Treatment of Diabetes

The Past, The Present and The Future

جامعة الشارقة
UNIVERSITY OF SHARJAH

The Past.

Old Civilizations

- Little was known; remedies were based on beliefs and practices
- Oils of roses, dates; broken red coral; sweet almonds; jelly of vipers' flesh.

Pre-insulin Era

- Most common: calories restriction.
- Some literature about ketosis in diabetic coma.

19th Century

- Diet and exercise were the best treatment; led by Joslin and Fitz.
- Opium or 'syrup of poppies' was used from 1675-1898; relief of symptoms (such as gangrene).

20th Century: Insulin Discovery

- Extracted by the Canadian surgeon Banting and his assistant Best; experimented on dogs.
- The bovine extract was infused into a 14 yo boy in 1922; started the revolution in diabetic treatment and research.

Banting and Best

In the 1950s and After.

- Discovery of the first oral antidiabetics, sulfonylureas.
- Followed by metformin, glucosidase inhibitors, insulin sensitizers.
- 1979: the first needle-free insulin delivery systems were introduced by Dereta; relatively pain-free and metered. Triggered the later development of insulin pumps, inhaled insulin, and oral/nasal sprays.

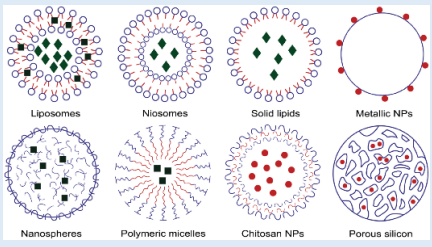
1980s: Human Insulin

- Graham Bell manufactured the first human insulin.
- The first biosynthetic insulin, humulin, was developed.

The Present.

Class	Mechanism of Action	Side Effects
Sulfonylureas	Increase insulin release from the pancreas. Main action is on islet beta cells, stimulating insulin secretion and reducing the plasma glucose concentration. Therefore are useful only in patients with some beta cell function.	Weight gain, hyperinsulinemia, and hypoglycemia.
Meglitinide Analogs	Quite similar to SU.	Advantage of reduced risk of hypoglycemia, which happens if a meal is skipped, delayed, or has inadequate amount of carbohydrates.
Biguanides: Metformin	Reduction of hepatic gluconeogenesis. Increases glucose uptake and use by target tissues; decreases insulin resistance. Slows intestinal absorption of sugars.	No effect on insulin section, therefore no risk of hyperinsulinemia and the risk of hypoglycemia is reduced.
Thiazolidinediones	Decrease insulin resistance. Decrease glucose levels but no increase in insulin; no risk of hyperinsulinemia. Modulate the expression of genes involved in lipid and glucose metabolism, insulin signal transduction, adipocyte and other tissue differentiation. The available agents do not share an exact MOA.	Fluid retention, weight gain, loss of bone mineral density.
Alpha-glucosidase inhibitors	Inhibit alpha-glucosidase, an enzyme that converts polysaccharides into monosaccharides. Therefore they decrease the intestinal absorption of glucose, particularly postprandial absorption which modulates insulin secretion.	Flatulence, diarrhea, abdominal pain.
SGLT2 inhibitors	Reduce the reabsorption of glucose from the renal proximal tubule, which leads to increased urinary excretion of glucose with an associated loss of calories. The mechanism of action is independent of insulin.	Female genital mycotic infections, urinary tract infections, and urinary frequency.
Insulins	Commercial insulin is a protein hormone with two linked chains of amino acids that cannot be administered orally because it is degraded by digestive and intestinal enzymes. Currently, attempts to achieve good metabolic control in patients with diabetes include treatment with exogenous insulin, which is an effective therapy option in cases of partial and/or total deficiency of insulin secretion by the pancreas.	

The Future: Nanosystems.



Nanocarriers used to deliver antidiabetics

Ideal profile of nanodrugs:

- Responding to current glucose levels and adjusting drug release as needed
- Prolong the drug blood concentration of the agent for maximum glucose level control
- Achieve sustained drug release to minimize dosing frequency

Nanoparticles

Smart nanocarriers: "closed systems"; detect glucose levels in real time and release the appropriate dose of the drug.

Gliclazide in niosomes: achieved sustained release kinetics, maintaining low glucose levels for more than 12 hours.

Metformin in liposomes, coated with chitosan cross linked with glycerolophosphate: bioavialability of this form of metformin was twice as high as the pure agent on its own, as well as the achievement of sustained release.

Zinc oxide NPs: common cofoactor, found to be involved in glucometabolic disorders; ZnONP stimulate insulin release and can restore function to beta cells.

Drawbacks of nanosystems:

- Potential instability due to size.
- Proven difficulty to reproduce certain characteristics and effects.

Superiority over others:

- Higher efficacy at lower doses with less side effects.
- Therefore lower dosng frequency.
- Protect the agents from gastric degradation.

Done by:
Sara Abdallah U18100479
Salma Kamal U18100234
Raya AlJobowry U18100253

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