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FACT SHEET

Oral Glucose Tolerance and Mixed Meal Tolerance Tests

General Uses and Considerations

The oral glucose tolerance test (OGTT) and mixed meal tolerance test (MMT) are widely used in clinical metabolic research and diabetes drug development. The OGTT and MMTT provide an integrated assessment to the β-cell response to an intestinally-delivered insulin secretory stimulus that includes activation of the incretin axis. The major incretin hormones are glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP) secreted, respectively, by the L and K cells of the intestine. The incretin effect comprises enhancement of glucose-stimulated insulin secretion from islet β-cells in concert with reduced glucagon release from α-cells. When assessing the response to therapeutic agents whose primary mode of action is via the incretin axis, e.g. dipeptidyl peptidase (DDP)-4 inhibitors, the response of GLP-1 and GIP can be quantified with respect to stimulation of insulin secretion and suppression of glucagon secretion.

Oral glucose tolerance test - The 75 g oral glucose tolerance test is the reference method for diagnosing defined categories of glucose intolerance and type 2 diabetes.

Mixed meal tolerance test – This provides a more comprehensive physiological stimulus to insulin secretion since β-cells are responsive to certain amino acids and fatty acids in addition to glucose.

Subjects and Preparation

OGTTs and MMTTs are performed in the morning following an overnight fast of >8 hours. Limitations are placed on strenuous exercise, alcohol, caffeine and tobacco use, all of which may influence insulin sensitivity. Overnight admission to the clinical research facility prior to the clamp procedure helps ensure compliance with these restrictions. Since dietary carbohydrate restriction in the days preceding an OGTT may impair glucose tolerance 100-150 g/day carbohydrates should be consumed for three days prior to study. Longer-term influences on glucose tolerance are the macronutrient composition of the diet, e.g. percentage of calories derived from carbohydrate vs. fat, the proportion of monounsaturated fat, and micronutrient status.

Procedure

After overnight fast, a cannula is placed in a forearm vein. Blood is drawn for baseline glucose and insulin concentrations. For adults undergoing a 75 g anhydrous glucose is dissolved in 250 ml water which may be made more palatable with a non-calorie flavor additive. This should be consumed within 5 min with the subject sitting quietly throughout the test. For children, the glucose load is calculated according to body weight, i.e. 1.75 g per kg of weight to a maximum of 75 g. Venous blood samples are withdrawn every 30 min until 120 min. Sampling may be extended, e.g. to 5 hours, to capture the return of glucose and insulin concentrations to baseline. Note that the diagnosis of impaired glucose intolerance (IGT) or diabetes is based solely on the baseline and 120 min blood glucose levels. In an MMTT, a standardized meal of specified macronutrient content or a proprietary meal substitute, e.g. Ensure®, may be used with sampling at similar time points as for the OGTT.

Assessment of Insulin Secretion and Insulin Action

In addition to providing detailed information about glucose responses OGTT/MMTTs may also be used to provide exploratory data on insulin secretion and insulin sensitivity.

Insulin secretion - Since neither the OGTT nor MMTT is standardized in terms of the attained blood glucose concentrations methods for normalizing insulin secretion to the glucose stimulus have been developed. A number of empirical indexes of varying levels of sophistication that use different modeling approaches have been proposed which relate insulin responses to increments in blood glucose. For example, the insulinogenic index is calculated as the ratio of the increment of insulin to glucose above baseline 30 minutes (Δinsulin/Δglucose).

Insulin sensitivity - Several whole body insulin sensitivity indexes based on data derived from OGTTs have been published, e.g. the Matsuda Index. These have been validated against the reference method hyperinsulinemic euglycemic clamp technique and are regarded as providing reliable, if indirect, assessments of whole body insulin sensitivity. The rise in blood glucose following an oral challenge is determined in part by the degree of suppression of hepatic glucose production. Radiolabelled tracers may be used to ascertain the metabolic fate of ingested glucose thereby quantifying the contribution of endogenous glucose production to the post-challenge blood glucose concentration. This may be of interest in the assessment of drugs with putative inhibitory effects on hepatic glucose production. Stable isotope (non-radioactive) tracer techniques may also be used to quantify the disposal of ingested glucose via the glycolytic pathway.

Interpretation and Limitations

- The diagnosis of impaired fasting glucose (IFG), impaired glucose intolerance (IGT) or diabetes requires a 75 g glucose challenge and is based on fasting and 120 min blood glucose levels. This permits progression or regression from one diagnostic category to another, e.g. IGT to diabetes or IGT to normal glucose tolerance, in response to therapy to be determined.
- Note that IFG and IGT cannot be reliably diagnosed using the MMTT since the latter test provides a non-standardized oral glucose challenge.
- For paired comparisons, i.e. before and after a therapeutic intervention in individual subjects, the area under the curve (AUC) for serum insulin (or C-peptide) offers an exploratory assessment of glucose-lowering effects and the change in endogenous insulin secretion in response to a therapeutic intervention that incorporates both the early and later phases of insulin secretion.

The OGTT has a relatively high within-subject variability on repeat testing with a reported co-efficient of variation in the literature of >15%. Contributory factors to intra-individual variability include inconstant rates of glucose absorption and splanchnic glucose uptake, gastroparesis due to diabetic autonomic neuropathy, and the modulating effects of impaired incretin hormone secretion and/or action in states of glucose intolerance and type 2 diabetes. This variability can be minimized by standardizing the experimental conditions before and during the procedure.

References and Further Reading

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