THE STATE AND FUTURE OF CLOSED LOOP INSULIN PUMPS / ARTIFICIAL PANCREAS

by

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The State and Future of Closed Loop Insulin Pumps (CLIPs) / Artificial Pancreas (AP)

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The State and Future of Closed Loop Insulin Pumps (CLIPs)/ Artificial Pancreas (AP)

Abstract

by

CHANDRAVADHANA UMAPATHY

I. Abstract

With the advent of continuous glucose monitoring therapy and support from the Juvenile Diabetes Research Foundation (JDRF) the Artificial Pancreas Project has been developed to understand the clinical and economic benefits of closed loop systems and continuous glucose monitors. These complex systems are intended to completely take over the insulin dosing and keep the blood sugar under target range. The critical factor in the entire artificial pancreas equation is the insulin. The fast acting analogs have been altered to improve their pharmacokinetic profiles and decrease the time they take to enter the bloodstream. Next generation insulin analogues offer faster kinetics, efficient blood glucose control and better automation for the closed loop systems. This thesis deals with the challenges and the various solutions offered to counter the colossal task of ‘closed loop’ solutions.
II. Introduction: The hormone- Insulin

The two polypeptide hormones, insulin and glucagon work synergistically to maintain normal glucose levels in the body. Insulin is produced in the pancreas and released when stimulated by glucose produced in blood after ingestion of carbohydrates. The elevated glucose concentration triggers the secretion of insulin by the pancreas, which in turn, signals the body tissues (liver and muscle) to uptake glucose. The glucose is then stored in these tissues in the form of glycogen. Depressed glucose concentration in blood stimulates pancreatic alpha cells to release glucagon. Glycogen then in turn triggers the conversion of stored glucagon to glucose in the body tissues and thus increases the level of glucose into the blood.

A. Structure of Insulin

Insulin, a peptide hormone is a post translation product of a single chain precursor and is a globular protein containing two chains; A chain (21 residues) and B chain (30 residues). The amino acid sequence of insulin varies from species to species but certain segments of the molecule are highly conserved. The highly conserved regions include

a) Three disulphide bonds,

b) C-terminal residue of B-chain and

c) Both ends of the A-chain.\(^1\)

These similarities lead to 3-D conformations that are similar among species and therefore the insulin of a particular species can be used to treat disorders in others, because the insulin is very likely to be biologically active. The insulin molecule has a tendency to forms dimers, due to hydrogen bonding between the C-terminus and the B-chain.
The dimers and monomers diffuse easily into the blood stream where as the hexamers diffuse poorly. Insulin dimers associate to form hexamers in presence of zinc ions. The hexameric form provides long term stability and serves as a way to protect insulin. The commercial insulins have zinc ions in their formulation that prevents the formation of fibrils, this is necessary to achieve FDA stability requirements. When insulin is injected into the skin the hexamers form a depot which delays absorption into the blood stream. The time required for disassociation limits the rate of insulin monomer absorption. This leads to slower kinetics and delays the activity of insulin. The hexameric-monomeric conversion is one of the critical aspects of insulin formulation. These interactions between the dimers and the hexamers have clinical ramifications.

B. Biosynthesis

The insulin gene encodes a single-chain precursor preproinsulin. The signal peptide is cleaved and is translocated to the endoplasmic reticulum to yield proinsulin. The preproinsulin and the proinsulin have a connecting domain between the B-and the A-domain. The folding in the endoplasmic reticulum is coupled with pairing of the disulphide bridges which is essential for stability and bioactivity. Once the proinsulin
passes through the Golgi apparatus into the immature secretory granules, the C-peptide is excised to yield mature insulin and the Zn-stabilized hexamers start to assemble. The hormone is stored as Zn +2–stabilized hexamers and dissociate upon secretion into the portal circulation.

C. Role of insulin in the body

The hormone insulin is central in regulating fat and carbohydrate metabolism in the body. The main role of the hormone is carried out in liver, muscles, and fat tissues and controls the storage of the three major nutrients sugar, protein and fats in the body. Insulin is also known to influence other body functions such as vascular compliance and cognition. Studies have been carried out that have suggested one of the effects of insulin is in improving memory function. The hormone not only enhances learning but also particular benefits verbal memory. Intranasal administration of the insulin also enhances
glucoregulatory and thermoregulatory response to food intake indicating its control on the whole-body homeostasis in humans.\(^8\)

1. *Regulation of glucose metabolism*

Glucose is liberated on consumption of food such as starch or sucrose by hydrolysis in the small intestine and then is absorbed in the blood. A high concentration of glucose in the blood stimulates the secretion of insulin throughout the body, which stimulates glucose uptake, utilization and storage. In addition to promoting glucose storage, the hormone inhibits the release and production of glucose in liver by blocking glycogenolysis and gluconeogenesis.\(^9\) Two important effects are

a. Insulin facilitates the entry of glucose into muscle, adipose tissue and several other tissues. The only mechanism by which the cells take up glucose is though a family of hexose transporters. The major transporter in many cells is GLUT4 which is made available in the plasma membrane through the action of insulin.\(^10\) Certain tissues like the liver and the brain do not require insulin for efficient uptake of glucose. They can do so with transporters that is not insulin-dependent.\(^11\)

b. The hormone is also responsible for the storage of glucose in the form of glycogen in liver.

A large amount of glucose is trapped from the small intestine by the hepatocytes to convert it into the storage polymer glycogen. Insulin has several effects that stimulate the glycogen synthesis. Insulin activates hexokinase which traps the glucose in the liver cell and coincidently activates other enzymes responsible for glycogen synthesis.\(^12\)
synthesis including phosphofructokinase and glycogen synthase and inhibits activity of glucose-6-phosphatase.\textsuperscript{12}

2. Regulation of lipid synthesis

a. Insulin stimulates the synthesis of fatty acids in the liver. When the liver is saturated with glycogen, any glucose molecules taken up by the liver is shunted. These glucose molecules are then converted to fatty acids and are exported as lipoproteins by the liver. The lipoproteins provide free fatty acids that are used by tissues like adipocyte, which use them to synthesize triglycerides.\textsuperscript{13}

3. Other effects

a. Insulin stimulates the uptake of amino acids and promotes protein synthesis, thus contributing to an overall anabolic effect.\textsuperscript{14}

b. It increases the DNA and RNA replication with the influx of amino-acids and promotes cell proliferation.

c. Insulin increases the permeability of cell membranes to Na, K and Mg ions.\textsuperscript{15}

d. Is involved in modifying the activity of numerous enzymes.
D. **Mechanism of insulin action**

Like all the proteins in the body, the insulin receptors are embedded into the plasma membrane. The receptors are composed of two alpha and two beta subunits linked together by disulphide bonds. The insulin binding sites are present on the extracellular alpha sub-units whereas...
the beta sub-units are embedded into the plasma membrane.\textsuperscript{16} The receptors are tyrosine kinase, which acts to transfer phosphates groups from ATP to tyrosine residues. The beta sub-unit autophosphorylates when an insulin molecule binds to the alpha sub-unit thus activating the receptor. The activated receptor in turn signals a number of intracellular proteins and starts a cascade of biological response.\textsuperscript{17}

Some of the major mechanisms of insulin actions are described below:

1. High concentration of glucose in the body stimulates the release of insulin. The insulin then acts on various cells throughout the body to stimulate uptake, storage and utilization of glucose. As mentioned earlier the major glucose transporter is called GLUT4.

![Figure 7: Insulin signaling leads to the movement of GLUT4 glucose transporters from the cytoplasm into the plasma membrane, allowing glucose to enter the cell. (Bowen n.d.)](image)

The GLUT4 glucose transporters are present in the cytoplasm where they cannot help in transport of glucose in absence of insulin. When insulin is present in the blood, the binding of the insulin to the alpha sub-unit of the receptors leads to fusion of the glucose transporters to the plasma membrane. The fusion of the GLUT4 with the plasma membrane results in the transport of glucose into the cytoplasm. During low insulin
levels, the receptors are no longer occupied and the transporters are recycled back into the cytoplasm.

2. Insulin is also responsible for storage of glucose in the form of glycogen.

![Insulin action in liver](Figure 8: Insulin action in liver. (Bowen n.d.))

Insulin has several effects in the liver among which is the stimulation of glycogen synthesis. Glucose is converted into glycogen in presence of glycogen synthase and phosphofructokinase. By inhibiting the intracellular lipase that breaks down the triglycerides to fatty acids, insulin prevents the breakdown of fatty acids in the liver. With the entry of glucose into the adipose tissues, glucose is used to synthesize glycerol. Glycerol along with other fatty acids is then used to synthesize triglycerides in the adipose tissue that further help in the accumulation of triglycerides in the fat cells. Thus the insulin has a fat-sparing action that drives the cells to preferentially use carbohydrates and stimulates the accumulation of fat as an energy source.
3. A well known factor is that insulin decreases the concentration of glucose in blood and that as blood glucose concentrations fall, insulin secretion ceases. In absence of insulin the cells in the body switch to using alternative fuels like proteins and fatty acids for energy as glucose is unavailable. In absence of insulin, glycogen synthesis in the liver stops and the enzymes responsible for glycogen breakdown become active. The breakdown of glycogen is stimulated not only in absence of insulin but also by the presence of glucagon which is released when the blood glucose level fall below range.

E. Diabetes

Diabetes Mellitus is a group of metabolic diseases characterized by high blood sugar levels caused either because of the body’s inability to produce insulin (Type I DM) or because the body cells do not respond to the produced insulin (Type II DM).

4. Causes

In a healthy individual the sugar in the body is broken down into glucose and is used as a source of fuel. Insulin helps in the movement of glucose into the muscle, liver and fat cells, where it can be used as a fuel. In a diabetic patient as there is no movement of glucose into the cells, the organs and tissues are exposed to high
glucose levels. High blood glucose not only harms the organs and the tissues but also harms cells that need energy for fuel. The following are the causes of diabetes

a. Age: The disease may occur at any age, but 80% of the cases occur after 50 years of age. The incidence increases with age.

b. Poor Diet: Low protein and fiber diet, improper nutrition and high intake of refined products causes high risk of developing diabetes.

c. Lifestyle: People with sedentary lifestyle are more prone to diabetes than people who exercise three times a week.

d. Hereditary or inherited traits: Genes play an important role in diabetes. It is believed that the disease passes from one generation to another.

e. Obesity and fat distribution: An overweight individual has increased insulin resistance, that is if the body fat is more than 30%, waist girth 35 inches in women and 40 inches in males, and BMI 25 +.

f. Stress: Stress caused due to emotional disturbance or a physical injury can lead to the disease.

g. Drug induced: Many drugs such as Clozaril, Zyprexa, Risperdal and Geodon are known to induce the disease.

h. Infection: Certain bacteria like the Strephylococci that infect the pancreas are known to be a responsible to induce the disease.

i. Sex: Diabetes is commonly seen in elderly men and women. It is also prominent in females with multiple pregnancy or females suffering from polycystic ovarian syndrome (PCOS).
j. Hypertension and high alcohol intake: Studies have shown a direct relationship between high blood pressure and diabetes.

k. Serum Lipids and lipoproteins: High cholesterol and high triglycerides in the blood are related to high blood sugars in the body.

5. **Types of Diabetes**

a. **Type I Diabetes:**

   Type I Diabetes is also known as Insulin Dependent Diabetes Mellitus (T1DM). This condition results from the body’s inability to produce insulin. The classical symptoms of T1DM include polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger) and weight loss. The causes of T1DM are not fully understood but it is believed to have immunological origin. T1DM is also a polygenic disease in which different genes contribute to its expression. In T1DM the pancreas undergoes an immune attack by the body itself and renders the pancreas incapable of making insulin. The immune system manufactures antibodies and inflammatory cells that are directed against body’s own tissues. The beta cells in the pancreas are attacked by the immune system and it is believed that the abnormal antibodies are genetically inherited.

b. **Type II Diabetes:**

   Type II Diabetes (T2DM) is a metabolic disorder that is characterized by high glucose content due to insulin resistance. The disease is also known as adult onset diabetes mellitus (AODM). In Type II the patients still produce insulin, but do so relatively inadequately for the body’s needs. A major feature with type II is the lack
of sensitivity to insulin by the body cells. Other problems include suboptimal or
defective release of insulin by the pancreas and a steady decline in beta cell
production of insulin in type II. The classical symptoms of diabetes are also observed
in T II. T II is caused due to life style factors, poor eating habits, lack of exercise,
higher body weight and genetics. Insulin resistance means that the body cells do not
respond appropriately when insulin is present, i.e. the problem lies with the cell that
responds to insulin rather than a problem with production of insulin (TIDM).
Hyperinsulinemia is caused by insulin resistance and could lead to type II diabetes.
This is a condition when the body is resistant to insulin and the pancreas produces
more insulin to compensate. Eventually the pancreas is no longer able to secrete more
insulin and is not able to keep the blood glucose levels normal.²¹

c. Gestational Diabetes

Gestational diabetes or GDM is also caused due to insufficient insulin production and
lack of response and hence it resembles type II diabetes. The condition is commonly
observed in pregnant women. These women have increased risk of type II after
pregnancy and their offspring’s are prone to developing childhood obesity with type
II diabetes later in life.


d. Chronic and acute complications

Acute Complications

Diabetic ketosis is also a condition seen in patients with Type I that may lead to coma
and metabolic derangement if not treated on time. Hyperosmolar nonketogenic coma
is a condition similar to the diabetic ketosis. The body becomes extremely
dehydrated in presence of high glucose level in the blood. The water from the cells is drawn into the blood and glucose is dumped into the urine as a result the body is extremely dehydrated. \textsuperscript{22}

\textit{Chronic Complications}

Heart disease and hypertension are the most common complications associated with diabetes. Untreated diabetes can lead to ‘Diabetic Retinopathy’ damage to the retina leading to blindness. Other common complications are ‘Diabetic Nephropathy’, which occurs when high concentration of sugar in blood is filtered through the kidneys damaging the blood vessels. ‘Diabetic Neuropathy’ is usually limited to the peripheral nervous system characterized by feeling of numbness and pain.\textsuperscript{23} Ischemic ulcers results from the lack of oxygen and peripheral nerve damage that causes foot ulcers.

6. \textit{Treatment}

Patients suffering from diabetes are advised to follow healthy lifestyle choices in diet, exercise and routine daily habits. These would help maintain glycemic control and prevent diabetic complications.

a. \textit{Diet}

A healthy diet is a key in maintaining blood glucose levels in the body and preventing diabetes. The patient should depend on consistent, well balanced diet that is high in fiber, protein and low in sugar. A balanced diet will help keep glucose levels constant and avoid fluctuations, which could be dangerous.
b. Exercise

Exercise is crucial for a diabetic patient. Exercise will help in weight reduction, improve body’s sensitivity to insulin and thus control blood sugar levels.

c. Oral Medication

An alternate form of treatment is diabetic oral medication that helps to maintain blood glucose levels. These medications are normally prescribed along with balanced diet and appropriate exercise regimen. Some of the categories of diabetic pills include Sulfonylureas, Biguanides, Thiazolidinediones, Alpha-glucosidase inhibitors, Meglitinides, DPP-IV inhibitors.24

d. Glucose monitoring

Self monitoring of blood glucose is critical in insulin treated diabetic patients for a number of reasons. Monitoring determines appropriate insulin dosage, if changes in glucose levels occur due to stress, physical activity, food and medicines. Frequent monitoring of glucose will indicate blood glucose trends over the course of the day. This provides insights into discrepancies in glucose trends and investigates hypo and hyperglycemia episodes. The most common method of glucose monitoring is through strips and lancets Trials have indicated that 4 to 5 point daily profile indicates an optimal routine for SMBG. A small drop of blood is obtained by pricking the skin with a lancet. The drop of blood is then placed on a disposable test strip that is read by the glucose meters to calculate the blood glucose levels.
e. **Insulin therapy today**

Insulin is used to treat all forms of diabetes. Patients with Type I diabetes depend entirely on external insulin. Type II patients frequently need to use large quantities of insulin when the drug therapy fails to maintain their insulin resistance and their pancreas fails to produce high levels of insulin needed to overcome their insulin resistance. Like any other protein, insulin when ingested into the stomach is broken down into amino acids fragment and the ‘insulin activity’ is lost therefore, insulin cannot be taken orally. Extensive research has been carried out to create oral insulin but they are purely experimental. Insulin is typically administered subcutaneously through needles, syringes, pens and insulin pumps. These systems are designed to mimic the physiological secretion by the pancreas. Other forms of uptake like trans-dermal, inhalable trans-nasal are currently being investigated and are under development.

7. **Diabetes Management**

The primary issue in managing diabetes is the glucose cycle, which is affected by two factors, entry of glucose into the bloodstream and level of insulin to manage glucose transport outside of the blood stream. The main complexity stems from the fact the glucose cycle is a feedback system and is sensitive to external factors such as diet, stress exercise, lifestyle choices. Management is intrusive and compliance is a problem as the cycle is dependent upon regular testing and measuring of blood glucose multiple times a day. Controlling other risk factors that may give rise to other complications is one of the aspects of diabetes management. Checking of cholesterol, HDL, LDL, triglycerides, blood pressure is important to protect against cardiovascular, retinal and renal complications of diabetes. Annual visits for eye appointment and podiatrists are normally
recommended. Thus the expense, inconvenience and discomfort caused due to frequent testing, doctor’s visits are challenges of diabetes management. Along with the SMBG, the testing of Hb A1C at least two times a year is recommended by the American Diabetes Association (ADA)\textsuperscript{25}. HbA1C test also known as glycated hemoglobin measures average blood glucose over three months. Hemoglobin molecules are removed from circulation with aged red blood cells, so their lifespan is about 120 days. When conditions such as hemolytic anemia or erythropoetic stimulation occur in a patient this can falsely reduce A1C levels. The ADA recommends that people with diabetes should have an A1C goal of less than 7% and A1C of a normal healthy person is around 4% to 6%.\textsuperscript{26} The A1C test helps in assessing the treatment efficacy as it measures the patient’s average glycemia over a span of three months. A1C is an important tool but it cannot replace daily self testing of blood glucose as it does not measure day-to-day control.

\textbf{a. Glycemic control}

Glycemic control is fundamental to diabetes management. There is a growing body of evidence that maintaining intensive glycemic control can help reduce the risk of macro vascular and micro vascular complications. Trials conducted by the Diabetes Control and Complications Trial (DCCT) on diabetic patients for 10 years that achieved A1C results less than 7.2 \% proved that maintaining a strict control dramatically reduced the risk of small blood vessel complications especially retinopathy.\textsuperscript{27} Glucose levels that are above or below 4.5 to 7.0 mmol/L or (80 to 125 mg/dl) can lead to complications. Increase levels of blood sugar (13-15 mmol/L (230–270 mg/dL) can lead to hyperglycemia that can turn in to ketoacidosis and coma. Whereas low blood sugar levels (<3.8 mmol/L (<70 mg/dL) cause hypoglycemia, a dangerous condition as lack of glucose causes lack
of oxygen, which produces brain damage or even death. Failure to manage glucose under strict regimen can accelerate symptoms of hypoglycemia or hyperglycemia and thus it is imperative for a diabetic patient to maintain glucose levels. With appropriate glycemic controls

- A1C levels are maintained below 7%
- Risks of micro vascular and neuropathy complications are reduced
- Aggressive glucose management with diet and exercise may reduce the use of insulin, thus in turn reduce the cost associated with insulin therapy and reduce morbidity, weight gain, reduce the risk of myocardial infarction, high blood pressure, cholesterol and stroke.

III. Insulin replacement therapy

A. Insulin Analogs

Insulin is available in three basic forms and is classified according to the following:

<table>
<thead>
<tr>
<th>Onset</th>
<th>how quickly the insulin starts to work after it is injected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Time</td>
<td>the period of time when the insulin is most effective in lowering blood sugar levels</td>
</tr>
<tr>
<td>Duration</td>
<td>how long the insulin remains working in the body</td>
</tr>
</tbody>
</table>

The insulin acts differently on different individuals, so the times of onset, peak time and duration vary. There are mainly four types of insulin available and they are summarized in the table below.  

28
Different combinations of insulin are normally taken by people suffering with diabetes to control their blood sugar levels. Some can be purchased already mixed (Regular or NPH insulin) and some insulin that cannot be mixed together requires separate injections. The choice of insulin depends on the patient’s preference, ability to adhere to a treatment regimen and other factors that include: Regular glucose monitoring, daily routine, stability of blood sugar levels and diet.

B. Competing insulin delivery technologies

There is a constant demand for novel insulin delivery methods in the current era. Most of the pharmaceutical companies are showing interest in developing alternative modes of insulin delivery that can be cost effective, user friendly and non-invasive. The medical goals for insulin therapy include:  

- Lowering A1c levels for better glycemic control
- Improve blood glucose variability
- Prevent Hypoglycemia
- Reduce the amount of insulin use
- Regulation of insulin concentration in the liver and muscles

(When the amount of glucose in the blood increases the energy storage mechanism of the body kicks in. The liver being the largest organ in the body can store up to 10% of its volume in glycogen in contrast to 1% stored by the muscle. The glycogen stored in the liver is used for energy production and as well as for regulation of blood glucose, whereas in energy stored in the muscle is used for energy production only.

In a normal healthy individual the pancreas is responsible for releasing stored glycogen and the liver converts this into glucose and vice versa when the blood glucose level fluctuates. With impaired insulin production in the pancreas these technologies will have to maintain a careful balance in maintaining the amount of energy consumption and healthy blood glucose levels)

The American Diabetes Association (ADA) recommend four tests/day to maintain efficient glucose levels, but due to pain of pricking; inconvenience of using strips, meters, lancets, blood disposal and social stigma, on an average people test less than two times a day. Effective treatment of diabetes is possible only if the glucose levels are constantly maintained and tracked. In the past decade rigorous research has been undertaken to replace the old invasive methods by more accurate and noninvasive routes.

The methods are characterized below:
<table>
<thead>
<tr>
<th>Technology</th>
<th>Name</th>
<th>Pros</th>
<th>Cons</th>
<th>Market Niche</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle Free Technology</td>
<td>Bioject &amp; Antares Pharma</td>
<td>No needle disposable, faster injection, no pain, high compliance</td>
<td>Poor quality of injection, bruising and bleeding at site</td>
<td>Vaccination, Drug delivery</td>
</tr>
<tr>
<td>Insulin Inhalers</td>
<td>Pfzier &amp; MannKind</td>
<td>Noninvasive, convenient, stable – dry form, high compliance</td>
<td>Absorption, cannot be used be used in patients with asthma, lung cancer.</td>
<td>Diabetes Management market</td>
</tr>
<tr>
<td>Insulin Spray</td>
<td>Generex Biotechnology</td>
<td>Noninvasive, convenient, stable – dry form, high compliance</td>
<td>Not yet tested on humans</td>
<td>Diabetes Management market</td>
</tr>
<tr>
<td>Insulin Pill</td>
<td>Novo Nordisk</td>
<td>Noninvasive, convenient, no pain, high compliance</td>
<td>Insulin kinetics, destroyed by stomach acids</td>
<td>Diabetes Management market</td>
</tr>
<tr>
<td>Implantable Insulin Pumps</td>
<td>OmniPod</td>
<td>Tubeless, automatic insertion, painless, small size, high compliance</td>
<td>Inadequate adhesive, poor quality of injections.</td>
<td>Insulin Pump market</td>
</tr>
<tr>
<td>SmartInsulin</td>
<td>SmartCell</td>
<td>One injection/day, has feedback mechanism, less expensive</td>
<td>Compatibility with pumps</td>
<td>Diabetes Management market</td>
</tr>
<tr>
<td>Transdermal Patch</td>
<td>Altea Pharmaceuticals</td>
<td>Noninvasive, convenient, high compliance</td>
<td>Itching, erythema, irritation, edema at the site</td>
<td>Drug delivery</td>
</tr>
<tr>
<td>Artificial Pancreas</td>
<td>Bioengineering</td>
<td>Complete replacement of pancreas</td>
<td>High cost, burden of immunosuppressant, high chance of rejection</td>
<td>Insulin delivery market</td>
</tr>
<tr>
<td></td>
<td>Gene Therapy</td>
<td>More efficient and specific,</td>
<td>Limited capacity, unknown long term effects because of viral vectors</td>
<td>Insulin delivery market</td>
</tr>
</tbody>
</table>

Table 2: Overview of insulin delivery technologies
1. **Needle free technology**

Chronic diseases like diabetes that needs injection two to three times a day require a replacement of the needle injections. To overcome problems associated with needle based technologies, there is a technology that received considerable attention in the past few years. The Needle Free Injection Technology (NFIT) was first described in 19th century in France and was commercialized in the US in 1960s. Several companies like BioJect Medical Technologies, Antares Pharma Inc, and BioValave Technologies are actively pursuing the further development of the technology. The technology offers benefits such as fast injection, no needle disposal, and re-usable devices and reduces the pain caused by needles.

2. **Insulin Inhalers**

Insulin inhalers could have a big role in the diabetes management market. Some insulin inhalers have been brought into the market and some are under development. The inhalers used compressed dry insulin powders or dissolved rapid acting insulin that is inhaled through the mouth and goes directly into the lungs, where in theory it is absorbed and passes into the bloodstream. Most of the insulin inhalers are rapid acting and thus they do not replace insulin injections.
3. **Insulin Spray**

The most recent way of delivery insulin in the body is through using a mouth spray. Scientists from the Beth Israel Medical Center in New York City claim that the buccal lining has a lot of blood vessels, which enable quick absorption of the drug into the bloodstream. The new form of insulin called Orallyn is delivered through a RapidMist device developed by Generex Biotechnology. The patient does not inhale the insulin; instead the insulin is sprayed and held inside the mouth for few seconds till the drug is absorbed through the cheek lining.

![Figure 12 & 13: Exubera by Pfizer and Insulin Inhaler by MannKind](image)

![Figure 13: Insulin Spray (RapidMist Device)](image)
4. **Insulin pill**

The scientists at Novo Nordisk are working towards increasing the oral viability of insulin tenfold through protein engineering. They believe that an insulin pill can survive the digestive tract system but might face problem in absorption by the epithelial cells of the gut. The scientists have designed a pill that can transverses through the stomach without being broken down by the stomach acids facilitating its transfer through the cells in the blood stream. Clinical trials are being carried out to encapsulate insulin into an easy-to-swallow dose.

![Figure 14: Insulin Pill](Insulin in a Pill 2010)

5. **Implantable insulin pumps**

These pumps function very similar to the external insulin with two major differences. The pumps are implanted just under the skin and the insulin is delivered through the peritoneal cavity. Omnipod is a tubing-free insulin pump system developed by Insulet Corporation. The pod is also called as a patch pump as it is small, discreet, durable, waterproof and wireless. The system has two units; one the pod, which has the pumping mechanism, needle, cannula and insulin reservoir and the second is the PDA (Personal diabetes Manager) that wirelessly calculates and delivers insulin doses.
6. **SmartInsulin**

![Figure 15: Action of SmartInsulin (Smart Insulin n.d.)](image)

SmartCell, Inc is developing SmartInsulin, a once a day self-regulating, injectable formulation for diabetes. The SmartInsulin is an injectable drug that senses the concentration of glucose in blood and automatically dispenses insulin on demand. As the glucose level goes down the drug stabilizes, trapping the insulin until the next glucose spike. SmartInsulin works via competitive binding, in which insulin (orange lines), attached to a sugar group (orange hexagons), binds with a sugar-binding molecule (blue circle) in solution.\(^4^3\)

7. **Transdermal Patch**

The product developed by Altea Pharmaceutics – PassPort System is the first in development in clinical trials to provide an efficient, non-invasive way of insulin delivery via a patch system. The patch is placed on the skin that provides constant basal insulin and avoids skin depots of insulin that normally occur with subcutaneous injections.\(^4^4\)
8. **Fixing the Pancreas**

The artificial pancreas is a developing technology that automatically controls blood sugar levels by providing a substitute for insulin production that would mimic the natural endocrine functionality. The goal of the artificial pancreas system is to mimic normal pancreas function, ease the burden of therapy and improve insulin replacement therapy. Different approaches are considered for the developing the artificial pancreas. The three main approaches are:

a. **Bioengineering approach**

![Figure 16: Insulin Transdermal Patch by Altea Pharmaceuticals](image)

![Figure 17: Islet Cell Transplant & Islet Sheet Technology](image)
The bioengineering approach is to implant cells that produce insulin, glucagon and amylin required for effective glycemic control in the body. The Islet cells from a donor’s pancreas are transferred into the recipient. Once transplanted the islets begin to make and release insulin, thus regulating the insulin level. 49 One more concept of bio-artificial pancreas is the encapsulation of the islet cells a protective coating implanted to function as artificial pancreas. 50

b. Gene Therapy

An oral medication of viral vectors containing the insulin sequence is delivered to the upper intestine. Upon infection, the site produces insulin protein and the virus can be controlled to infect specific cells which respond to the presence of glucose such that insulin is produced only in the presence of glucose in the blood stream. The amount of vectors in the oral medication can be varied depending on the amount of insulin required by the patient. 51 Gene therapy can be used to adapt duodenum cell and duodenum adult stem cells into beta cells that can produce insulin and amylin naturally. 52 By delivering the beta cell DNA into the intestine cells, a few cells will change into beta cells and consequently self replenish the duodenum with beta cells that will produce insulin in presence of glucose. 53

![Figure 18: Gene Therapy using Vectors](image)
IV. Closed loop Insulin pumps/Artificial pancreas system

The Juvenile Diabetes Research Foundation (JDRF) has accelerated in the development of the Closed Loop Insulin Pumps (CLIPs) or the Artificial Pancreas (AP) to revolutionize diabetes care. The Artificial Pancreas consists of

- Continuous Glucose Monitor (CGM), which measure glucose concentration & glucose trends. It sends out wireless signals to a PDA or a computer.
- Algorithm, which determines the amount of insulin to be delivered. Algorithms are the brains of the system and they use the data from the sensor to figure out insulin dosage and maintain the patients’ glucose levels within range.
- The pump delivers insulin doses directed by the wireless signals transmitted from the PDA or the laptop

The closed loop pumps deliver insulin according to the real time changes occurring in the glucose levels and have the potential to manage glucose control. The first generation closed loop system would probably be available by 2015 with more sophisticated life changing models to follow. The Artificial Pancreas consortium is carrying out extensive clinical trials to optimize the process of linking insulin pumps to continuous glucose monitors with the inclusion of algorithms that can communicate with the sensor and the pumps.
In 2006 the JDRF initiated the Artificial Pancreas project that funded seven research teams based in US, UK, Italy and France. The Artificial Pancreas consortium is summarized below:
The closed loop insulin pumps utilize four underpinning technologies and are described in detail below:

- Insulin Pumps
- Glucose sensors
- Continuous glucose monitors
- Algorithms
- Next generation insulin

A. **Insulin Pumps**

1. **Pumps today**

   In the past two decades the use of external pumps has become a standard treatment for Type I diabetes patients. Diabetic patients who would need multiple daily insulin
injections have turned to insulin pumps as it provides precise control over insulin
delivery. The pumps today have features of convenience, easy bolusing, accurate
carbohydrate counting, precise bolus adjustment, accessible history and reminders to
reduce skipped bolus. The marketed pumps are “open loop” requiring the user’s input to
set the basal infusion dose and deliver pre-meal boluses based on their blood glucose
level. The second generation integrated system combines innovative Continuous Glucose
Monitoring (CGM) feature that predicts and alerts the oncoming hypo or hyperglycemia.
These pumps allow numerous modifications to bolus dose and basal rate and thus manage
insulin fluctuations during events like exercise, eating and sleeping. These insulin pumps
improve quality of life and reduce long term complications by providing efficient glucose
control. The FDA regulates the design and the manufacture of insulin pumps. They are
passed through stringent evaluation of product development, precisely documented
process of development testing and field maintenance. The pump is designed to
continuously deliver insulin 24 hours a day according to the set program planned by the
pump wearer. There are two main types of insulin delivery offered by the pumps one is
pulsed and the other is continuous. Basal insulin is delivered continuously which
maintains glucose levels between meals and a bolus dose of insulin is delivered by the
pump to match the glucose level when food is consumed. Pumpers experience better A1C
levels than the patients on injections. They experience better control and can have the
freedom for different lifestyle choices. Most of the pumps also calculate correction bolus
or the pump offer an option to alter the dose recommended by the pump.

The correction bolus depend on three important variables
• Correction Factor- it is the amount of blood glucose in mg/dl lowered by one unit of rapid /short acting insulin

• Duration of insulin action- the amount of time insulin takes to lower blood glucose levels

• Insulin on board- the amount of active insulin from previous bolus

Not all diabetic patients are good candidates to use the pump. A skilled, disciplined individual; competent enough to calculate any changes occurring in dose due to stimulus like ingestion, stress, travel, exercise and sleep variations is a good candidate. When a patient well suited uses the pump correctly they show better A1C levels, fewer complications and episodes of hypoglycemia.

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients Perspective</strong></td>
<td>✓ Flexibility of lifestyle</td>
</tr>
<tr>
<td>✓ Freedom with food</td>
<td></td>
</tr>
<tr>
<td>✓ Optimal glucose control</td>
<td></td>
</tr>
<tr>
<td>✓ Easy Adjustment</td>
<td></td>
</tr>
<tr>
<td>✓ Weight control</td>
<td></td>
</tr>
<tr>
<td>✓ Better control with exercise</td>
<td></td>
</tr>
<tr>
<td>✓ Costly</td>
<td></td>
</tr>
<tr>
<td>✓ Inconvenience</td>
<td></td>
</tr>
<tr>
<td>✓ Technical issue</td>
<td></td>
</tr>
<tr>
<td>✓ Skin Irritation</td>
<td></td>
</tr>
<tr>
<td>✓ Training</td>
<td></td>
</tr>
<tr>
<td>✓ Skill to use is a requirement</td>
<td></td>
</tr>
<tr>
<td>✓ Trouble shooting</td>
<td></td>
</tr>
<tr>
<td>✓ Inconvenience with sports and intimacy</td>
<td></td>
</tr>
</tbody>
</table>

| Clinical Perspective | ✓ Optimal glucose control  |
| ✓ Precision dosing  |
| ✓ No MDI  |
| ✓ Historical data  |
| ✓ Better control with exercise  |
| ✓ No long acting insulin  |
| ✓ Fewer injections  |
| ✓ Increased risk of Diabetic ketoacidosis  |
| ✓ Dependence on medical professional  |
| ✓ Skin Irritations or ‘pump bumps’  |
| ✓ Changing of infusion sets  |

Table 3: Strengths and weakness from patients and clinical perspective

a. Pump component and technology

Insulin pumps are small wearable pager size gadgets that are normally light weighted. They typically measure about 2in x 3in x 0.8 in and they weigh around 1.5 oz to 4 oz. These form very important characteristics as the manufacturers of insulin pump compete
on size and compatibility. The pump consists of an actuator, insulin reservoir, infusion set and control system/interface. The pump reservoir delivers insulin into the body through the infusion sets that are subcutaneously inserted under the patient’s skin. The reservoir is a piston based syringe that is controlled through the pump. This continuous delivery of insulin through the reservoir is monitored through the control system interface that allows the patients to control exact amounts of insulin delivery. There are also certain patch pumps like the Omnipod described earlier in the market that offer tubeless option.

b. Need

Hardware and software problems are of the major issues with insulin pumps. Over the span of five years the FDA has recalled 18 pumps due to software and hardware issues in the pumps. A review conducted by the FDA on pump related adverse events found 17,000 reports from Oct 2006, through Sept.30, 2009. This serves as a red flag for investigation by the FDA but does not necessarily mean that the device caused the problem. Defective pumps can lead to changes in the insulin levels and can lead to fatal consequences. Apart from having device issues, not all pumps have yet gained the FDA’s approval for pediatric use (17 to +/- 2.8 year). Diabetes is one of the most common chronic diseases in children and about 151,000 children below the age of 20 have diabetes. Medtronic is the only insulin pump company that has the FDA’s approval for pediatric use.

c. Current and emerging technologies

The emerging trends focus on getting smarter, smaller technologies to market. Solo MicroPump is the smallest, thinnest and lightest tube-free pump in the market. The pump can be disconnected without wasting any insulin. The insulin NanoPump developed by
DeBiotech uses the MEMS technology that delivers 0.02U of drug. NiliMEDIX Adi insulin pump uses a patent protected platform technology based on a proprietary Discrete Pressure Compensation (DPS) mechanism, controlled by a unique valves and sensors system. Insulin delivery is based on pressure-triggered mechanism, tightly controlled by a series of sophisticated valves and sensors.

d. Current players and their offering

Animas Corporation- Is a leading manufacturer in the insulin pump industry. Animas is under a non-exclusive partnership with the JDRF to develop an automated system to help type I diabetes control their disease. The 1st generation systems would utilize an insulin pump connected wirelessly to a continuous glucose monitor supplied by DexCom Inc. Medtronic is known for its integrated systems approved by the FDA have recently launched the first ‘semi-closed loop systems’ that includes a LG (low glucose) suspend feature that automatically suspend insulin release when glucose levels are low. Roche Diabetes Care along with Sansum Diabetes Research and University of California Santa Barbara (UCSB) has expanded collaboration with the JDRF. The AccuChek Spirit Combo pumps are being used by the member of the Artificial Pancreas Consortium for clinical trials. SOOIL is a Korean based company that has been developing pumps for the last 30 years. Of the four brands the only pump available in US is the DiabeCare II is a good alternative to expensive pumps are it typically retails 25-35% lesser than its competitors. Insulet Corporation-The OmniPod by Insulet is one of the most famous brands in the insulin pump industry. The pod is a small, discreet wireless pump with no tubes. It is the first tubeless insulin infusion system that is durable and waterproof.
B. Glucose sensors

Different types of glucose sensors are used to manage diabetes for the past 30 years. The current methods provided point sample information but with the recent development in the continuous monitoring technology more detailed information on glucose trends are available. A number of technologies are under development with an intention to be integrated into the closed-loop insulin pumps. The different types of sensor available and currently under development are enlisted below. A sensor may be invasive, minimally invasive or noninvasive. This depends on the technologies used by the sensor to measure amount of glucose. The techniques measure glucose directly or through proxies for changes in the glucose concentration. Other sensor includes a CGM sensor used by Medtronic; is a subcutaneous amperometric enzyme electrode that is based on glucose oxidation. The CGM sensor system of subcutaneous needle-based electrode is been used in the Paradigm Systems developed by Medtronic.\textsuperscript{70}
Table 4  Different types of Sensors *Adapted from (N. S. Oliver 2009)

<table>
<thead>
<tr>
<th>Related to Finger Sticks</th>
<th>Types</th>
<th>What is measures</th>
<th>FDA approved</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strip Lancet</td>
<td>Blood Glucose</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Dip Stick Method</td>
<td>Blood Glucose</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensor Sticks</td>
<td>Subcutaneous</td>
<td>ISF (Interstitial Fluid)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Implantable</td>
<td>ISF</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Microdialysis</td>
<td>ISF</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Micropore</td>
<td>Capillary Blood</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Optical</td>
<td>IR</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Spectroscopy</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Polarimetry</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Thermal IR</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Fluorescence</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Raman Spec</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>MIR spec</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>NIR spec</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Kromoscopy</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Trans dermal</td>
<td>Impedance spec</td>
<td>Capillary Blood</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Skin Suction</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Sonophoresis</td>
<td>ISF</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Reverse Ionophoresis</td>
<td>ISF</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

2. **Technology Highlights**

a. **Traditional finger stick with meter**

Most of the finger stick glucose meters employ an enzyme based method of glucose detection. The meter either uses the oxidation of glucose or uses the electrochemical method of glucose detection.\(^{71}\)
b. **Implantable electrodes**

Glucose can also be sensed using enzyme electrode. These electrodes use the reduction-oxidation reaction and in doing so accept and donate electrons. An implantable sensor (0.5 x 0.5 x 0.5 mm) developed by Biorasis can read glucose concentration and transmit the information to a communicator.\(^{72}\) The biocompatible coating allows the sensor to function for a period of 3 months.\(^{73}\) The technology has not yet received FDA approval and still is under the development stage.

c. **Optical and Transdermal**

Transdermal technologies focus on physical energies to extract glucose, blood or measure interstitial fluid (ISF). Transdermal method is viewed as noninvasive method as it does not rupture the skin cells.\(^{74}\) The method can cause blistering or irritation of the skin. Optical technology on other hand uses the properties of light to measure glucose concentration and is truly a non invasive method.\(^{75}\)

d. **Future developing sensors**

The fluorescent technology has been exploited by GluMetrics and has developed a proprietary fluorescent technology with a miniature fiber-optic platform.\(^{76}\) The microdialysis based sensor has been developed and marketed by Menarini in Europe. These systems use fine, hollow microdialysis fiber placed subcutaneously that allows the diffusion of ISF glucose freely, where it is then pumped to an electrochemical based sensor.
e. Past and present challenges

Lag time

The concentration of glucose in the ISF (interstitial fluid) lags behind the blood glucose concentration. The glucose molecule is freely transferred across the capillary endothelium to the interstitium. The process is mediated by a simple Trans cellular or Para cellular diffusion. The equilibrium kinetics between the two is not clear but there is a direct relationship, as changes in the interstitial glucose are correlated with changes in the blood glucose pool. The ISF is found in the interstitial space and surrounds the cells in multi-cellular animals. The glucose concentration in this fluid depends on numbers of factors such as metabolic rate, rate of uptake/exchange of glucose within cells, blood flow, peripheral glucose utilization, and possibly prevailing insulin levels. Studies have shown that the mean lag time in around 6.7 mins. When there is a drop in the blood glucose levels the ISF may lose its glucose concentration before the blood. Thus, ISF measuring sensor may act to predict hypoglycemia. The lag time occurring due to ISF also depend on the sensor type, the stimulus, patients physiology, sensor size etc and this can be prevented by calibrating the sensor to blood glucose values at regular intervals. The lag time between the ISF and the blood glucose can be prevented through calibration. The FDA approves calibration of the sensor every 12 hours in steady state. Accuracy of the sensor can also be largely overcome with calibration. Inaccuracy in calibration can occur due a wide variety of reasons major one includes the variability of strips

Life of the sensor

The sensors available have a short life span. Most sensors approved by the FDA have a life span of around 72 hours to 5 days but there are FDA approved sensors that have a life span of 7 days. The users report significantly longer life spans.
Recent progress on sensors and emerging alternatives

Many technologies are under development with their final goal to be incorporated into the closed-loop systems. The future technologies are:

- Highly selective for glucose with fast turnaround time
- They have long operational life time under normal physiological conditions
- They are non invasive and do not require patient calibration
- These sensors provide accurate real time glucose excursions and trend

The data provides insights into the duration, magnitude, direction, frequency, fluctuations of glucose and alarms for hypoglycemia or rapid change in glucose concentration. Some of the novel technologies are commercially available but none of them are applicable for autonomous CLIP’s system yet.

C. Continuous glucose monitor (CGMs)

The CGM devices continuously record blood glucose levels throughout the day. The monitor uses a sensor which is implanted under the skin that checks for glucose levels in the tissue fluids. The sensor stays for several days to a week and then it has to be replaced. The transmitter on the sensor transmits signals about blood glucose levels to a hand held receiver or insulin pump every one to five minutes depending on the manufacturer for the duration the sensor is in place.\textsuperscript{80} The CGMs do not replace regular blood glucose monitoring and hence have to calibrate with the conventional finger stick method. The patient is required to calibrate their ISF glucose reading with finger stick (self monitoring blood glucose) three times a day due to the physiological lag between the interstitial glucose and blood glucose.\textsuperscript{81} This calibration is essential to avoid any discrepancies in the glucose concentration data. The results can be downloaded from the
sensor electronically on to a computer and the results can be displayed as charts or graphs. The new systems can display real time glucose readings so that the user can see it rising or falling. The three companies Medtronic, DexCom and Abbot have developed and distributed FDA approved CGM systems. The three devices have two different uses

a. Blinded CGM

The system is used as a diagnostic tool to show interstitial blood glucose values retrospectively. It does not allow the patient to react to interstitial reading and provides an accurate profile of the patient. The system provides glycemic day and night profiles and also offers trend information for low blood sugar at night and high blood sugar between meals.

- It also provides a comparative analysis of glycemic profiles obtained from different modes of administration.

- This method of monitoring has potential use in research.

b. Real Time CGM

In contrast, the real time CGM systems display interstitial blood glucose readings, which can be used at any point in time to react to abnormal blood glucose levels. The system can improve glucose control even if it is not associated with an insulin pump. Additional benefits offered by the real time CGM systems include alarms when the glucose levels are above or below the predetermined value and their use in the Intensive Care Unit (ICU), cardiac surgery and intensive exercise regimens.
1. Technological Highlights

a. Drawbacks today

Accuracy of the CGMs has been a long standing issue with these systems. An ideal CGM system would have consistent accuracy, along with uninterrupted information which is not affected by physiological conditions and other factors. One major problem is the lack of accuracy for each single data point calibration as compared to the accuracy of intermittent glucose measurement. CGMs are generally less accurate in the hypoglycemic and the hyperglycemic range as compared to the mid range where most the calibration points are collected. Hence it is important to incorporate the trend information on blood glucose data. The systems are getting smaller, more accurate and user friendly but sometimes unexpected errors occur. This is mainly due to biofouling, because when the sensor gets inserted a wound is formed, decreasing vascularization and the wound is unstable. The instability of the wound is contributing to other elements of accuracy such as

- When inserted it is unstable for the first 12 hours
- The system is less accurate during high times of activity due to disturbance of tissue-sensor interface

Table 5: Comparative chart of different types of CGMs Adapted from (Continuous glucose monitor comparisons 2009)
Calibration of the devices is necessary to prevent discrepancy between interstitial blood glucose and finger stick capillary blood glucose. The systems provide enormous glucose trend data. This data is confusing and difficult for patients to interpret. Developments in hypoglycemia predicting algorithms are needed that raise the alarm threshold to prevent episodes of hypoglycemia.

b. Current Systems

The current systems are approved only for glucose trending and tracking and not approved for glucose monitoring. The systems provide opportunities for improved glucose control in two areas: a.) They provide alarms for high and low values of glucose and b.) The trends data generated by these monitoring systems allow the review of glycemic excursions based upon food intake, activities, exercise, stress levels, insulin uptake etc.

2. Current competitors

Most of the commercial sensors are highly compact that include a wireless transmitter, receiver/display unit and subcutaneous sensor. The features of the three CGM systems approved by the FDA are summarized below.\(^9\)
### Table 6: Features of continuous glucose monitors.

<table>
<thead>
<tr>
<th>Features</th>
<th>Medtronic Real Time</th>
<th>DexCom Seven</th>
<th>Navigator FreeStyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensor Size</td>
<td>Compact</td>
<td>Compact</td>
<td>Bulky</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Poor</td>
<td>Medium</td>
<td>Most accurate</td>
</tr>
<tr>
<td>FDA approval</td>
<td>2.3 – 17 years, Above 18 yrs</td>
<td>Above 18 years</td>
<td>Above 18 years</td>
</tr>
<tr>
<td>Avg life of sensor</td>
<td>4-6 days</td>
<td>10-12 days</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Warm up period</td>
<td>2 hours</td>
<td>2 hours</td>
<td>10 hour</td>
</tr>
<tr>
<td>Calibration</td>
<td>2-3 times/day</td>
<td>2 times/day</td>
<td>Fewest required 4 per 5 days</td>
</tr>
<tr>
<td>Minutes between data update</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Sensor insertion Technique</td>
<td>Hard</td>
<td>Hard</td>
<td>Easy</td>
</tr>
<tr>
<td>Presence of Predictive alarms</td>
<td>Predictive alerts may go unnoticed</td>
<td>Vibrates prior to alarm</td>
<td>Separate alarm ranges</td>
</tr>
<tr>
<td>Sensor charging</td>
<td>Every 6 days</td>
<td>3-5 days</td>
<td>No charging disposable batteries</td>
</tr>
<tr>
<td>Skin effects</td>
<td>Need tape to hold the sensor and this can cause irritation</td>
<td>Minimal skin irritation</td>
<td>Skin adhesion issues and causes irritation</td>
</tr>
</tbody>
</table>

### 3. Potential application

The CGMs provide information about magnitude, direction, frequency of glycemic fluctuation and help in therapeutic adjustment that would avoid hypo and hyper glycemia. Studies carried out using the Glucowatch and the CGMS gold systems indicate that the CGMs have decreased HbA1c levels more than SMBG in TI and TII diabetes. A study evaluated by Garg et al. and Diess et al indicated that the use of “DexCom and Medtronic Guardian RT has decreased amount of time spent in hyper- and hypoglycemic ranges while increasing the time in the euglycemic range”. These systems are proving to be accurate and reliable in different conditions and longevity under daily life conditions and thus bring us a step closer in the development of CLIPs.
D. Algorithms

1. Role of algorithms

One of the major components of the CLIP, the algorithm controls and adjusts the rate of insulin delivery, and automatically adapts to continuously monitoring insulin program. An ideal algorithm would address medical needs, deal with challenges in the CLIPS system and also regulate the blood glucose considering different scenarios. In a closed loop pump the algorithm acts like the brain of the entire system. The algorithm normally compares the ideal glucose concentration to the concentration obtained from the continuous glucose monitoring device. The algorithm then adjusts the rate of glucose accordingly and signals the insulin pump to deliver insulin. This insulin affects the glucose concentration, which is then sensed by the sensing device and feedback is passed to the algorithm. With impaired insulin production in the pancreas the algorithms will have to maintain a careful balance in maintaining the amount of energy consumption and healthy blood glucose levels.

2. Approaches

A large number of approaches have been proposed for control algorithms. Some of them include logic control, linear regression, statistical prediction based on past patterns, the classical feedback control and the prediction algorithms. The goal of the algorithms is to improve glycemic control for the diabetic patient.

a. PID (Proportional Integral Derivative)

The PID controller was originally used in the chemical plants. The PID aims to mimic the mechanism of beta cell which maintains tight glucose control. The PID controller
generally looks for deviations from the set point. The term PID indicates that the control action is composed of three functions of error 94:

- One is proportional to the error
- Second is the proportional to the integral of the error
- Third is proportional to the derivative of the error

In the marketed pumps the basal delivery is determined by the slow component – Integral, once the meal begins the rate of change of component is determined by – Derivative, this results in the rise of insulin delivery determined by the Proportional component as the level rises above the set point.95 The proportional component is generally zero if the glucose is within the target concentration, the derivative component counteracts to rapid changing glucose levels and the integral component adapts to changes in insulin sensitivity and considers the difference between ambient and target glucose while administering insulin.96 The PID system has a tendency to overshoot, resulting in hypoglycemia and this is normally experienced after meals. The derivative component is super sensitive to noise as it deals with counteracting rapid changes in glucose levels.

b. MPC (Model Predictive Control)

The model predictive control is a simulation model which predicts future glucose excursions and takes into account the estimation of insulin sensitivity. The model predicts how the insulin would affect future glucose trends and also calculates the first insulin delivery value. The algorithm optimizes future insulin plan versus goals and takes the first step for insulin action. The model revamps its plan after the data has been updated to deliver the next insulin step. The predictions of the model is based on past
blood glucose trends, historical insulin and glucagon values, individual’s variability and sensitivity, future insulin plans and known disturbances.  

**Issues**

- The MPC model uses the optimization approach that weighs different objective or uses the ‘rank order’ to rank the highest objective e.g. avoid hypoglycemia. The optimization algorithm faces a number of challenges.

- The algorithm is basically built using heuristic models using experience for solving problems, learning and discovery. A high chance of chaotic risk is associated with these algorithms as they are sensitive to initial conditions and these can have long term variations in the systems.

- Tuning of the algorithm to fit individual sensitivities and variability has to be considered. These tunings or calibrations can be manual, auto calibrated or the algorithms could use self learning programs.

3. **Challenges faced by Algorithms**

The algorithm as a control has to deal with a number of problems and challenges associated with different elements of the CLIP’s system. The four challenges the algorithms encounter are with insulin pumps, glucose sensors, meal disturbances and insulins.

**a. Pumps**

The algorithm has to be designed to deal with failures and faults in the pumps. These could include clogging of the tubes due to fibrillation of insulin, shutting of the motor or leaks caused in the pumps due to breaks or splits. The algorithms should be able to
recognize these faults individually and act by setting off an alarm indicating a fault/failure in the pump. The preferred area for insulin pump insertion is the abdomen as the insulin absorption is the fastest and the most predictable, as compared to other parts of the body. The common challenges for algorithms associated with pump placement include

- Tissue buildup or ‘hypertrophy’ caused due to repeated injections. Injections in these areas can have poor or unpredictable insulin absorption.\(^98\)
- Appropriate site selection and site rotation promotes predictable insulin absorption and protects the sites from hardening.
- The changes occurring due to placement variability, post placement variability, site selection can affect the insulin levels injected in the body.\(^99\) These challenges can be dealt with by changing the area of insertion, site preparation by using alcohol and antiseptics to clean the area before insertion and use of dressing material to prevent infection and control infections.\(^100\)

b. Sensors

Noise

All algorithms are troubled by some form of disturbance noise. In the artificial pancreas, noise is generated by the subcutaneous sensor. Optical estimation methods can be incorporated in the algorithms that can compensate for the noise and perform sensor recalibration when the sensitivity changes.\(^101\)

Calibration

- Placement disturbances, site insertion and variability - The flow caused by enzyme catalysis is proportional to the glucose at the insertion site, which is measured by the
sensor inserted subcutaneously. With this technique a signal drift is induced by the reaction of the subcutaneous tissue to the electrode and causes a change in glucose and oxygen diffusion. Thus, a change of site insertion can cause variability and sensor drift, which can be compensated by frequent recalibrations.

- **Encapsulation / site healing**- Sensor insertions can cause irritation and occasional infection at the site insertion. The infections occur due to the friction normally caused by the needle or the plastic infusion set on the skin. Immune system response to irritation and infection can cause a change in the subcutaneous chemistry and ISF, affecting the readings from the sensor. Long term insertion can lead to tissue build up or encapsulation at the site. These site discrepancies result in disturbances that affect sensor’s reading of glucose concentrations.

c. **Disturbances**

- One of the biggest challenges of glucose control is meal disturbances. The detection of the onset and the end of blood glucose increase with noise signal. The challenge with meal disturbances is the uncertainty of size, carbohydrate content, and duration associated with meals. Using manual input the planned meal can be used to improve glucose regulation but if the entire meal is not consumed or the meal is smaller than usual the chances of hypoglycemia is very high. The other challenge is modeling and understanding the shape of disturbances.

- Other transient disturbances would include exercise, stress, sickness, weight gain, getting into shape etc.

---

1 The most common sites are the stomach, upper arms, buttocks and hips as they have a layer of fat below the skin which helps in absorption of the insulin and not too many nerves. Injection into subcutaneous tissue is recommended. Using all the available sites with some predictable pattern of rotation is advised.
• A model has been proposed by Lehman and Deutsch to counter meal disturbances. The model emphasizes on gastric emptying of glucose into the intestines and the absorption of glucose into the bloodstream.\textsuperscript{104}

d. Insulin

The closed loop insulin pumps rely on subcutaneous insulin infusion, which poses a control challenge due to the delayed absorption of the insulin into the blood stream. Even with rapid acting insulin analogs, the prolonged absorption from excessive accumulation in the subcutaneous tissue results in hypoglycemia. The insulin sensitivity can vary among individuals over a long period of time due to changes in their diet, fitness and health. Insulin sensitivity is also known to change with the time of the day and the stress levels in an individual.\textsuperscript{105} This lag time also varies within individual diabetic patients and within patients of different age groups. The incorporation of bolus on board (BOB) feature in to the algorithm would help in preventing insulin stacking. The feature would consider the remaining ‘insulin on board’ from both basal insulin and previous boluses of insulin. Problems with pumps can be dealt with appropriate care for the insertion site, for the sensor predictable rotation patterns would help in decreasing the noise and for meal disturbances glucose absorption models are created that can help in decreasing the discrepancies. The algorithms have to be optimized to counter these challenges due to insulin by tracking the glucose trends and acting in light of subcutaneous accumulation of insulin as directed by the pharmacokinetics of insulin in vivo. Excessive accumulation of insulin is harder to deal with than any other problems countered by the algorithms. There is a greater need for ultra fast acting insulins as the MPC systems have a hard time dealing with meal disturbances and long acting insulins.
4. **Regulatory Issues**

A number of regulatory issues would be raised with the use of different algorithms. Issues include

- **Faulty mode** – Approval for different faults in the pumps, sensors, insulins have to be countered by the algorithms. Testing the faulty mode in real life would be time consuming and tedious.

- **Engaging patients** – The involvement of patients in the diabetes management is always a debate. What percent of engagement is essential for efficient glucose control is a major issue. Several algorithms are under evaluation but a self adjustment of diabetes management by patients has proved to be more effective in pilot studies. A semi-automatic system with partial control has also raised a lot of interest. The idea behind developing the CLIP’s system is to minimize any human interactions and improve the life of diabetic patients but there are clinical trials that contest this idea.

- **Safety issue** – The safety factor behind these algorithms have to be tested through extensive clinical trials in order to get through the regulatory approval.

- **Testing the extreme** – All aspects and issues relating to the algorithms can be tested only through heuristic methods. Testing for extremes can only come through experience, time and its use in real life situations.

E. **Insulin**

The control of insulin delivery in the AP will be through the control of algorithms. The biggest challenge in CLIPs system is optimizing the algorithm to mimic the physiologic natural pancreas and help maintain glucose homeostasis. The challenges faced by the algorithms are due to the slowness of the available insulins.
Sensors+ CGMs+ Insulin pumps+ Algorithms + Insulin= AP/CLIPs

The next generation ultra-rapid analogs address the slow kinetics of current rapid-acting insulins which cause post-prandial hypoglycemia, and the kinetic limitations of these insulins have impeded artificial pancreas (closed loop) pump systems. These insulins with enable tighter control by the closed loop pumps and improve diabetes management.

5. **Kinetics of Insulin**

Insulin form dimers in solution due to the presence of hydrogen bonding between the A and the B chain. Insulin dimers associate to form a hexamers in presence of zinc ions. The hexameric form provides long term stability and serves as a way to protect insulin; without this stability, insulin would form fibrils, lose potency, clog pumps, become immunogenic, be unsafe, and not meet FDA requirements. The commercial insulins have zinc ions in their formulation that prevent fibrillation. When insulin is injected into the skin the hexamers form a depot which delays absorption into the blood stream. The time required for disassociation limits the rate of insulin monomer absorption. This leads to slower kinetics and delays the activity of insulin.

6. **Next generation, ultra rapid acting insulins**

The novel insulins like Linjeta by Biodel, Halozyme and Mannkind’s Afrezza use vastly different approaches for rapid glucose control.

   a. **Linjeta by Biodel**

Linjeta is a rapid acting form of injectable insulin developed by Biodel for patients with T-I and T-II diabetes. This formulation consists of commercially available recombinant human insulin and proprietary formulation of ingredients. The drug has been tested in
more than 850 patients and Phase I, II and III clinical trials in US, India and Germany. Biodel has submitted an application for the FDA approval of the drug. One of the issues associated with Linjeta is its reconstitution. The powdered drug has to be diluted before use, and with the absence of zinc ions the formulation is highly unstable. Biodel claims to have solved this problem for their liquid formulation of Linjeta, but the data has not been made public and experts are highly skeptical the liquid formulation will meet FDA requirements. The prevalence of site injected pain and irritation is very high with Linjeta formulations due to pH variability. Recently a number of issues were raised by the FDA regarding clinical trial data submitted by Biodel. The FDA has requested two new Phase III clinical trials using commercial formulation, one in TI patients and the second in T II patients. The FDA has also requested additional data on stability and manufacturing.

b. Halozyme

Halozyme is a therapeutically driven company developing recombinant human hyaluronidase enzyme, rHuPH2O their lead enzyme (matrix modifying enzyme) along with the insulin temporarily degrades the hyaluronan (HA) and removes the barrier to bulk fluid flow, enables rapid dispersion and promotes disassembly and absorption. The formulation is currently under clinical development and has demonstrated accelerated kinetics of insulin absorption. A number of concerns surround the method of delivery.

- A problem of insulin hexamer formation is not resolved with the Enhanze technology
- Repeated injection at the same sites makes it inappropriate to use with pumps and long term side effects on the injection sites raise concern.
c. Afrezza by Mannkind

Afrezza is ultra-rapid acting inhalable insulin with a very different pharmacokinetic profile. Afrezza approach uses an active agent Technosphere Insulin (TI), a dry powder insulin formulation, upon inhalation disperses throughout the lung and dissolves immediately. There are a couple of regulatory questions raised with the use of inhalable insulin

- With the past debacle of Exubera, would Afrezza require Risk Evaluation and Mitigation Strategy (REMS) approval
- Will the drug be used on patients suffering from other diseases like asthma, lung cancer and other pulmonary disorders
- As inhalable insulin, Afrezza is not compatible to be used in CLIPs systems.

d. New analogs

Fast acting analogs of insulin have altered their structure to have charge repulsion at central positions, which prevent the formation of hexamers and thus decrease the time required by the insulin to be absorbed into the blood stream. The new analogs would need less stable hexamers and more stable monomers. One group based in Cleveland has a strong solution for each of the mentioned issues. The Single Chained Insulin (SCI) monomeric insulin has been developed by Thermalin Diabetes that prevents self assembly has faster kinetics and increase the insulin absorption rate. The Ultra thermostable insulin from Thermalin Diabetes exhibits intrinsic resistant to non-native aggregation and fibrillation and thus represent a class of insulin analogs whose pharmaceutical formulation could enhance the safety and efficacy of insulin therapy.
The development of these next generation insulin analogs forms an important step towards the development and success of the closed loop pumps.

V. Market for Closed Loop Insulin Pumps

A. Market Size

1. Diabetes in the United States

An estimated 285 million people, corresponding to 6.4% suffer from diabetes worldwide according to the WHO (World Health Organization).[^112] In 2011, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Institute of Health (NIH) estimates that 25.8M people of all ages in the U.S. will suffer from diabetes i.e. is approximately 8% of the U.S. population.[^113] Diabetes is a primary cause of heart disease and stroke and is also a leading cause of kidney failure, lower-limb amputation and new cases of blindness amount adults in the United States.[^114] The seventh leading cause of deaths in the U.S. is Diabetes.[^115] The competitive value proposition analyzes basic fundamental questions required to surpass competition. A good value proposition is specific and quantitative and highlights key points that define these systems.

2. Growing population

In 2010 about 1.9 M people of ages 20 or older were newly diagnosed with diabetes and the number of people diagnosed with diabetes has risen from 1.5M in 1985 to 18.8M in 2011.[^116] The diabetic population is estimated to grow at a compound annual growth rate of (CAGR) 4.5%.[^117] It is estimated that over 30% of the diabetes population was undiagnosed in the year 2001.[^118] The diagnosed and the undiagnosed diabetic population...
trends in the US are shown below. The diagnosed population seems to be growing by a CAGR of 5.6% as compared to the undiagnosed population of 1.6% and the trend seems to be decreasing.

![Diagnosed and Undiagnosed Diabetic Population](image)

Figure 21: The numbers have been obtained from (U.S. Emerging Insulin Delivery Technologies Market 2008).
B. Need for Closed Loop Insulin Pumps (CLIPs)

- Monitor blood glucose levels and deliver insulin automatically
- Optimize accurate and reliable delivery of insulin and at the right amount
- The need is to make the process easier, user friendly, less painful, non-invasive, efficient and accurate.
- Have adult support at home and in school for children and adolescents
- To have access to diabetes team 24x7 offering problem solving and support.
- Offer decision making points around fluctuations in blood glucose, carbohydrate intake, illness, activity variables etc.
- The major driving force in the diabetes controlled market is the search for fundamentally better and automated systems that would ease the burden of therapy for insulin-dependent. The current open loop systems and pumps normally require user interface prior to insulin dosing and does predict glucose trends that could forecast hyper or hypoglycemia.

C. Approach

- The Closed Loop Insulin Pumps (CLIPs) automatically provide glucose readings without the use of finger sticks, thus reduce the ease of therapy for insulin-dependents.
- The CLIPs monitor real time glucose trends and predict a fall in glucose levels and thus avoid hypoglycemia (Overnight hypoglycemia)
- These systems provide continuous insulin to the body at predetermined breaks and do not involve user interaction. This is especially useful during night time.
The system carries out comparative analysis between the present and future glucose readings and prompts or suggests changes in the insulin plan.

Unlike other industries where technology advancement reduces cost, new devices and automation increase cost in the healthcare sector. The development of CLIPs is important for patients with diabetes as the technology would not only ease daily life but also help in the prevention of diabetes related complications. The system would help in early diagnosis, intervention and better safety, which would help to save a large amount of health care cost associated with diabetes.

D. Competition

The diabetes market includes devices and pharmaceutical drugs. The leading segments include insulin, blood glucose meters and supplies (lancets, test strips), insulin delivery devices (pens, syringes), insulin pumps and anti diabetic drugs.

The world diabetes market for 2010 is summarized below.\textsuperscript{119}

<table>
<thead>
<tr>
<th>MARKET SEGMENT</th>
<th>VALUE (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic drugs</td>
<td>$13,610 M</td>
</tr>
<tr>
<td>Insulin</td>
<td>$14,000</td>
</tr>
<tr>
<td>Insulin Delivery Devices</td>
<td>$ 125 M</td>
</tr>
<tr>
<td>Glucose meters and supplies</td>
<td>Meters: $ 6000M, Strips $ 5100M, Lancets $ 475M</td>
</tr>
<tr>
<td>Insulin Pumps</td>
<td>$ 1573M</td>
</tr>
<tr>
<td>Total value</td>
<td>$ 40,000 M</td>
</tr>
</tbody>
</table>

Table 7: World diabetes market 2010

The pump market along with the disposable / supplies market accounts for a whopping $ 7148M. The major companies in the insulin pump and continuous glucose monitoring
sector include Medtronic, Roche, Animas, Sooil and Deltec. The worldwide insulin pump and disposable market share is described below.

Figure 22: Worldwide Insulin pumps and disposable market (Numbers are obtained from (Pham 2005)

Sooil (Dana Diabecare pump) and Nipro (Amigo pump) are the newest entrant in the insulin pump industry. OmniPod by Insulet Corporation is the only disposable insulin pump available in the market. Although no closed loop pumps are in the market, their approval may occur within the next couple of years. Currently Medtronic offers a CGM/insulin pump system that is patient or physician controlled rather than by algorithms.
E. The Closed Loop Pump Market

The diabetes population is segmented as follows.

5% of the diagnosed diabetic population suffers from the Type I form and 90%-95% of the diagnosed population suffers from Type II form of the disease. An estimated of 500,000 insulin pumps are used worldwide and about 20% of the Type I diabetic patients (approx. 200,000) use infusion pumps and some Type II patients in the US. This is changing as people understand the benefits of tight insulin control and gain familiarity and confidence using the pump 24x7. Recent studies have shown that the use of insulin pumps along with insulin injections have helped maintain glycemic control in Type II. A study carried out at the American College of Endocrinology illustrated that approximately 20% of Type II patients used insulin pump therapy. With increasing
prevalence of diabetes and growing awareness among patients there is a substantial
demand for noninvasive insulin delivery systems. The closed loop insulin pump systems
market primarily is driven by high demands among the patients population that are able
to manage their insulin delivery effectively.

Medicare has established criteria for insulin pump coverage and continuous glucose
monitoring.\textsuperscript{123}

- Require at least three injections of insulin a day
- Makes self adjustments of insulin for six months
- Documents self monitoring of glucose four times a day for two months
- Patient must complete the diabetes education program
- Meet one/more criteria
  - Hemoglobin A1C> 7.0%
  - Has a history of hypoglycemia
  - Fluctuations of blood glucose before meals
  - Has severe glycemic excursions

To understand the potential market for closed loop pump a sample set of very efficient
insulin pumpers are selected who fit the criteria established by Medicare.\textsuperscript{2} The insulin
pumpers are skilled, disciplined enough to calculate their own insulin under stress,
exercise, variation in diet and are effective problem solvers. Thus this group of insulin

\textsuperscript{2} The data is adapted from Nonprofit Public Benefit Corporation called Insulin Pumps and Insulin Pumps Foundation.\textsuperscript{2} The database consist of 21000 families and individuals’ coping with diabetes and are very actively involved in maintaining blood glucose levels.
pumper represents a potential market for analysis of CLIPs in a total population of 21000.

<table>
<thead>
<tr>
<th>Potential CLIPs Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents/caretakers of person with diabetes</td>
</tr>
<tr>
<td>Type II</td>
</tr>
<tr>
<td>Male Pumpers</td>
</tr>
<tr>
<td>Female Pumpers</td>
</tr>
<tr>
<td>Person with Diabetes</td>
</tr>
<tr>
<td>Type I</td>
</tr>
</tbody>
</table>

Figure 24: Potential Closed Loop Insulin Pump Market

a. Intellectual property: Defensible strategy or a barrier for Artificial Pancreas.

The patent activity in the medical device industry especially in the Artificial Pancreas division has increased tremendously over the recent years. According to a study carried out by a group of the Artificial Pancreas consortium the number of patents in the closed loop glucose control has increased from 24 filed in 1991 to 247 filed in 2001. With systems as complex as the Artificial Pancreas the risk of infringement becomes very high, as a large number of patents are filed in the technology arena. The outcome of this situation could be a decline or reduce in innovation.
Figure 25: No. of patents filed in Closed Loop Glucose control systems from 1987-2006 in the US\textsuperscript{125} (U.S. applications begin only in 2001, as the USPTO did not previously publish patent applications but only granted patents)

The patents filed in the past years were pending and therefore the number of granted patents from year 2001 and onwards is expected to increase rapidly. The total number of US applicants is around 500 filings per year.\textsuperscript{126} A patent thicket is formed when a large volume of patent concentrated towards a particular technology is filed. Due to vast number of patents the path to product development becomes blurry and successful exploitation of the innovation becomes difficult. It is quite possible that the development process could come to standstill, if a patent holder with a broader scope blocks the development of Artificial Pancreas by enforcing their right.
Alternative approaches may involve

- Standardization efforts to ensure interoperability of different components among manufacturers.
- Design of an Artificial Pancreas system that would be compatible with other medical devices.
- Develop standards such that similar devices adhere to same specifications
- Sufficient incentives can be provided to the patent holder to dispose of their rights for the society.

VI. Economics of Closed Loop Insulin Pumps

A. Burden of Diabetes

The National economic burden of diabetes reached $218 billion in 2007 and this estimate included $153 billion in higher medical cost and $65 billion in reduced productivity.\(^{127}\)

The annual cost for each patient segment of diabetes is described in the table below:\(^{128}\)

<table>
<thead>
<tr>
<th>Segment</th>
<th>Cost per case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undiagnosed</td>
<td>$2864</td>
</tr>
<tr>
<td>Diagnosed</td>
<td>$9975</td>
</tr>
<tr>
<td>Type I</td>
<td>$14856</td>
</tr>
<tr>
<td>Type II</td>
<td>$9677</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>$443</td>
</tr>
</tbody>
</table>

Table 8: Annual cost for each patient segment of diabetes

Cost can be a formidable obstacle to Artificial Pancreas system. The system includes insulin pumps, initial supplies, including tubing, syringes, cartridges, sensor and an algorithm.
1. **Initial cost associated with pump**

<table>
<thead>
<tr>
<th>Pump Manufacturer</th>
<th>Initial cost of insulin pump</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animas</td>
<td>$ 7322 (^{129})</td>
</tr>
<tr>
<td>Medtronic Paradigm</td>
<td>$ 9004 (^{130})</td>
</tr>
<tr>
<td>Roche ACCU-CHEK</td>
<td>$ 5740 (^{131})</td>
</tr>
</tbody>
</table>

Table 9: Costs associated with insulin pumps

2. **Annual Cost associated with Insulin Delivery systems\(^\text{132}\)**

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Annual Insulin Cost</th>
<th>Annual Cost of Supplies</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pen Injected Insulin</td>
<td>$2592-$3960</td>
<td>$ 336</td>
<td>$ 2938-$4296</td>
</tr>
<tr>
<td>Syringe Injected Insulin</td>
<td>$ 720-$ 1164</td>
<td>$288- $ 332</td>
<td>$1008-$ 1496</td>
</tr>
<tr>
<td>CSII</td>
<td>$ 720-$1164</td>
<td>$ 1554-$ 2160</td>
<td>$ 2274-$ 4234</td>
</tr>
</tbody>
</table>

Table 10: Annual cost with insulin delivery systems

The initial cost of insulin pumps is more the $ 5000 from the above mentioned information. Infusion sets and catheters are purchased on regular basis as long as continuous subcutaneous insulin infusion is used at an annual cost of $ 1500.\(^\text{133}\) A diabetic patient using the basic Roche ACC-CHEK system with a continuous glucose monitoring would have an annual cost of $ 8014. The insulin pumps in the market do not have advanced algorithms within them. These algorithms would add to one time initial cost along with the insulin pumps. A report issued by Medtronic in 2010 mentioned the cost of Artificial Pancreas could cost up to $ 10,000 per unit.\(^\text{134}\)

**B. Reimbursement Issues**

Reimbursement issues are challenging factors towards the development of closed loop pumps. An ideal closed loop system would automatically fine tune insulin based on small changes in the blood glucose levels just as the pancreas does. But there are huge regulatory steps required before these systems can be used. Closed-loop systems are complex and they consists of different components that fit together to work harmony. It is important that the individual components and the whole system get regulatory approval.
Reimbursement not only involves payment but also involves issues of coverage and coding. With the CLIPs system constantly evolving it becomes very difficult to assign codes to described the product or treatment and determine the appropriate payment of the product. For e.g. the Continuous Glucose Monitors is an innovative treatment whose adoption suffered because of unfavorable reimbursement. The FDA approved the first CGM device for patient use in 2005. But until recently, insurance companies have not covered or paid for CGM. Medicare, Medicaid and most of the insurers’ plan cover the cost of continuous glucose monitoring after prospective approval. However patients whose plans cover 80% of the total cost still pay initial and recurrent out-of-pocket costs, Medicare normally covers insulin pump therapy for Type I and Type II diabetes if certain conditions and criteria are met, whereas Medicaid coverage varies within states. A pump on rental basis is also provided by Medicare. A number of factors pose a threat for the adoption of Artificial Pancreas system.

- FDA approved CGM as an adjunctive therapy to standard glucose monitors and not as replacement therapy. The CGMs are an additive therapy rather than replacement they represent additional cost for payers. For the CLIPs system all the components could be approved an adjunctive therapy and this would only increase the cost for the payers.

- FDA approval is necessary but not adequate for reimbursement. Large amount of clinical data on safety and effectiveness is essential for the insurers to cover a product before patient use.

- The CLIPs systems would have to prove itself in real life situations like exercise, and snacking. This seems like a daunting task as trials are needed for every situation
possible. Generating clinical data for safety and efficacy in real life situations is definitely a challenging task for the CLIPs system

- Pediatrics is a big market in this industry. Although the insulin pump therapy has been successful in adults very few pumps in the market are approved for pediatric use.

- Normally providers receive payment for face to face interactions with the patients for performing procedures but phone calls, emails and other virtual interactions do not result in payment. Lack of reimbursement for physicians, nurses and certified diabetes educators is a barrier to wide spread adoption.

- Physician may be unwilling to or unable to prescribe the system if they cannot afford the level of care to manage patients.

- One of the biggest barriers is that the system could be responsible for the replacement of endocrinologists, diabetes care takers and educators

- Absence of a CPT code specific to intensive insulin management may delay adoption and use of this technology

In order for this technology to be easily adopted a new CPT code specific for insulin management should be introduced or a new CPT code should be created for the Artificial Pancreas. The driver for success is not just engineering development but human factors to establish safety and usability, clinical research and training and education.

To be successful all the stakeholders must collaborate to bring the system into the market. The JDRF, FDA, NIH and the industry have joined together to
help shape future studies and make recommendation on the problems faced by the technology.

VII. Development of Artificial Pancreas system

The incidence of diabetes has been growing at an alarming rate in the U.S and world over. In spite of increasing effective treatment modalities a large portion of the diabetes population are unable to achieve appropriate glycemic control. The difficulty is a trade-off between improved glycemic control and increased risk of hypoglycemia, which can lead to coma, seizure or death. The development of Artificial Pancreas is essential because the current methods of diabetes improve but do not normalize blood glucose, the burden of insulin therapy is extremely high and other alternatives such as islet cell replacement and pancreas transplant therapy have high morbidity related to immunosuppression. The development and design of the closed loop pumps or Artificial Pancreas is tricky as it raises scientific, regulatory and clinical challenges.

A. Role of the FDA

The U.S. Food and Drug Administration have identified the Artificial Pancreas as one of its critical path initiatives. It has formed the Interagency Artificial Pancreas Working Group (IAPWG) that collaborates with stakeholders, private organizations, patient group, product developers, academic researchers, industry and other government to accelerate the development of Artificial Pancreas. The Artificial Pancreas is defined by the FDA as an autonomous system as it delivery the insulin to the patient without the patient’s knowledge. In theory the system can benefits diabetic patients and help is maintaining
appropriate glycemic control but there are large number of limitations, design challenges and safety issues associated with the development of the Artificial Pancreas.

1. **Class III Device – Premarket Approval**

Class III is the most stringent regulatory category for medical devices. The criteria for Class III devices include: 138

- Insufficient information exist to assure for safety and effectiveness solely through general or specific controls
- Class III devices support or sustain human life
- The devices are important in preventing impairment of human health
- The artificial pancreas is regulated as a class III device requiring premarket approval (PMA) as general and specific controls does not exist to assure safety and efficacy.

The Artificial pancreas is regulated as a significant risk device and requires Investigational Device Exemption (IDE)

B. **Product and Technology Milestones**

2. **Roadmap for the Closed Loop Insulin Pumps**

A “closed loop” system would automatically dose insulin unlike the available “open loop” systems in which the patients interpret the insulin dosage. The closing of the loop or creating an Artificial Pancreas system involves a series of clinically significant steps that will improve as the system evolves. The roadmap for the CLIPs system would depend on robustness, safety, accuracy, features in the today’s continuous monitoring system and insulin pumps. The idea behind automation in
stages is to create a system with proper specifications and control targets which reduce risk targets.\textsuperscript{139}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{automation_stages.png}
\caption{Automation stages for Closed Loop Insulin Pumps. The figure has been adapted from (Klonoff 2007)}
\end{figure}

\textbf{a. Low Glucose Suspend}

The first step is to prevent or minimize exposure to severe hypoglycemia. Seizures caused due to hypoglycemia are one of the most common aspects of diabetes in patients. Study suggests that seizures normally occur after prolonged 2-4 hours of low blood sugar.\textsuperscript{140} In the present day systems when a patient experiences hypoglycemia the insulin pump continues to dispense basal insulin. A logical step would be a very low glucose insulin pump shut off system with a goal to reduce severe hypoglycemia exposure/seizures. There could be very little risk with such a pump that turned off when in fact the glucose levels are not low, this could lead to hyperglycemia or ketoacidosis.
b. Hypoglycemia Minimizer

Second very low risk but important step in the development of CLIPs is a predictive hypoglycemia minimizing system. When hypoglycemia is predicted and the patient is unresponsive, this system would automatically reduce or stop the insulin delivery with the help of an algorithm. The algorithm would continuously monitor glucose levels and would help in the prediction of hypoglycemia. The risk of hyperglycemia is very low in theory and using an algorithm approach the system could resume basal delivery in shorter time frame.¹⁴¹

c. Hypoglycemia and Hypoglycemia Minimizer

The next proposed step is a development of a system that automatically doses insulin. The third system would function exactly as the predictive hypoglycemia minimizing system but with the capability to act on hyperglycemia. Such a system could maximize the strengths of today’s CGM devices and help in the evolution of the sensor by setting aggressive targets. The system may be the most effective in adolescent and young adults.¹⁴²

d. Automated Basal

The next proposed challenge is to automate to a euglycemic set point overnight with few meal announcements to further reduce hyperglycemia exposure. Additional improvement in sensors will be required as the system evolves from anti-hypoglycemia/anti-hyperglycemia system to a system that targets a lower set point.¹⁴³

e. Automated Basal & Bolus and Automated Multi-Hormonal

The goal of the next two closed-loop and multihormonal systems would be to minimize/eliminate user interactions, restore euglycemia and mechanically mimic the
normal physiology. Stages 1-4 do not represent the artificial pancreas but the incremental automation for insulin delivery. The Artificial Pancreas like system would require robust and more accurate glucose sensors. It would require two systems operating simultaneously:

a. Controlling insulin delivery

b. Second system monitoring the primary sensor and monitoring the overall system performance.

Improved glycemic control can be achieved by use of bi-hormonal system. Studies performed by a group demonstrated the feasibility of bihormonal closed-loop blood glucose regulation using subcutaneous infusion of insulin and glucagon governed by an algorithm. This is the first practical implementation of an Artificial Pancreas that has hormonally derived counterregulatory capability. A multihormonal approach will require the development of dual pumps and introduction of other hormones in the system will be utilized. Though the development sounds very appealing, the time to deliver such a system in the market may be longer.

3. **Product development goals in the Artificial Pancreas (Closed Loop Systems)**

The approval of the system by the FDA in the market hinges on the system being safe and effective. The preliminary studies of the closed loop systems have shown exceptional efficacy. A fully automated hands-off system would probably require a more reliable glucose sensing technology that is reliable, accurate and minimizes the risk of miscalibration. The system would also require rapid acting insulin that has faster pharmacokinetics and pharmacodynamics. A number of challenges are present in
developing the artificial pancreas system. The challenges represent the goals for the product development of the Closed Loop systems. The JDRF along with the NIH have enlisted some of the future goals for the development of the Artificial Pancreas systems.

a. **Glucose sensors**
   
   a. Development of novel, miniaturized, non-invasive range specific glucose sensors.
   
   b. Development of novel implantable sensors technology (biomaterials) that have higher durability, reduce befouling and improve biocompatibility.
   
   c. Construction of an imminent alarm system that is able to predict and effectively track hypoglycemia and shut off insulin delivery when necessary.
   
   d. Development of non invasive or minimal invasive continuous glucose monitors that would link the glucose sensor to insulin delivery.

b. **Algorithm**
   
   a. Development of predictive and advanced algorithms able to sense glucose and deliver insulin.
   
   b. Use of novel technology that would understand the glycemic response to various insulin routines for e.g. exercise, stress, dieting etc
   
   c. Use of novel algorithms that would incorporate counter-regulatory hormones that would prevent or correct hypoglycemia.

c. **Insulin**
   
   a. Developing novel, monomeric rapid acting insulin having improved pharmacokinetic profiles
   
   b. New insulin delivery modes and devices.
   
   c. Development of implantable glucose regulated insulin delivery systems.
4. **Discovery to launch**

![Diagram of stages in drug development](image)

**Current State**

- **In silico model**: Developed of Boris Kovachev in collaboration with the FDA.\(^{147}\)
- **Safety and efficacy Trials**: A large number of trials are be carried out to develop on the Closed Loop Insulin Pump generations
- **Low glucose suspension**: Paradigm Veo developed by Medtronic is a LGS (Low Glucose Suspension) pump that halts insulin delivery automatically when the sugar levels are low.

Figure 27: Development process of Artificial Pancreas (Adapted from *Coles 2007*)
The development process of the Closed Loop Insulin Pumps from exploratory research to launch is long, tedious and complicated process.

1. Testing the CLIPs system in animal models and further testing the system in-silico models that would mimic real life conditions and situations. The biosimulation model developed by Boris Kovatchev incorporates a Glucose-Insulin Model, a model of sensor error, a model of insulin pump and subcutaneous insulin kinetics.\(^ {148} \) The system had three principal components a. Large cohort of 300 simulated subjects (100 adults, 100 adolescents and 100 children), b. CGM error sensor representing FreeStyle Navigator, Guardian RT or Dexcom, 7 day sensor and c. Simulator similar to the OmniPod system of the Deltec Cozmo pump.\(^ {149} \)

2. Clinical Development – This stage of development involves carrying out safety and efficacy studies, conducting phase I, II, III human trials and testing of the CLIP system in home setting.

3. Launch or exit strategy – For a company developing the CLIP system there could be two ways of exit.

   a. Transfer of the technology to an incumbent or seek a corporate partner to advance the technology to the market.

   b. The second strategy would involve getting regulatory approval for the technology by collaborating with regulatory bodies like the JDRF, NIH and FDA. Carrying clinical trials in collaboration and obtaining clinical adoption and health care insurance coverage for the system.
VIII. Future of Closed Loop Insulin Pumps

Use of telemedicine to improve outcomes in diabetes is an emerging technology. Telemedicine incorporates telecommunication to support health care. Telemedicine includes timely transmission and remote interpretation to facilitate interaction between the patient and the healthcare provider in order to achieve improved treatment and lower costs.\textsuperscript{150} Intensive insulin therapy has an inherent risk of hypoglycemia that can lead to death in bed syndrome caused due to loss of consciousness, seizures, cardiac arrhythmia and death. In automated engineering systems the risk of malfunction is very high, so safety mechanisms are implemented in layers of protection. The same concept can be used to integrate a hypoglycemia prediction algorithm with GPS (Global Positioning System), a message service that can deliver the current glucose readings and location of the patient can be communicated.\textsuperscript{151} The following are the different layers of protection that would be provided by the futuristic Artificial Pancreas system. The layers are divided into two categories Alters and Alarms algorithms.\textsuperscript{152}

Alarms\textsuperscript{153}

a. An Artificial Pancreas system with CGM, continuous subcutaneous insulin infusion and a control algorithm that regulates glucose levels

b. Predictive alarm that alerts the patient and suggests changes/correction

c. Active alarm for hypoglycemia that makes a sound or emergency contact

d. Automated dialer to emergency services (911)

Alerts

a. The monitoring layers of the CGM alert algorithms include incorporation of the GPS locator, SMS and email such that the current glucose value with rate of change is communicated to the caregiver, physician or emergency services.
b. An alert system module incorporated in to the artificial pancreas software was approved by the FDA for clinical trials along with GPS and a wireless internet connection to a computer/laptop.¹⁵⁴

Figure 28: Schematic illustration of prototype telemedicine system adapted from (Eyal Dassau 2009)

A number of barriers could limit the use of telemedicine in Diabetes. The barriers are both technical and systemic. Technical barriers include fear of computers, lack of training in computers, no access to a computer and privacy breaches. Access to information could
be easy and security breaches could occur in the hospital industry. The major barrier would be adoption of telemedicine, systemic one where problems like inadequate or nonexistent reimbursement concerns.\textsuperscript{155}

The monitoring alert and alarm system not only provides safety to the future Artificial Pancreas but also can be easily implemented in the current continuous glucose monitoring systems. These systems will especially be useful for patients above 65 years of age, for parents to monitor their children with Type I diabetes attending school or at play away from home. As the communication technology improves, decision support software and data management progress and as the payers and regulatory, legal bodies get comfortable with the telemedicine approach then the diabetes telemedicine will become increasing adopted. Telemedicine promises to become a novel 21\textsuperscript{st} century tool for diabetes health care providers to communicate with patients to improve their quality of life.
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