Considerations and Recommendations when Reporting Studies on Glucose Metabolism in Mouse Models

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MMPC
Mouse Metabolic Phenotyping Center

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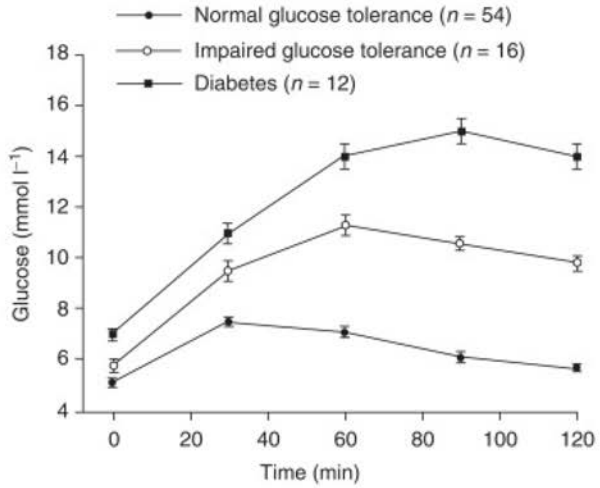
Discovering new roads to recovery

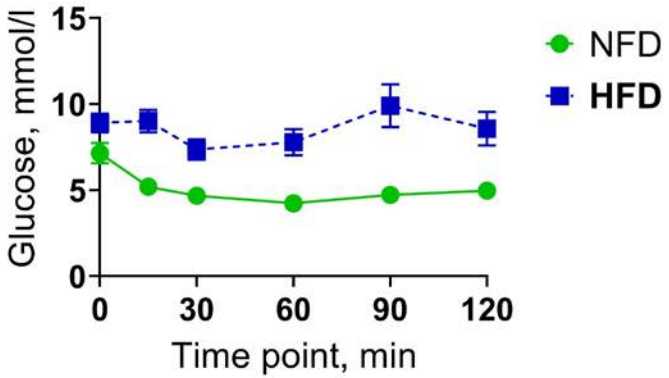
Typical Tests of Glucose Metabolism in Mouse Models

Mouse model with aberrant glucose phenotype

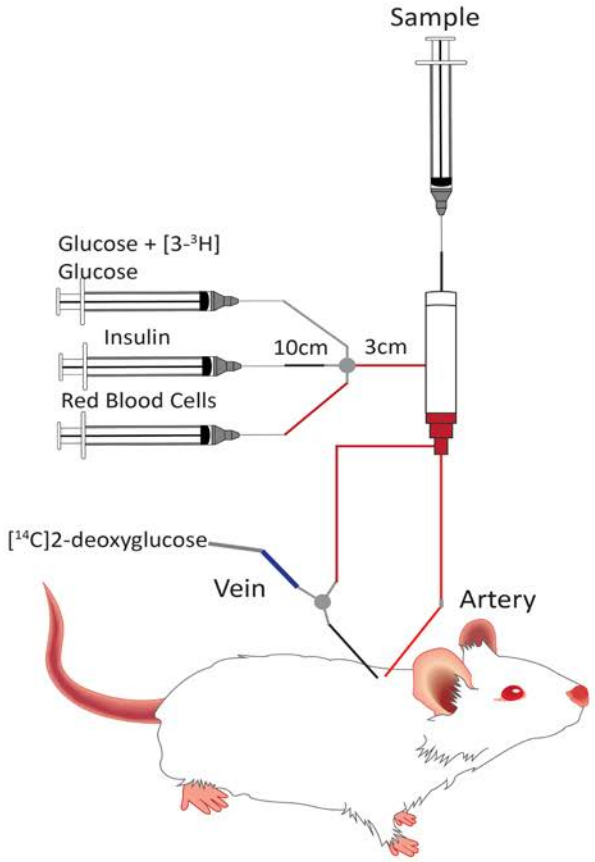
Glucose Tolerance Test



Insulin Tolerance Test



Hyperinsulinemic-euglycemic Clamp



Glucose Tolerance Test (GTT) and Insulin Tolerance Test (ITT)

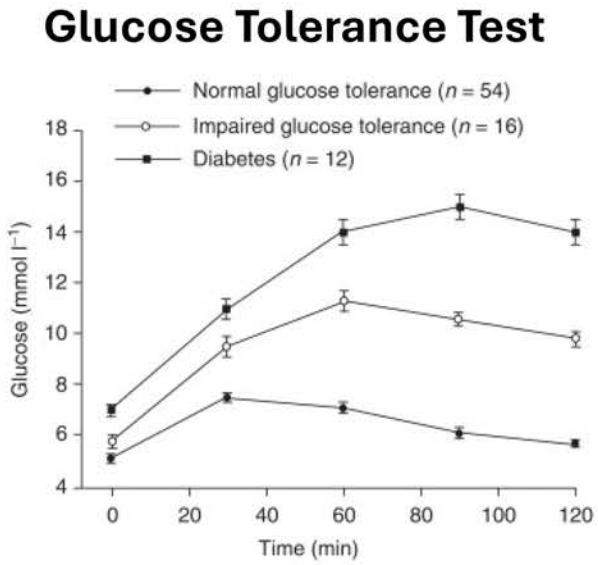
Mouse model with aberrant glucose phenotype

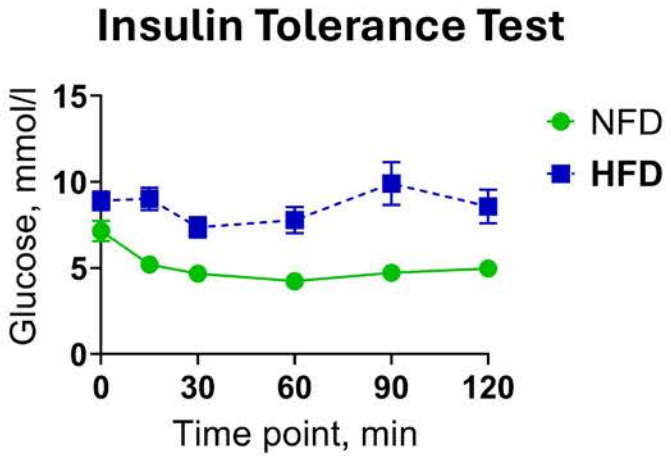
Glucose Tolerance Test

Fast ➡ Dose Glucose: IP, IV, Oral ➡ Measure blood glucose over 90-120 min

Insulin Tolerance Test

Fast ➡ Dose Insulin: IP, IV ➡ Measure blood glucose over 90-120 min



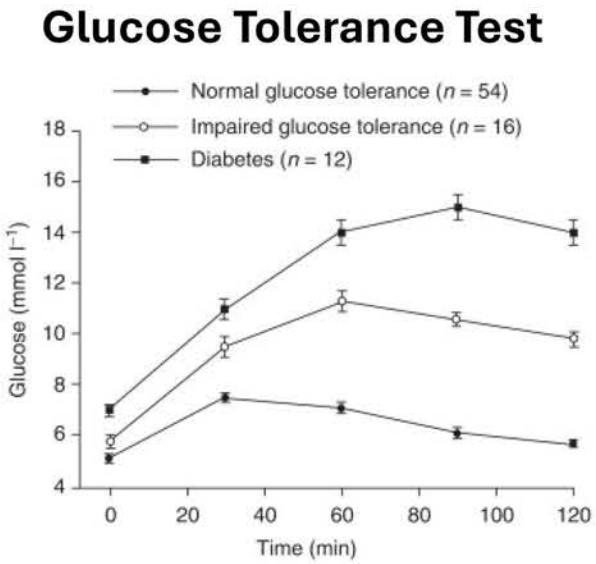


Glucose Tolerance Test (GTT)

Mouse model with aberrant glucose phenotype

Glucose Tolerance Test

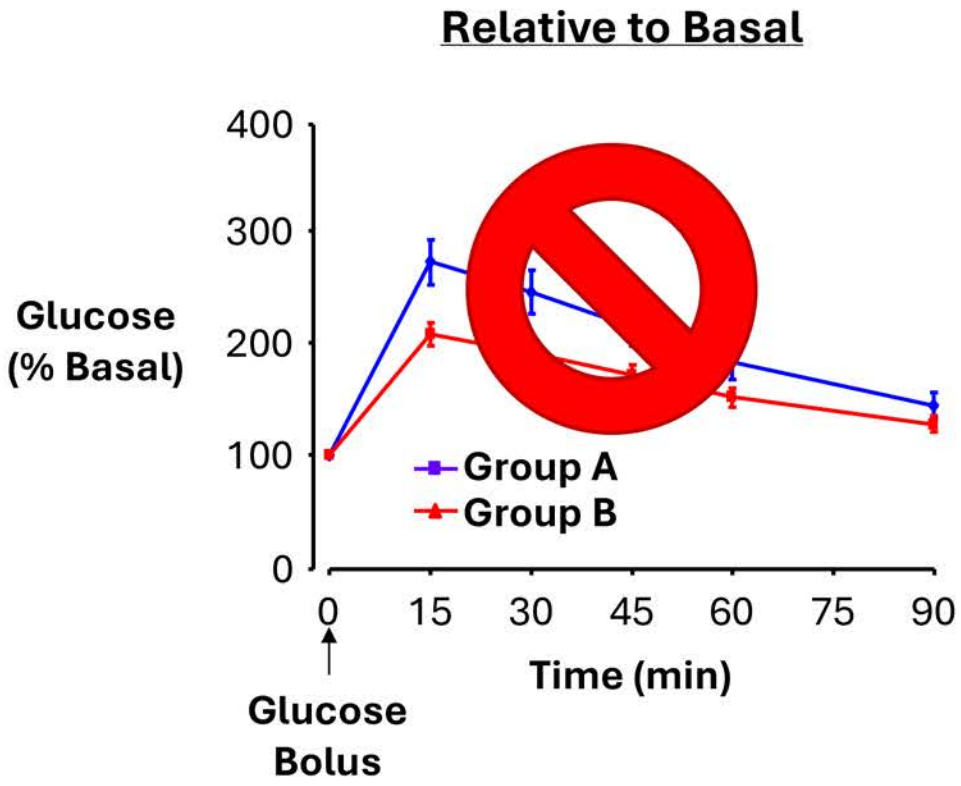
Fast ➡ Dose Glucose:
IP
IV
Oral
➡ Measure blood glucose over 90-120 min

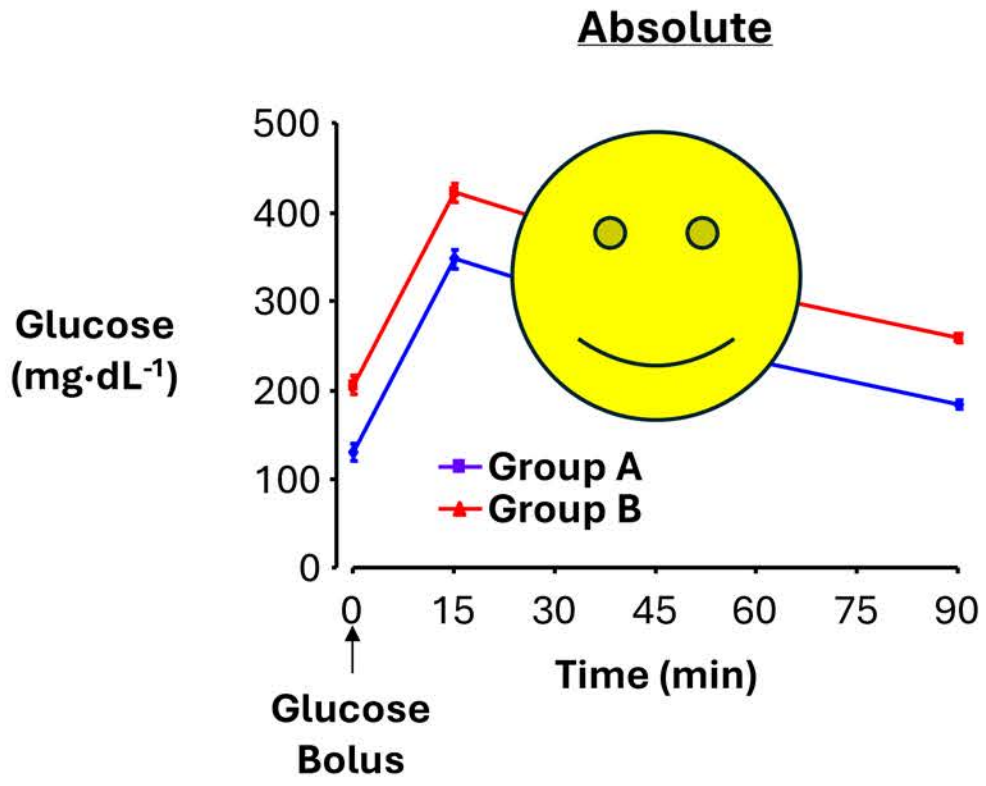


- Translated from a diagnostic test in humans to a “quantitative” phenotyping test in mice
- Not indicative of insulin sensitivity
  - Insulin secretion
  - Insulin action
  - Glucose effectiveness

GTT: How to present results

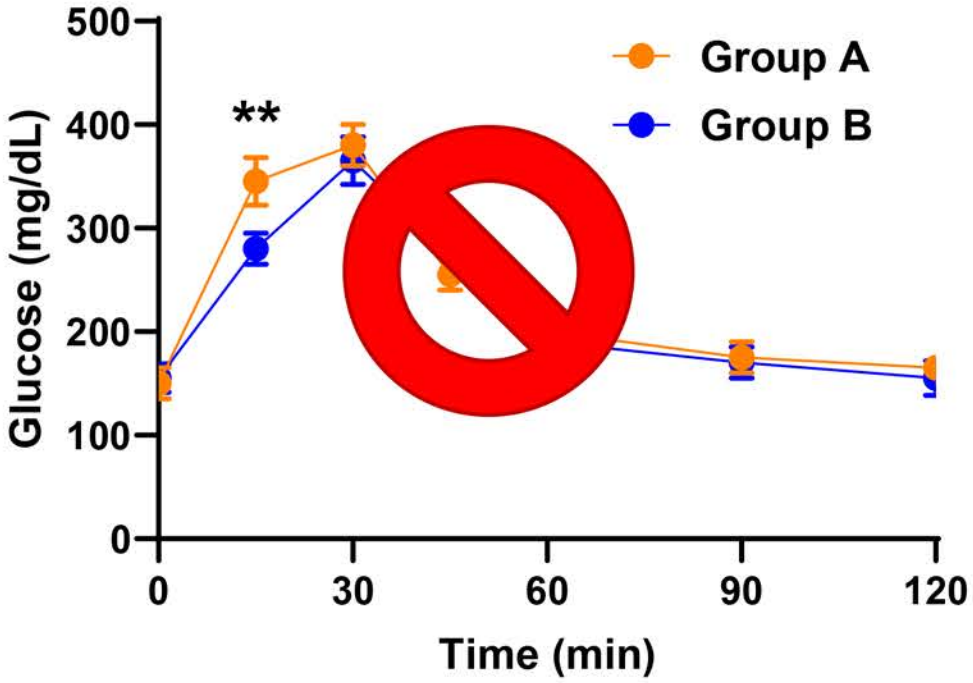
Relative to basal vs. absolute glucose

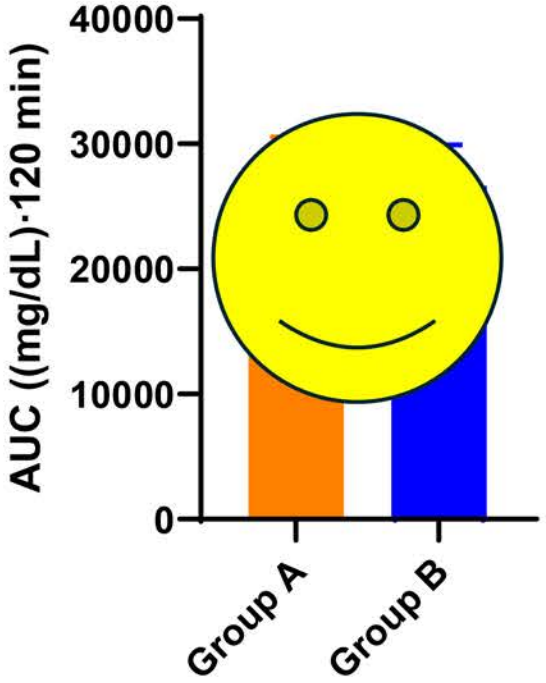




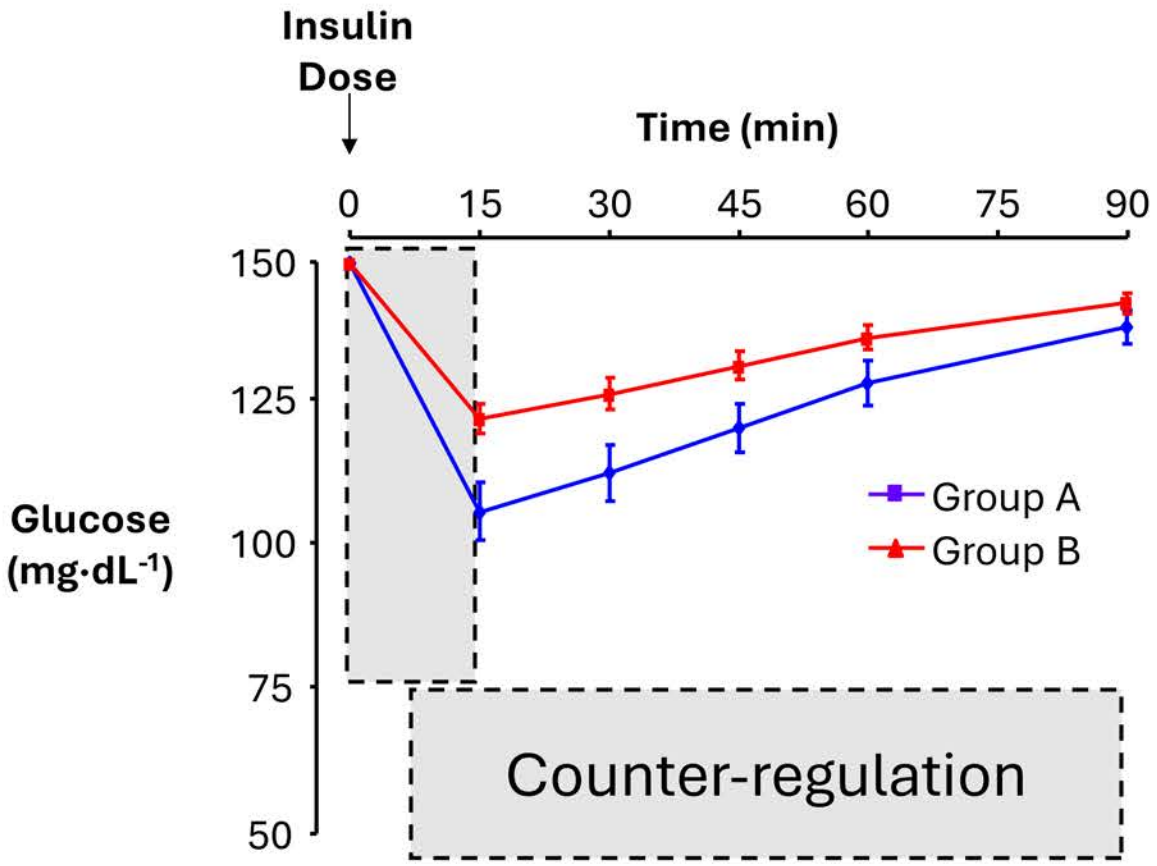
GTT: How to present results

Statistics





ITT: How to present results



<u>Similar issues as GTT</u>

- Absolute vs. relative fall in glucose
- Time point vs. AOC statistics

<u>Other considerations</u>

- Insulin has a short half-life
- Counter-regulation

- Rate of fall in glucose during the first 15 min

Hyperinsulinemic-euglycemic clamp

Constant Insulin Infusion
Variable Glucose Infusion
Isotopic Glucose Tracers

Insulin

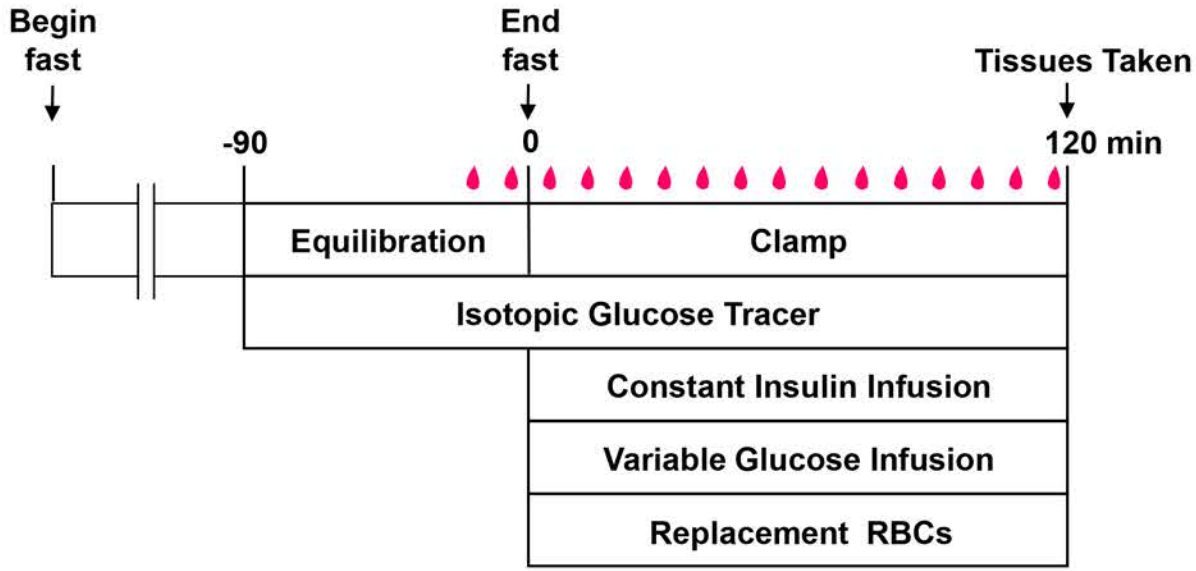
Glucose

Glucose Infusion Rate (GIR)

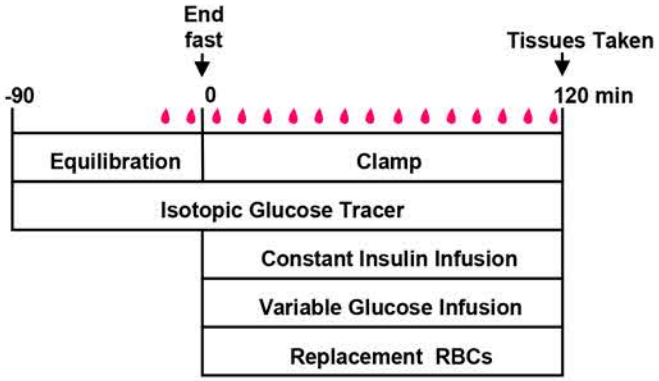
Endogenous Glucose Production ($EndoR_a$)

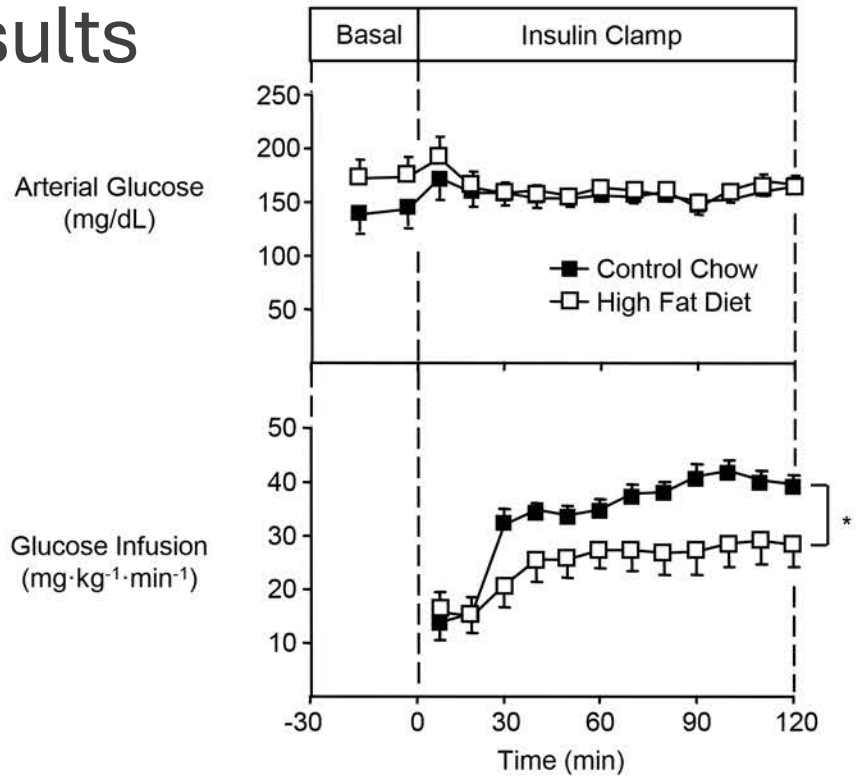
Glucose Disappearance (R_d)

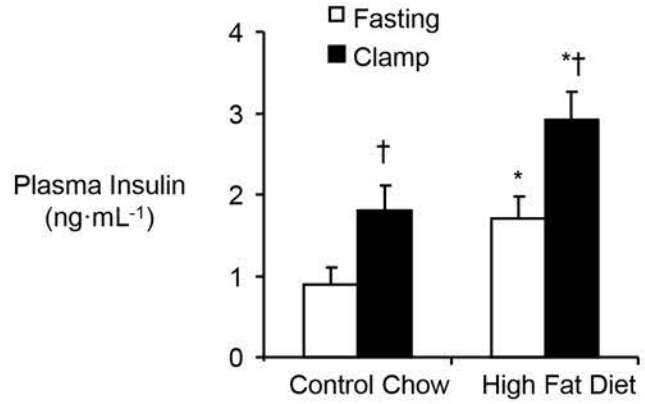
Glucose Metabolic Index (R_g)

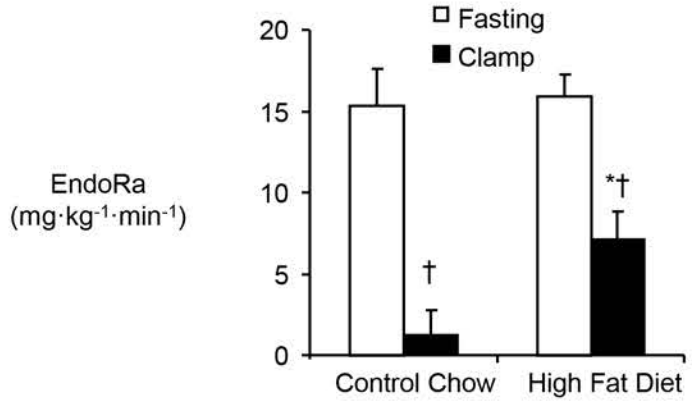


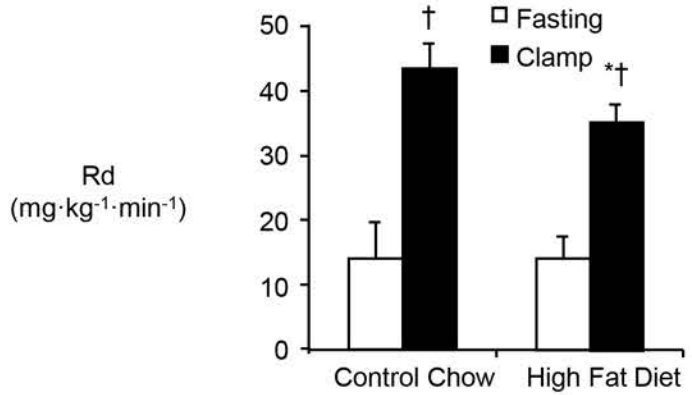
Hyperinsulinemic-euglycemic clamp:
How to present results

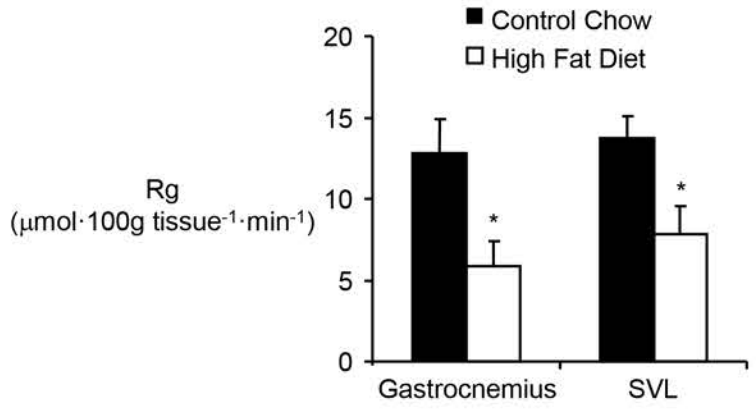










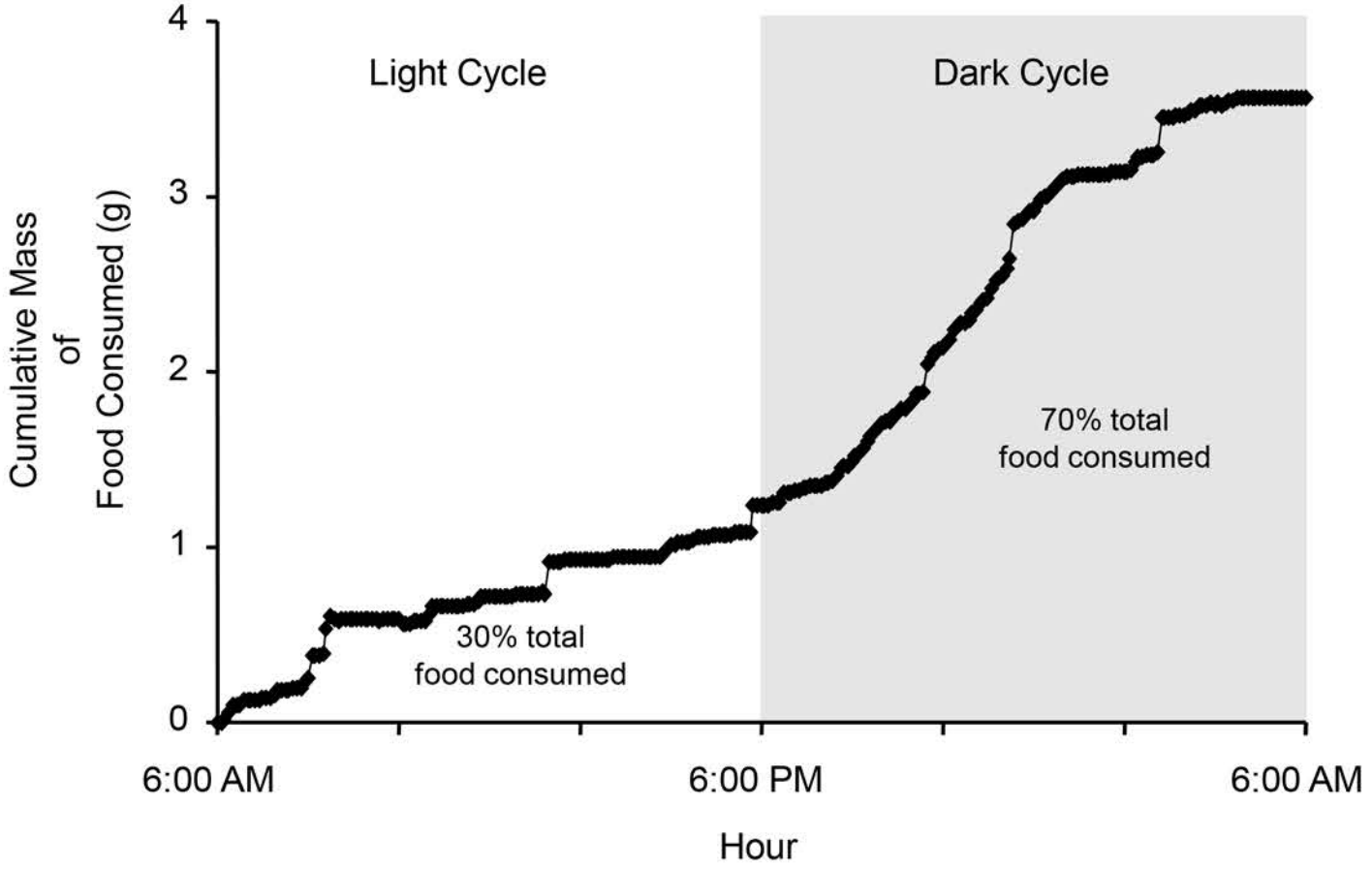


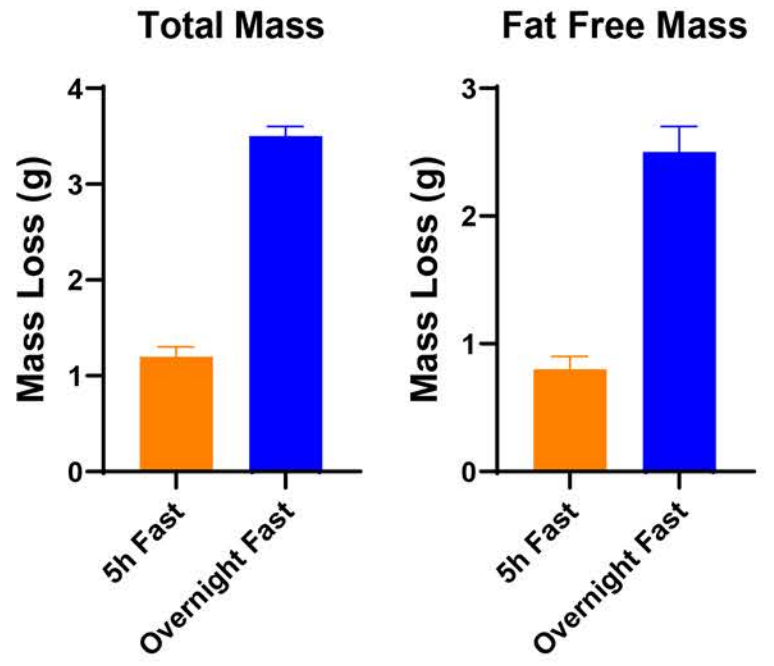
Other Considerations

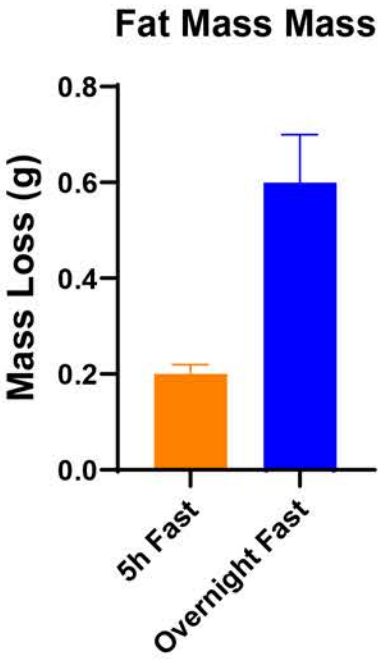
Parameters to Report in Publications

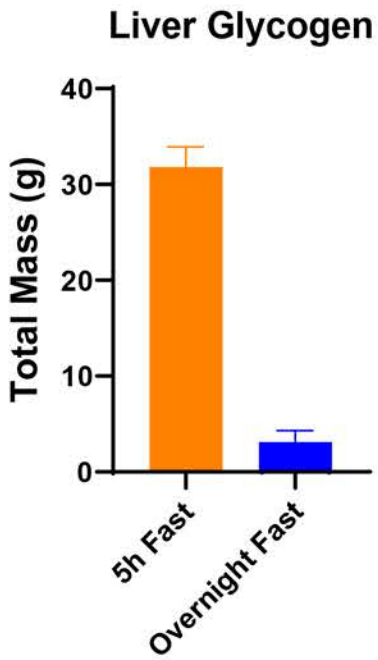
- **Mouse Traits:**
  - **Age**
  - **Sex**
  - **Strain**
  - **Details of genetic modifications**
- **Environment:**
  - **Light:Dark cycle**
  - **Housing temperature**
  - **Breeding scheme**
- **Procedural Parameters:**
  - **Fast duration**
  - **Dosing calculation**
  - **Sampling method**

Fast Duration



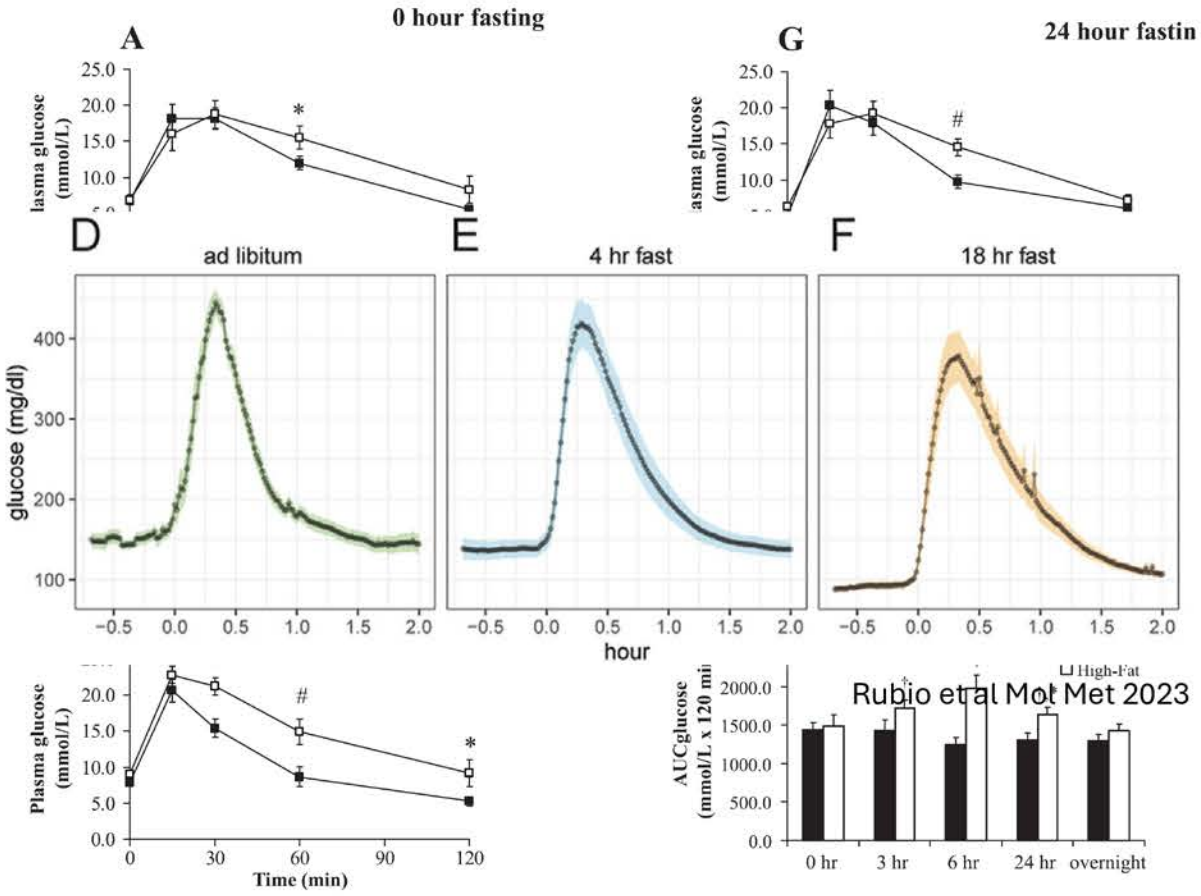






Fast Duration: Effects on Metabolic Tests

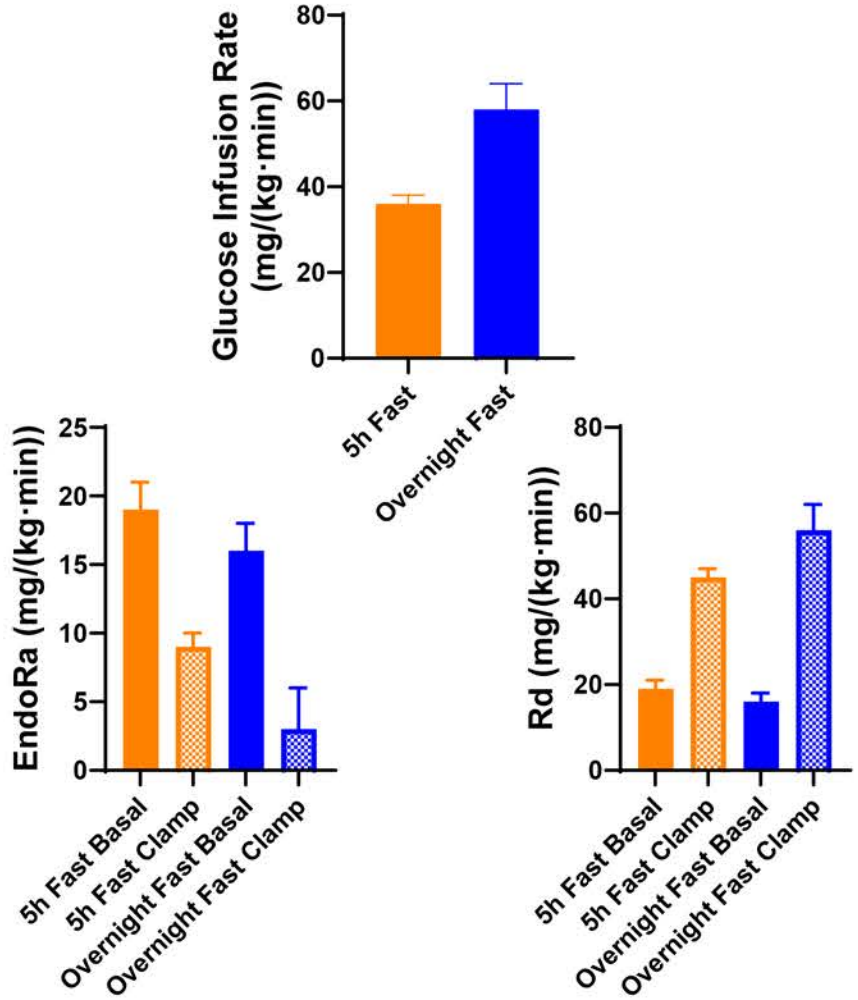
Glucose Tolerance Test



Rubio et al Mol Met 2023

Andrikopoulos et al Am J Physiol Endo Metab 2008

Hyperinsulinemic-euglycemic clamp



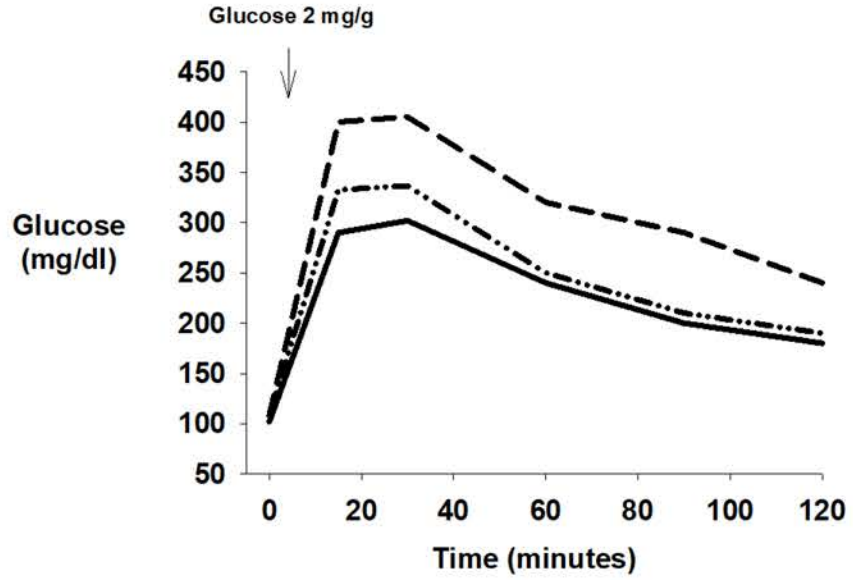
Dosing Calculation

The norm

Humans: fixed dose regardless of weight

Mice: based on **total** body weight

	body weight (g)	% body fat	glucose dose (mg)
lean	20	3	40
obese	30	35	60
obese (adjusted)	30	35	40



Recommendation

- **If body composition is known, base the dose on lean mass**
- **Otherwise, a fixed dose is appropriate**

Deficiencies in the Field

- Lack of detailed description of methods
- Lack of detailed presentation of results

How to fix them

- Describe how the experiment was performed
- Present data in a manner that can be interpreted

Ayala JE, Bracy DP, McGuinness OP and Wasserman DH. Considerations in the design of hyperinsulinemic-euglycemic clamps in the conscious mouse. (2006) *Diabetes* 55: 390-397.

McGuinness OP, Ayala JE, Laughlin MR and Wasserman DH. NIH experiment in centralized mouse phenotyping: the Vanderbilt experience and recommendations for evaluating glucose homeostasis in the mouse. (2006) *Am J Physiol Endocrinol Metab* 297: E849-855.

Ayala JE, Samuel VT, Morton GJ, Obici S, Croniger CM, Shulman GI, Wasserman DH and McGuinness OP for the NIH-Mouse Metabolic Phenotyping Centers. Standard operating procedures for describing and performing metabolic tests of glucose homeostasis in mice. (2010) *Dis Model Mech* 3: 525-534.