed all combinations with three time points. Adding 120-min plasma glucose to any of the combinations led to at least a 0.1 higher κ coefficient. Similar results were obtained in the external validation cohort.

The original model with five time points had a strong discriminative power in both cohorts (relative entropy = 0.79 in both). Dropping the 90-min glucose measurement led to 5–7% lower relative entropy compared with the reference.

This study demonstrates that glucose response patterns can be captured by only three glucose measurements during the OGTT. However, there was a large variation in agreement and discrimination according to the time points included. The 60-min plasma glucose measurement seemed to have more value than the 30-min measurement for capturing glucose patterns. This is partly a natural consequence of the larger between-person variation at the 60-min time point (3).

In conclusion, this study extends the utility of our glucose response pattern classification to cohorts with glucose measurements at fewer than five time points during the OGTT. Even though the OGTT is likely to lose its role in clinical practice, such studies can contribute with new pathophysiological insights to our current knowledge on determinants (e.g., genetic) and consequences (e.g., diabetes complications) of glucose response during the OGTT.

Table 1—Agreement (κ) between glucose pattern classification using five time points as reference and discrimination power (relative entropy) for different combinations of time points

Time points (min)					RISC cohort		TUEF cohort (external validation)	
0	30	60	90	120	κ (95% CI)	Relative entropy	κ (95% CI)	Relative entropy
X				X	0.41 (0.37–0.45)	0.38	0.46 (0.43–0.49)	0.40
X	X				0.46 (0.42–0.49)	0.47	0.34 (0.31–0.36)	0.44
X		X			0.70 (0.67–0.73)	0.63	0.66 (0.64–0.68)	0.58
X	X			X	0.62 (0.58–0.65)	0.60	0.61 (0.59–0.63)	0.58
X	X	X			0.75 (0.72–0.77)	0.69	0.71 (0.69–0.73)	0.65
X		X		X	0.80 (0.77–0.83)	0.71	0.79 (0.77–0.81)	0.69
X	X	X		X	0.85 (0.82–0.87)	0.74	0.84 (0.82–0.85)	0.73
X	X	X	X	X	1 (reference)	0.79	1 (reference)	0.79

κ = 0 means agreement only by chance, while κ = 1 means perfect agreement. Relative entropy is a measure of adequate separation between classes taking values between 0 and 1. Higher relative entropy indicates that individuals can be classified with higher confidence (5).

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