Diabetes Mellitus

A biochemical/biomedical overview
Diabetes Mellitus:
a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both

- 20.8 million in US (7% of population)
- Estimated 14.6 million diagnosed (only 2/3)
- Consists of 3 types:
  1) Type 1 diabetes
  2) Type 2 diabetes
  3) Gestational diabetes

Complications:
- Stroke
- Heart attack
- Kidney disease
- Eye Disease
- Nerve Damage
Diabetes Mellitus

♦ **Type 1 Diabetes**
  - cells that produce insulin are destroyed
  - results in insulin dependence
  - commonly detected before 30

♦ **Type 2 Diabetes**
  - blood glucose levels rise due to
    1) Lack of insulin production
    2) Insufficient insulin action (resistant cells)
  - commonly detected after 40
  - effects > 90%
  - eventually leads to β-cell failure (resulting in insulin dependence)

**Gestational Diabetes**
3-5% of pregnant women in the US develop gestational diabetes
A depiction of insulin receptors (active and not active) and the glucose cell transport system. More on this later…

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We will cover the ‘membrane transport system’ later in the Biotech course, but this is how glucose gets admitted to the cell (or not)
Insulin

- Discovered in 1921 by Banting and Best
- Consist of A & B chains linked by 2 disulfide bonds (plus additional disulfide in A)

- A = 21 amino acids  B = 30 amino acids
Insulin differs slightly among animals. Pig insulin was pretty close, and relatively easy to get.

| Amino acid differences among mammalian insulins in A 8, 9, 10 and B 30 |
|-----------------------------|----------------|----------------|----------------|
|                             | A 8 | A 9 | A 10 | B 30 |
| Beef                        | Ala | Ser | Val  | Ala  |
| Sheep                       | Ala | Gly | Val  | Ala  |
| Pig                         | Thr | Ser | Ileu | Ala  |
| Sperm whale                 | Thr | Ser | Ileu | Ala  |
| Sei whale                   | Ala | Ser | Thr  | Ala  |
| Human subject               | Thr | Ser | Ileu | Thr  |
| Rabbit                      | Thr | Ser | Ileu | Ser  |
| Horse                       | Thr | Gly | Ileu | Ala  |
Insulin synthesis in the body

- Produced within the pancreas by β cells → islets of Langerhans
- Insulin mRNA is translated as a single chain precursor called preproinsulin
- Removal of signal peptide during insertion into the endoplasmic reticulum generates proinsulin (signal peptides are 15-30 amino acid extensions which direct the insertion of the protein into the ER membrane)
- Within the endoplasmic reticulum, proinsulin is exposed to several specific endopeptidases which excise the C peptide, thereby generating the mature form of insulin
- Stored as β granules in the pancreas (see next slide)
Insulin beta granules
The structure of insulin. The left side is a space-filling model of the insulin monomer, believed to be biologically active. Carbon is green, hydrogen white, oxygen red, and nitrogen blue. On the right side is a ribbon diagram of the insulin hexamer, believed to be the stored form. A monomer unit is highlighted with the A chain in blue and the B chain in cyan. Yellow denotes disulfide bonds, and magenta spheres are zinc ions.
High-resolution model of six insulin molecules assembled in a hexamer, highlighting the threefold symmetry, the zinc ion holding it together (pink sphere), and the histidine residues (pink sticks) involved in zinc binding.

Inactive insulin is stored in the body as a hexamer, while the active form is the monomer.
Types of Diabetes

- Type 1 Diabetes Mellitus
- Type 2 Diabetes Mellitus
- Gestational Diabetes
- Other types:
  - LADA (maturity-onset diabetes of youth)
  - MODY (maturity-onset diabetes of youth)
  - Secondary Diabetes Mellitus
Type 1 diabetes

- Was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes.

- Type 1 diabetes develops when the body’s immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin that regulates blood glucose.

- This form of diabetes usually strikes children and young adults, although disease onset can occur at any age.

- Type 1 diabetes may account for 5% to 10% of all diagnosed cases of diabetes.

- Risk factors for type 1 diabetes may include autoimmune, genetic, and environmental factors.
Type 2 diabetes

- Was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes.
- Type 2 diabetes may account for about 90% to 95% of all diagnosed cases of diabetes.
- It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin.
- Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.
- African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians or Other Pacific Islanders are at particularly high risk for type 2 diabetes.
- Type 2 diabetes is increasingly being diagnosed in children and adolescents.
Other types of DM

- Other specific types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, drugs, malnutrition, infections, and other illnesses.

- Such types of diabetes may account for 1% to 5% of all diagnosed cases of diabetes.
Now back to the cell transport system....
The pancreas is an amazing chemical factory:

The bulk of the pancreas is an exocrine gland secreting pancreatic fluid into the duodenum after a meal.

Inside the pancreas are millions of clusters of cells called islets of Langerhans. The islets are endocrine tissue containing four types of cells. In order of abundance, they are:

- Beta cells, which secrete insulin and amylin
- Alpha cells, which secrete glucagon
- Delta cells, which secrete somatostatin
- Gamma cells, which secrete a polypeptide
Pancreatic Hormones

♦ Insulin – allows your cells to take up glucose
♦ Amylin – slows gastric emptying, thus serving to curtail the onslaught of glucose into the bloodstream
♦ Glucagon – raises glucose in the bloodstream (opposite of insulin)
♦ Somatostatin – inhibits the secretion of other hormones, including insulin
♦ Pancreatic Polypeptide – another metabolic regulator. Exact function still uncertain.
Beta cells have channels in their plasma membrane that serve as glucose detectors. Beta cells secrete insulin in response to a rising level of circulating glucose.

**Insulin** is a small protein consisting of an A chain of 21 amino acids linked by two disulfide (S—S) bridges to a B chain of 30 amino acids.
Another diagram of the amino acid sequence
Here's some relative sizes
Insulin affects many organs:

- It stimulates skeletal muscle fibers.
- It stimulates liver cells.
- It acts on fat cells.
- It inhibits production of certain enzyme.

In each case, insulin triggers these effects by binding to the insulin receptor.
The insulin receptor (IR) is a transmembrane glycoprotein, composed of 2α and 2β domains.

Its intracellular tyrosine kinase domain is activated by binding of insulin, leading to a cascade of signaling events.

This is better-depicted by the following two video clips.
Two video clips:
1. Insulin production
2. Insulin docking
Insulin drug evolution

Stage 1  Insulin was extracted from the glands of cows and pigs. (1920s)

Stage 2  Convert pig insulin into human insulin by removing the one amino acid that distinguishes them and replacing it with the human version.
Stage 3 - Recombinant DNA technology (late 1970’s)
Insert the human insulin gene into E. coli and culture the recombinant E. coli to produce insulin (trade name = Humulin®). Yeast is also used to produce insulin under trade name = Novolin® 1987.
Management of Diabetes Mellitus
Nutritional Management for Type I Diabetes

- Consistency and timing of meals
- Timing of insulin
- Monitor blood glucose regularly
Nutritional Management for Type II Diabetes

- Weight loss
- Smaller meals and snacks
- Physical activity
- Monitor blood glucose and medications
Nutrition Recommendations

- **Carbohydrate**
  - 60-70% calories from carbohydrates and mono-unsaturated fats

- **Protein**
  - 10-20% total calories
Nutrition Recommendations

- **Fat**
  - <10% calories from saturated fat
  - 10% calories from PUFA
  - <300 mg cholesterol

- **Fiber**
  - 20-35 grams/day

- **Alcohol**
  - Type I – limit to 2 drinks/day, with meals
  - Type II – substitute for fat calories
Diabetic Exchange Lists

Refer to the Diabetes exchange lists meal planning guide