Lecture # 9

The Artificial Pancreas

Endocrine Physiology

Before we talk about the artificial pancreas, we have to understand its structure and function. The pancreas, which is shown in Fig. 1 , is located below the stomach and above the duodenum. It releases endocrine hormones (insulin, amylin, and glucagon) into the portal vein, where it flows directly to the liver. The pancreas produces three hormones that are important to glycemic control: insulin , which lowers blood glucose; amylin , which slows digestion, slows the rate of glucose entering the bloodstream, and temporarily suppresses the release of glucagon; and glucagon , which raises the blood glucose. Upon digestion of carbohydrates, glucose levels in the blood will begin to rise. As the blood and glucose flow into the pancreas, insulin and amylin are secreted by the pancreatic beta cells directly into the bloodstream in response to elevated blood glucose levels. Insulin causes blood glucose to be removed from the bloodstream and stored in the liver and muscle cells. Notice that as the blood sugar goes higher, additional insulin will bring the blood sugar back down in a classic negative feedback loop. As insulin is released from the beta cells, amylin is also released into the bloodstream. Amylin slows gastric emptying and also inhibits the release of glucagon from the pancreatic alpha cells. The effect of amylin is to spread out the blood glucose peak after eating, reducing the quantity of insulin needed. As the blood sugar level comes back toward normal, the beta cells will stop spurting insulin and amylin. As the glucose level approaches a low mark, the pancreatic alpha cells will release glucagon directly into the bloodstream. Glucagon causes the liver to release stored glucose back into the bloodstream. Notice that increased glucagon will increase blood glucose levels to produce a positive error in the negative feedback loop. Together, the three endocrine hormones work as a system to maintain the blood glucose level between high and low boundaries. When the beta cell produces insulin from proinsulin, a connecting peptide (or C-peptide) is also manufactured and released into the bloodstream. The absence of C-peptide in the blood indicates that insulin has not been released from the

pancreas, and this fact confirms the diagnosis of diabetes type 1 . C-peptide was believed to be only a byproduct of natural insulin production, but recent studies suggest that C-peptide exerts a beneficial therapeutic effects on diabetic nociceptive neuropathy.

Ideally, to replicate the natural function of the pancreas as closely as possible, an artificial pancreas might someday replace all of the beneficial endocrine functions lost, including the delivery of insulin, amylin, glucagon, and C-peptide.

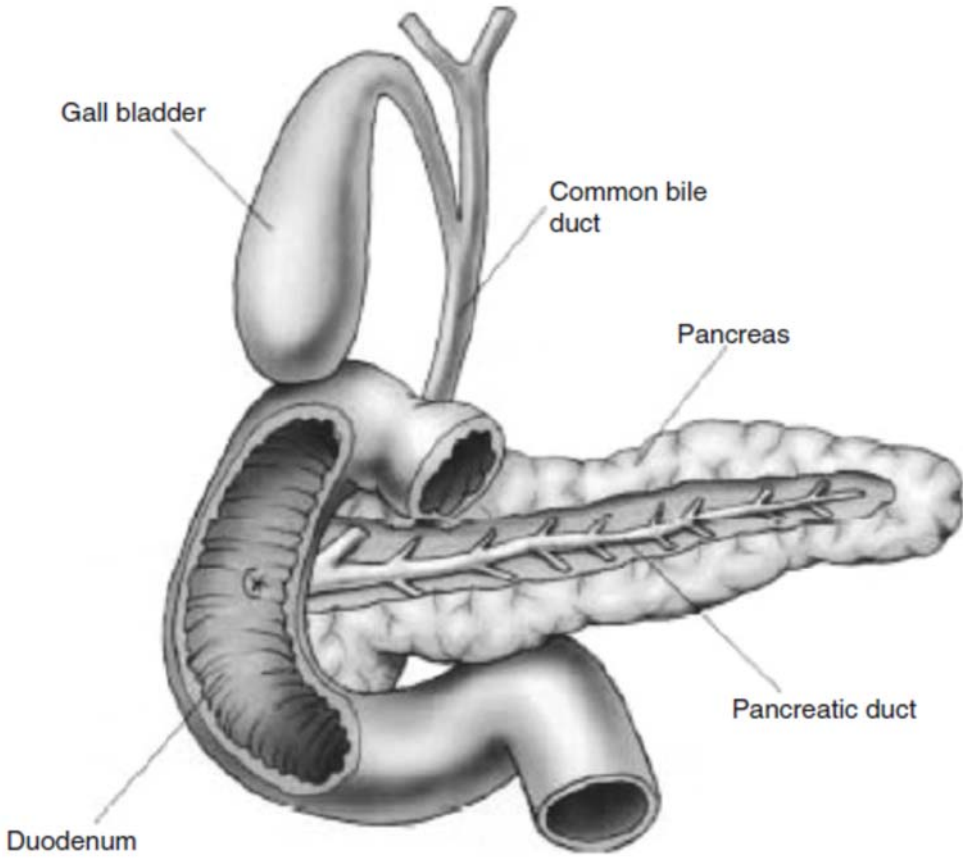

Figure 1: The cutaway view of the pancreas and its associated organs

Artificial Pancreas:

The artificial pancreas is a technology in development to help people with diabetes control their blood glucose level automatically by providing the substitute endocrine functionality of a healthy pancreas.

There are several important exocrine (digestive) and endocrine (hormonal) functions of the pancreas, but it is the lack of insulin production that is the motivation to develop a substitute. While the current state of insulin replacement therapy is popular for its life-saving capability, the task of manually managing the blood sugar level with insulin alone is arduous and inadequate for the patient.

The goal of the artificial pancreas is twofold:

1. To improve insulin replacement therapy until glycemic control is practically normal, as evidenced by the avoidance of the complications of hyperglycemia.

2. To ease the burden of therapy for the insulin dependency.

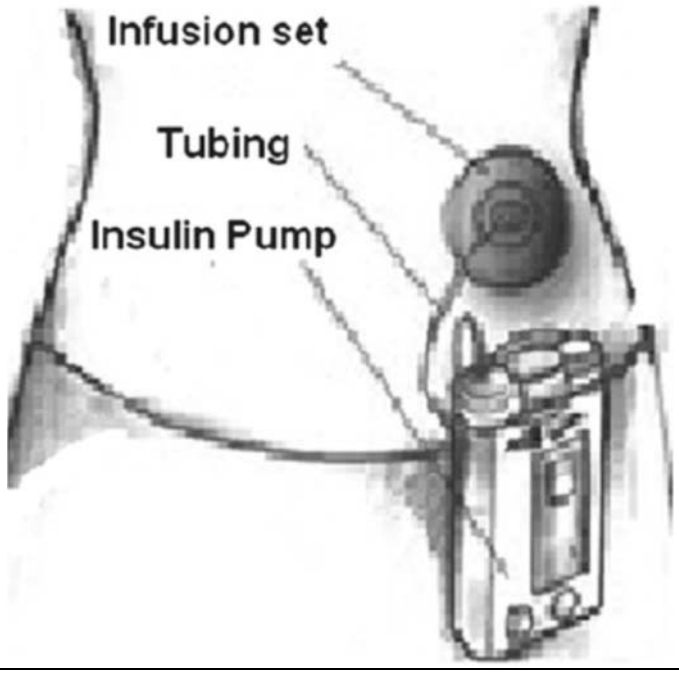

Figure 2: Artificial insulin therapy setup in place

Different approaches under consideration include

The medical equipment approach —using an insulin pump under closed-loop control using real-time data from a continuous blood glucose sensor. This is an emerging technology and will be discussed in detail.

The bioengineering approach —The development of a bioartificial pancreas consisting of a biocompatible sheet of encapsulated beta cells. When surgically implanted, the islet sheet will behave as the endocrine pancreas and will be viable for years.

The gene therapy approach — The therapeutic infection of a diabetic person by a genetically engineered virus that causes a DNA change of intestinal cells to become insulin-producing cells.

Intensive Insulin Therapy and Insulin Pump

The insulin pump is used to automatically deliver basal insulin continuously, and bolus insulin at meal times, by pressing the buttons. Before meals, a blood glucose value is entered into the pump to calculate the correction bolus to bring the blood glucose level back to the target value.

Insulin pump therapy, shown in Fig. 2 , is used by tens of thousands of people of all ages. Many studies have shown improved glucose management outcomes for those using insulin pumps. While it does allow for more flexibility in lifestyle and the potential to even out the wide blood sugar fluctuations that are often experienced when injecting insulin, it may not be the right choice for every person.

In insulin-dependent persons, blood glucose levels have been roughly controlled using insulin alone. The carbohydrate in the amount of food is estimated by weighing foods, and the measurement is used to estimate the amount of insulin necessary to cover the meal. The calculation is based on a simple open-loop model : The insulin-to-carbohydrate ratio (adjusted based on past success) is multiplied by the grams of carbohydrate to calculate the units of insulin needed. That quantity of insulin is then adjusted based on a premeal blood glucose measurement (insulin bolus increased for a high blood sugar or insulin bolus delayed and reduced for a low blood sugar). Insulin is injected or infused under the skin and enters the bloodstream in approximately 15 min. After the insulin has acted in the bloodstream, the blood glucose level can be tested again and then adjusted with the injection of more insulin, or by eating more carbohydrates, until balance is restored.

There are notable differences with insulin replacement compared to the function of pancreatic insulin delivery:

1. The insulin dose is predicted based on measured food (where an accurate measurement of carbohydrate is difficult), whereas pancreatic insulin is released in proportional response to actual blood glucose levels.

2. Pancreatic insulin is released into the portal vein, where it flows almost directly to the liver, which is the major organ for storing glycogen (50% of insulin produced is used by the liver).

3. Pancreatic insulin is pulsatile, which helps maintain the insulin sensitivity of hepatic tissues.

4. Injected insulin is delivered subcutaneously (under the skin) but not directly to the bloodstream, so there is a delay before injected insulin begins to reduce blood glucose (although this can be compensated for by injecting insulin 15 min before eating).

5. Replacement insulin therapy does not include amylin (although Symlin is now available for use), which can reduce the insulin need by 50%.

6. Replacement insulin is dosed as a best compromise between an aggressive use for lowering the blood sugar when eating but also a conservative use to avoid a postprandial low blood sugar due to excess insulin, whereas pancreatic function releases insulin aggressively and later includes automatic release of glucagon at the end of an insulin cycle to manage the blood sugar level and avoid hypoglycemia.

An insulin pump to infuse rapid-acting insulin is the first step in simulating the function of the pancreas. The pump can accurately deliver small increments of insulin compared to an injection, and its electronic controls permit shaping a bolus over time to match the insulin profile required for a given situation. The insulin pump is controlled by the pump user to bolus manually based on a recent blood glucose measurement and an estimate of the grams of carbohydrate consumed. This predictive approach is said to be open-loop. Once a bolus has been calculated and delivered, the pump continues to deliver its basal-rate insulin in the manner that has been programmed into the pump controls based on the predicted insulin requirements of its user.

While insulin replacement is appreciated as a life-saving therapy, its practical use in controlling blood glucose levels sufficiently to avoid the long-term complications associated with hyperglycemia is not ideal.

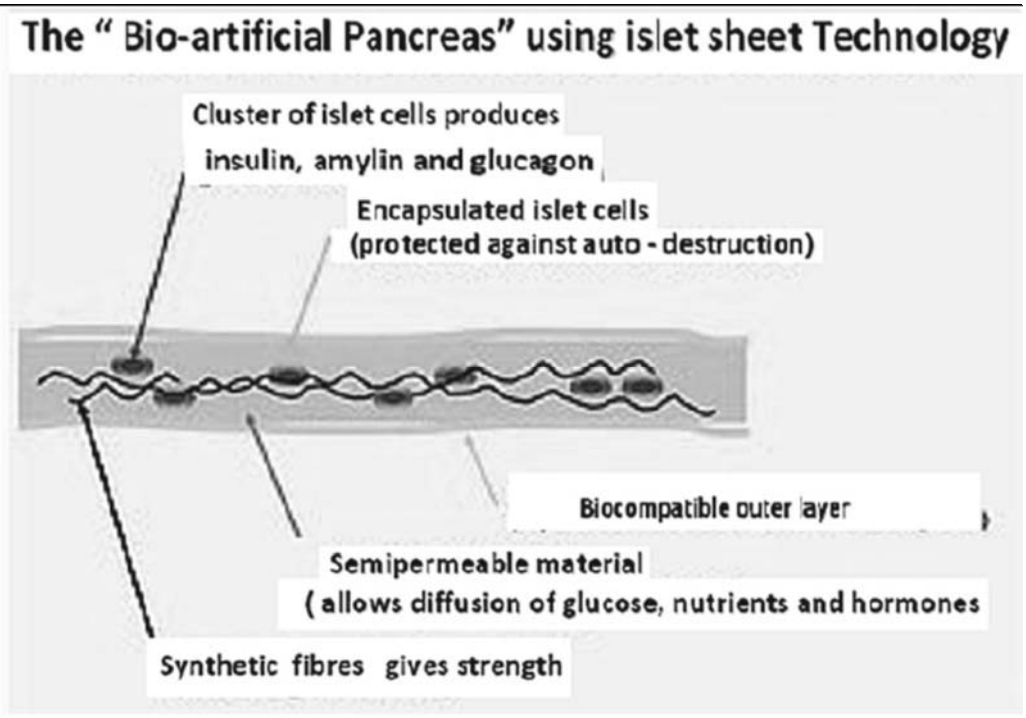

Figure 3: The bioartificial pancreas

Bioengineering Approach to an Artificial Pancreas

The bioartificial pancreas : Figure 3 shows a cross section of bioengineered tissue with encapsulated islet cells, which deliver endocrine hormones in response to glucose. A biological approach to the artificial pancreas is to implant bioengineered tissue containing islet cells, which would secrete the amount of insulin, amylin, and glucagon needed in response to sensed glucose. When islet cells have been transplanted via the Edmonton protocol, insulin production (and glycemic control) was restored at the expense of immunosuppression. Encapsulation of the islet cells in a protective coating has been developed to block the immune response to transplanted cells, which relieves the burden of immunosuppression and improves the longevity of the transplant.

One concept of the bioartificial pancreas uses encapsulated islet cells to build an islet sheet, which can be surgically implanted to function as an artificial pancreas. This islet sheet design consists of

1. An inner mesh of fibers to provide strength for the islet sheet.

2. Islet cells, encapsulated to avoid triggering a proliferating immune response, adhered to the mesh fibers.

3. A semipermeable protective layer around the sheet, to allow the diffusion of nutrients and secreted hormones.

4. A protective coating, to prevent a foreign-body response resulting in a fibrotic reaction, which walls off the sheet and causes failure of the islet cells.

Islet sheet research is pressing forward with large animal studies at the present, with plans for human clinical trials within a few years.

Gene Therapy Approach

In the gene therapy approach, a viral vector is designed to deliberately infect cells with DNA to carry on the viral production of insulin in response to the blood sugar level.

Technology for gene therapy is advancing rapidly such that there are multiple pathways possible to support endocrine function, with the potential to practically cure diabetes (Fig. 4).

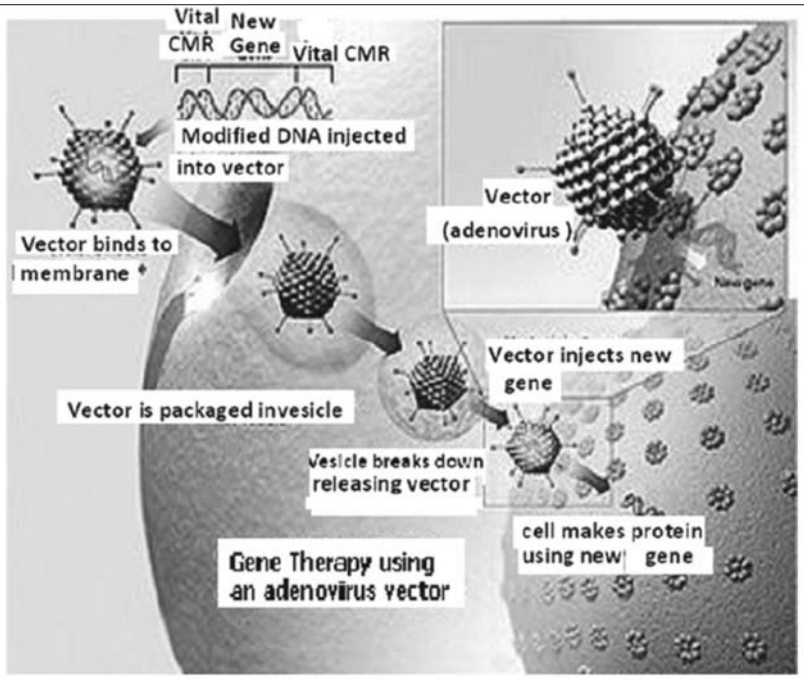

Figure 4: Gene therapy for control of blood sugar level

Gene therapy can be used to manufacture insulin directly : An oral medication, consisting of viral vectors containing the insulin sequence, is digested and delivers its genes to the upper intestines. Those intestinal cells will then behave like any viral infected cell and will reproduce the insulin protein. The virus can be controlled to infect only the cells that respond to the presence of glucose, such that insulin is produced only in the presence of high glucose levels. Due to the limited numbers of vectors delivered, very few intestinal cells would actually be impacted, and they would die off naturally in a few days. Therefore, by varying the amount of oral medication used, the amount of insulin created by gene therapy can be increased or decreased as needed. As the insulin-producing intestinal cells die off, they are boosted by additional oral medications.

Gene therapy might eventually be used to cure the cause of beta cell destruction , thereby curing the new diabetes patient before the beta cell destruction is complete and irreversible.

Gene therapy can be used to turn duodenum cells and duodenum adult stem cells into beta cells, which produce insulin and amylin naturally. By delivering beta cell DNA to the intestine cells in the duodenum, a few intestine cells will turn into beta cells, and subsequently adult stem cells will develop into beta cells. This makes the supply of beta cells in the duodenum self-replenishing, and the beta cells will produce insulin in proportional response to the carbohydrates consumed.