Regulation of glucose tolerance

Interaction with states of insulin resistance
What is a normal fasting Glucose concentration?

- Normal fasting level = <110 mg/dl
- Impaired glucose intolerance = 110-126 mg/dl
- Diabetes mellitus > 126 mg/dl

Steady State

\[ \text{In} = \text{Out} \]

\[ \text{Out} = \text{Clearance} \times \text{Concentration} \]
Relationship between Mass and Concentration

\[ \text{Concentration} = \frac{\text{Mass Injected}}{\text{Volume}} \]
Distribution of Total Body Water

- **ECF** = 16 Liters
- **ISF** = \(3/4\) ECF, 12 Liters
- **Plasma** = \(1/4\) ECF, 4 liters
- **ICF** = 28 Liters

70 kg lean male
Where is glucose?
If arterial glucose = 100 mg/dl and insulin is at a basal concentration, what is the glucose concentration in a muscle cell?

1. 100 mg/dl
2. Slightly less than 100 mg/dl ~ 98 mg/dl
3. Very low ~ 2 mg/dl
4. Greater than 100 mg/dl
Blood flow

Cell

Glu-6P

Glucose

A: GLU = 100 mg/dl

GLU = 98 mg/dl

V

Blood flow
If arterial glucose = 100 mg/dl, what is the interstitial glucose concentration outside a muscle cell in the presence of basal insulin?

1. 100 mg/dl
2. Slightly less than 98 mg/dl
3. Very low ~2 mg/dl
4. Greater than 100 mg/dl
Glucose mass (70 kg individual)

- Total body water (TBW)=60% Body Weight
- 42 L TBW (=0.60 *70 kg)
- Extracellular fluid volume (ECF)=1/3 TBW
- 14 L ECF {~volume of distribution of glucose}
- Glucose 100 mg/dl=1 mg/ml=1 g/L
- 14 grams glucose in ECF
- 9 g/hr flux rate= rate of liver glucose production
Ingest 75 grams glucose

- 75 grams in 300 ml water (~2 cokes)
- By 180 minutes the glucose levels return to normal
- Removed 5.3 times the mass of glucose in the body in 180 min
## The Diabetes Expert Committee Criteria for Evaluating the Standard Oral Glucose Tolerance Test

<table>
<thead>
<tr>
<th>mg/dl</th>
<th>Normal Glucose Tolerance</th>
<th>Impaired glucose tolerance</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting glucose</strong></td>
<td>&lt;110</td>
<td>100-125</td>
<td>&gt;126</td>
</tr>
<tr>
<td><strong>2-hour post oral glucose load</strong></td>
<td>&lt;140</td>
<td>140-199</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

Glucose given after an overnight fast in subjects receiving at least 150–200 g of carbohydrate daily for 3 days before the test.

50 g glucose load

- If you did nothing
- glucose level exceed 300 mg/dl
Liver: 9 g/hr
Glucose=90 mg/dl

CNS

Brain: 6 g/hr

Muscle Fat: 3 g/hr

Insulin + Glucagon

Overnight fasted state
Liver: 12 g/hr

↑ Glucose = 130 mg/dl

CNS

Brain: 6 g/hr

Muscle: 32 g/hr

↑ Insulin

↑ or ↓ Glucagon

↑ Insulin

↑ Cholinergic

Intestine: 50 g/hr

Fed state
Liver $\downarrow$ Glucose $\approx$ 70 mg/dl

CNS

Brain $\approx$ 5 g/hr

Muscle Fat 2 g/hr

$\uparrow$ Glucagon

$\downarrow$ Insulin

$\downarrow$ Glucose $\approx$ 70 mg/dl

Prolonged fasted state

Ketones
Liver: 46 g/hr

Glucose = ~90 mg/dl

CNS

Brain: 6 g/hr

Muscle: 40 g/hr

↑Glucagon
↓Insulin

"Fight or Flight" state

Increased
Muscle Energy Demand

Adrenergic

Increased
Muscle Energy Demand
Liver: 26 g/hr

Glucose > ~300 mg/dl

↑Glucagon

Brain: 6 g/hr

Muscle: <1 g/hr

Fat: <1 g/hr

Kidney: ~19 g/hr

Ketones

Type I Diabetic state (loss of insulin secretion)
Tight control improves glycemic response to a meal

Figure 1. Plasma glucose (left) and free insulin concentrations (right) in nondiabetic subjects and diabetic subjects when insulin deficient (ID) and while treated with continuous subcutaneous insulin infusion (CSII). The meal was taken at 0 min.
Defects in both alpha and beta cell function are present in diabetes (T2DM).

Types of Resistance to Insulin Action

Modified from Figure 1, C. Ronald Kahn, *Metabolism, 27:1893-1902, 1978.*
Steady State

In = Out

Out = Clearance x Concentration
If whole body glucose uptake is increased by 4-fold by meal levels of insulin, will glucose-dependent glucose uptake increase?

1. Yes
2. No
Tissue glucose uptake increases in proportion to the available glucose

Slope~clearance

Insulin facilitates this process in tissues that respond to insulin
- Vasodilation
- ↑transport
- ↑phosphorylation

Insulin resistance impairs this process
In the presence of hyperglycemia (~160 mg/dl) both insulin stimulated splanchnic and muscle glucose uptake are impaired.
Splanchnic metabolism during hyperglycemia

- Persistent glucose production
- Failure to take up glucose with additional insulin
Infusing glucose at a rate equal to endogenous glucose production suppresses glucose production.

Individuals with type II diabetes make glucose despite high glucose levels.
Liver
9 g/hr

Glucose = 120 mg/dl

CNS

6 g/hr
Brain

Muscle Fat

3 g/hr

↑↑ Insulin

Glucagon

↑↑ Insulin

Overnight Fasted Insulin Resistant state
The most common cause of insulin resistance is obesity
Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

**Obesity (BMI ≥30 kg/m²)**

- **1994**
- **2000**
- **2009**

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2009

Compensation for insulin resistance

- Increase insulin secretion
- Mild to severe hyperglycemia (Diabetes Type II; NIDDM) because of inadequate pancreas compensation
- Glucose production by liver and uptake by peripheral tissues can be normal or increased
The end