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Outpatient versus inpatient mixed meal tolerance and arginine stimulation testing yields comparable measures of variability for assessment of beta cell function

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A B S T R A C T

Standard practice to minimize variability in beta cell function (BCF) measurement is to test in inpatient (IP) settings. IP testing strains trial subjects, investigators, and budgets. Outpatient (OP) testing may be a solution although there are few reports on OP BCF testing variability. We compared variability metrics between OP and IP from a standardized mixed meal tolerance test (MMTT) and arginine stimulation test (AST) in two separate type 2 diabetes (T2DM) cohorts (OP, n = 20; IP n = 22) in test-retest design. MMTT variables included: insulin sensitivity (Si); beta cell responsivity (Φtot); and disposition index (DItot = Si* Φtot) following 470 kCal meal. AST variables included: acute insulin response to arginine (AIRarg) and during hyperglycemia (AIRargMAX). *Results:* Baseline characteristics were well-matched. Between and within subject variance for each parameter across cohorts, and intraclass correlation coefficients (ICC-a measure of reproducibility) across parameters were generally comparable for OP to IP. Table summarizes the ICC results for each key parameter and cohort.

Test/Parameter	Outpatient (95% CI)	Inpatient (95% CI)
MMTT: Si	0.49(0,0.69)	0.28(0,0.60)
MMTT: Φtot	0.65(0.16,0.89)	0.81(0.44,0.93)
MMTT: DI	0.67(0,0.83)	0.36(0,0.69)
AST: AIR Arg	0.96(0.88,0.98)	0.84(0.59,0.94)
AST: AIR Arg Max	0.97(0.90,0.99)	0.95(0.86,0.97)
AST: ISR	0.93(0.77,0.97)	0.93(0.82,0.96)

In conclusion, the variability (reproducibility) of BCF measures from standardized MMTT and AST is

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comparable between OP and IP settings. These observations have significant implications for complexity and cost of metabolic studies.

1. Introduction

Emerging interest in characterizing diabetes disease progression, as well as the surge in diabetes therapies, requires more routine inclusion of beta cell function (BCF) assessments in clinical trials. However, BCF testing is seldom incorporated in longitudinal outpatient trials, partly because such tests are traditionally conducted in an inpatient (IP) setting.

There is particular interest in BCF methodologies that are technically robust and operationally feasible to enable repeat testing in longitudinal settings. We have recently reported that standardized Mixed Meal Tolerance (MMTT) and Arginine Stimulation tests (AST) are reliable and reproducible methodologies that provide complementary information on BCF [1,2]. Both tests have variability metrics that support reasonable sample sizes to detect clinically relevant differences in BCF. In that series [1], all experiments were conducted in an IP setting (after an overnight stay), with a goal to reduce sources of variability.

However, the need to sequester subjects for an overnight stay places significant strain on trial execution, including hardship for volunteers; limiting trial execution to study sites with domicile capabilities; and increased cost. Furthermore, overnight confinement could be stressful for volunteers and impact overall quality of the test itself.

These considerations spurred interest in the conduct of these procedures in an outpatient (OP) setting, i.e., where subjects present to the clinical research unit on the morning of the procedure.

2. Methods

To address this question, we assessed variability and reproducibility of standardized MMTT and AST in an OP setting in a group of T2DM subjects using a test-retest paradigm that replicated the inpatient paradigm [1]. We compared these metrics against similar data previously reported in a separate, but similar cohort of IP T2DM subjects, using identical procedures and analytical methods [1].

Subjects: OP: 20 T2DM subjects were evaluated. Inclusion criteria included: fasting glucose of 126–270 mg/dL, HbA1c 6.5%–10.0% on stable metformin monotherapy (500–2000 mg/day) as described previously [1].

Study Design: After obtaining Institutional Review Board approval the study was conducted at two sites (ICON Development Solutions, San Antonio, Texas, and Celerion, Phoenix, Arizona). Following written informed consent and screening, all subjects underwent each procedure on separate days.

OP: four separate visits completed within a 28-day period, with subjects undergoing MMTT at the first and third, and AST at the second and fourth visits. The interval between the two MMTTs and ASTs was approximately a week. Each MMTT or AST was separated from the previous test by about 3 days.

Subjects fasted overnight prior to the procedure. Metformin was withheld the morning of each procedure. Subjects arrived approximately two hours prior to initiation of testing. To minimize stress and ensure timely arrival, subjects were provided transportation as needed. Following arrival and after an hour's rest, subjects underwent brief physical examination and a glucose check. If glucose exceeded 270 mg/dL, testing was deferred to another day. If fasting glucose remained over 270 mg/dL, then the subject was discontinued from the study and referred to their physician.

Procedures: MMTT and AST procedures were identical to those employed in the previously published, inpatient cohort [1]. Samples for glucose, insulin and C-peptide were measured using commercially available assays described previously [1].

2.1. MMTT

BCF parameters were derived as described previously [1]. Glucose, insulin, and C-peptide profiles were used to fit the minimal model to derive estimates of insulin sensitivity (Si); beta cell responsivity (Φtot); and disposition index (DItot = Si*Φtot) [3,4]. For the AST, the baseline corrected acute insulin response to arginine (AIRarg) was determined in the first 5 min post arginine infusion (5 gm IV) during the baseline glucose state or after the glucose infusion (AIRargMAX) [2,5]. Insulin secretory reserve (ISR) was calculated from AIRargMAX-AIRarg.

2.2. Statistical analyses

As described for the inpatient cohort [1] between- and within-subject variance component estimates across genders were derived using a mixed effects model on natural log transformed data, treating gender as a fixed effect, subjects grouped by gender as a random effect, and visits as a repeated effect. Results are reported as geometric coefficients of variation (GCVs) and respective asymptotic 90% confidence intervals. Model predicted adjusted geometric means (95% CI) for the inpatient and outpatient cohorts are provided. To characterize reproducibility of within subject measures of BCF, intra-class correlation coefficients (ICCs) and respective bootstrap 90% CIs were calculated.

Following the outpatient cohort analyses, a pooled analysis for assessment of variance component structures between- and within-subject across study cohorts was conducted. As the cohorts were composed of different individuals, comparability of cohorts was tested to allow adjustment for potential differences. Between- and within-subject variance components across cohorts were estimated using a mixed model analysis of covariance (ANCOVA) on the pooled results. Pooled analyses included fixed terms for study cohort and gender, as well as, age, BMI and HbA1cto adjust for minor covariate variation between cohorts. Sequential model reductions were performed testing different or common within- and between-subject variance component structures across genders. Subjects were grouped by cohort as a random effect and visits as a repeated effect. Likelihood ratio tests (LRTs) were used to assess variance component structures across cohorts to determine whether a common between- and within-subject variance structure across cohorts sufficiently described the data. A two-sided significance level equal to 0.00125 was pre-specified to protect against declaring spurious differences in variance component estimates across study cohorts in the model selection process. This alpha level corresponds to a replication p-value threshold (0.05×0.025) for detecting a difference in analysis models. If results indicated that a common within- and between-subject variance component structure across genders sufficiently described the data, then the pooled inpatient/outpatient results would be presented.

3. Results

OP: Of 26 subjects recruited, 20 (10 men/10 women) completed the study (two subjects were removed from the study for persistent elevation of fasting glucose over 270 mg/dL; four subjects discontinued for reasons unrelated to study). IP: Comparison inpatient data were derived from the previously reported cohort of 22 subjects (11 men/11women) [1]. Demographic and baseline characteristics for both cohorts are summarized in Table 1. Study cohorts were comparable with significant overlap in distributions of baseline characteristics.