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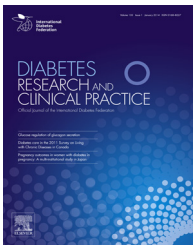

Emerging parameters of the insulin and glucose response on the oral glucose tolerance test: Reproducibility and implications for glucose homeostasis in individuals with and without diabetes

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ABSTRACT

Aims: Recent studies have suggested that novel parameters of the insulin and glucose response on the oral glucose tolerance test (OGTT) can provide metabolic insight beyond glucose tolerance, but have not evaluated their reproducibility. Thus, our aim was to evaluate the reproducibility of these parameters and, if confirmed, characterize their clinical/pathophysiologic relevance in healthy and diabetic individuals.

Methods: Thirty healthy adults each underwent 3 replicate OGTTs, enabling assessment of the reproducibility of the following 5 parameters: time to insulin peak, shape of the glucose curve, glucose nadir below baseline, 1-h post-challenge glucose, and time to glucose peak. The only reproducible parameter was then further evaluated in 63 patients with early type 2 diabetes (T2DM) before and after 4-weeks of intensive insulin therapy (IIT) designed to improve beta-cell function (measured by Insulin Secretion-Sensitivity-Index-2 (ISSI-2)).

Results: Of the five parameters, only time to glucose peak displayed reliable reproducibility on replicate testing ($\kappa = 0.76$). Over 80% of controls had their glucose peak at 30-min post-load, whereas all but one of the diabetic patients had their peak at 60-min or later. ISSI-2 was lower in T2DM patients with peak at $\geq$90-min than in those with peak at $\leq$60-min ($P = 0.012$). In patients in whom IIT improved beta-cell function by $\geq$20% from baseline, 39.1% had glucose peak on the post-therapy OGTT shift to an earlier timepoint, as compared to 15.4% with similar shift in those without such improvement($P = 0.03$).

Conclusion: Time to glucose peak is a reproducible characteristic on the OGTT and associated with beta-cell function in early T2DM.

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1. Introduction

The oral glucose tolerance test (OGTT) has long been used for the diagnosis of disorders of glucose metabolism in clinical practice [1]. However, the major drawback of the OGTT is its poor reproducibility [2,3]. In this context, high intra-subject variability of the OGTT has been demonstrated in studies of both normoglycemic individuals [4] and patients with diabetes [5]. In addition, several conditions such as time of day [6], duration of fasting before the test [6], differences in glucose load [7], and glycemic status [3] might impact the variability of the test. Thus, it emerges that reproducibility is an essential aspect that should be taken into consideration when evaluating any feature obtained from the OGTT.

The fasting and 2-h post-challenge blood glucose levels are the results from the OGTT that are typically considered in clinical practice [1]. Recently, however, a series of studies has demonstrated that other features of the insulin and glucose response on the OGTT might hold additional information pertaining to metabolic function and future risk of diabetes [8–15]. Specifically, these studies have evaluated the following 5 parameters from the OGTT: the time to peak serum insulin concentration [11]; the shape of the blood glucose curve (monophasic, biphasic, undetermined) [12,13,15]; the relationship between fasting glucose and the nadir of the post-challenge glucose response (i.e. whether or not the glucose nadir reaches a level lower than that at fasting)[8]; the 1-h post-challenge glucose [9]; and the time to peak glucose [14]. However, despite the potential promise of these additional characteristics of the OGTT, little is known about their reproducibility, a critical element which might limit their applicability and value in practice and research [16]. Thus, the objectives of this study were to first evaluate the reproducibility of these five parameters of the insulin and glucose response on the OGTT and then, for those that exhibit reproducibility, characterize their clinical and pathophysiologic relevance in healthy and diabetic individuals.

2. Methods

2.1. Study population

This analysis was conducted using 2-h 75 g OGTT data from two studies undertaken at our institution (Studies A and B). All participants in these studies gave written informed consent and the study protocols were approved by institutional research ethics committees.

Study-A was designed to assess the reproducibility of the 2-h 75 g OGTT at different dilutions of oral glucose [17]. The study population consisted of healthy adults without previously diagnosed hyperglycemia. In this study, 35 subjects completed three replicate OGTTs at each of three dilutions of 75 g glucose (300 ml, 600 ml, 900 ml) in random order approximately one week apart. Participants completed these OGTTs on nine separate mornings following overnight fast. They were instructed to maintain the same dietary and exercise patterns the evening before each test and consume a minimum of 150 g carbohydrate per day over the preceding 3 days. The current analysis was restricted to the OGTTs that used the standard 300 ml dilution and were conducted in the 30 subjects who had normal glucose tolerance on all 3 OGTTs (i.e. 5 of the 35 subjects had dysglycemia on at least one OGTT). These 30 individuals (17 males) had mean age 34.8 ± 12.1 years, body mass index 26.4 ± 4.7 kg/m^2, and normal glucose tolerance on all 3 OGTTs.

As previously described [18,19], Study-B consisted of 63 adult patients with early type 2 diabetes (T2DM) who underwent short-term intensive insulin therapy (IIT) for 4–6 weeks to determine eligibility for a clinical trial (NCT01270789). These patients had mean age 59 ± 8.2 years, duration of diabetes 3.0 ± 2.1 years, and A1c 6.8 ± 0.8%. At the outset of this study, they stopped all oral anti-diabetic medications (metformin or sulfonylurea) and underwent a 2-h, 75 g OGTT in the morning following overnight fast. Following the initial OGTT, they underwent a 4-week course of multiple daily insulin injection therapy consisting of basal insulin detemir and pre-meal insulin aspart with starting doses of 0.2–0.4 U/kg, divided as 60% meal insulin and 40% basal insulin. Insulin doses were titrated to target fasting glucose between 4.0 and 6.0 mmol/l and 2-h post-prandial glucose <8 mmol/l. On the final day of IIT, the last insulin dose was the bolus insulin aspart before dinner, with no bedtime basal insulin. An OGTT was performed the day after cessation of IIT, using the same protocol as at baseline.

2.2. Laboratory measurements

In both studies, venous blood samples were drawn at 0-, 30-, 60-, 90- and 120-min during the OGTTs for measurement of glucose and insulin. These assays were performed at the Banting and Best Diabetes Core Laboratory. Area-under-the-insulin-curve (AUC_{ins}) and area-under-the-glucose-curve (AUC_{gluc}) during the OGTT were calculated by trapezoidal rule. Beta-cell function was assessed with the Insulin Secretion-Sensitivity Index-2 (ISSI-2), a validated OGTT-derived measure of beta-cell function that is analogous to the disposition index obtained from the intravenous glucose tolerance test (ivGTT) [20,21]. ISSI-2 has been directly validated against the ivGTT disposition index, with which it exhibits stronger correlation than other OGTT-derived measures (including insulinogenic index-based measures and Homeostasis Model Assessment of Beta-cell function) [21], and has been used in both clinical trials and observational studies [18,22–24]. ISSI-2 is defined as the product of (i) insulin secretion measured by the ratio of AUC_{ins} to AUC_{gluc} and (ii) insulin sensitivity measured by the Matsuda index [20,25].

2.3. Novel parameters of the insulin and glucose response on the OGTT

The five novel parameters were defined as follows:

(i) *Time to insulin peak*: The time to peak insulin was defined as the timepoint on the OGTT when serum insulin was highest (either 30-, 60-, 90- or 120-min).
(ii) *Shape of the glucose curve*: The shape of the glucose curve on the OGTT was classified as ''monophasic'' when