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Development of Artificial Pancreas

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Abstract:- Diabetic patients who have an abnormal blood glucose level suffer from acute effects of hypoglycemia and long term effects of hyperglycemia which include disorders of eyes, kidneys and nerves. This paper introduces the concept of an artificial pancreas which is a revolutionary device for the diabetic population. The artificial pancreas (AP), known as closed-loop control of blood glucose in diabetes, is a system combining a glucose sensor, a control algorithm, and an insulin infusion device. The development of artificial pancreas can be sketched back 50 years to when the possibility for external regulation of a human's blood glucose was established by studies of type 1 diabetes using intravenous glucose measurement and infusion of insulin and glucose.The goal of the artificial pancreas is to relieve the person with diabetes from some of the burden of daily doses and medicines and insulin shots.

Keywords:*artificial pancreas, diabetes, glucose sensor, insulin infusion device, control algorithm*

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I. INTRODUCTION

Medical researchers have been intensely trying to find new aspects of overcoming the tyranny of Type 1 diabetes. A new concept of artificial pancreas has come into picture. An artificial pancreas is a device which helps to eliminate the procedure that a diabetic person has to go through and the constant health decisions that they have to make every day. Type 1 diabetes is a condition which is caused by autoimmune response in which the body's own immune system destroys the cells producing insulin. It is also known as juvenile onset diabetes as it occurs at a very young age. The pancreas in people suffering from type 1 diabetes can no longer produce insulin.If this condition is left untreated, the blood glucose levels could go dangerously high leading to 'hyperglycemia'. Exposure to hyperglycemia over many years can cause neuropathy, retinopathy, and damage to other tissue and organs. Diabetics have to resort to taking medications and insulin shots throughout their life. This becomes part of their daily routine. However it is not as easy as it seems. Many things have an effect on insulin levels in a person's body, including exercise, stress, what and how much they eat. So the insulin dose can vary. Also, a person unable to take insulin on time can go into insulin shock. Furthermore, episodes of hypoglycemia can occur without the patient realizing it, such as at nighttime while the patient is asleep. Another problem faced is the storage of insulin especially while travelling. This makes life for people suffering with diabetes very restrictive. Having blood glucose levels that are too high (hyperglycemia), or too low (hypoglycemia), can cause serious health problems. This leaves many type 1 diabetes patients constantly checking their blood glucose levels, calculating how their actions will change their levels, and adjusting their insulin doses to avoid a critical high or low. [1]

Scientists and engineers are working to create improved insulin pumps and artificial pancreasto take away the difficulties encounteredwhen fighting type 1diabetes. Artificial pancreas is basically a system of integrated devices substituting for an endocrine pancreas. Diabetics taking insulin supplementhave to take it in the form of insulin injections using needles or in the form of infusions using a pump. Currently a person who has to take insulin should closely monitor their blood glucose levels to determine the time when and the amount of insulin that has to be injected. Insulin pumps are typically a small device, as small as a mobile phone. They have to be integrated with a system which usually includes a continuous glucose sensor. An artificial pancreas senses blood glucose level in a person's blood, determining the amount of insulin needed via an electronic interface, and then delivering the appropriate amount of insulin. Components of an artificial pancreas include an automatic glucose monitor, an automatic insulin delivery system, and an algorithm to link blood glucose levels with insulin delivery. [2]

II. ARTIFICIAL PANCREAS: MILESTONES ACHIEVED

Artificial pancreas developments can be traced back 50 years to when external blood glucose regulation became possible and was established by studies in individuals

suffering from type 1 diabetes using intravenous glucose measurement and infusion of insulin and glucose.

The concept of a closed-loop artificial pancreas was first described by Kadish in 1964. After minimally invasive subcutaneous glucose sensing was commercially introduced, subcutaneous artificial pancreas was developed. It became a new wave in 1999 by the MiniMed continuous glucose monitoring (CGM) system. In September 2006, the Juvenile Diabetes Research Foundation International (JDRF) initiated the Artificial Pancreas Project. It also funded a consortium of centers for the research work of carry out closed-loop control system. European Commission launched the AP@Home project in 2010. It includes the involvement of seven universities and five companies throughout Europe [3].

Table 1: Key milestones in the timeline of artificial pancreas progress [3]

YEAR	MILESTONE	DEVELOPER
1964	IV Closed loop control	Developed by Kadish
1974	The auto syringe	Developed by Dean Kamen
1977	The Biostator	Developed by Albisser Pfeiffer
2005	The Minimal model of glucose kinetics	Developed by Bergman and Cobelli
1979	First use of CSII	Developed by Tamborlane
1999	SC glucose sensing unit	Developed by MiniMed CGMS
2000	IP Insulin pumps	Developed by Renard
2000	The EC ADICOL project	Developed by Hovorka
2006	First studies of automated SC closed loop	Initiated by Steil
2008	Human trials with system designed entirely in silico	Initiated by Kovatchev, Cobeli, Renard (JDRF)
2010	AP at home	Launched by EU

III. PROCEDURES

Researchers aim to build a system which is portable, easy to use and provide a better glycemic control in patients with Type 1 diabetes with manual interference. The system described in this paper is a simple one which consists of a glucose measuring unit, a control algorithm and an insulin delivery pump

A. GLUCOSE MONITORING SYSTEM

A glucose sensor suitable for use in the artificial pancreas must be accurate over the long term;it should be capable of frequent or continuous sampling of blood. One of the main concerns is biocompatibility as foreign body immune rejection causes a direct impact in the readings or may reduce the glucose concentration in the interstitial fluid. It is desirable that it is and easy to calibrate with only 3 calibrations a day needed.Initially, research into blood glucose sensors led to enzymatic devices but has recently the focushas been on developing noninvasive optical methods which is still a theoretical concept. Some categories of glucose monitoring system include [4]:

1. ENZYMATIC SENSOR

Enzymatic sensors have been under development for a long time since around 1960s. An enzymatic sensor consists of an enzyme which has been immobilized and an electrochemical transducer interface. Enzymatic glucose sensors have been developed in the form of venous implants. They are needle-like probes which penetrate the skin with the sensor tip in subcutaneous tissue. Devices can also fully implanted in the subcutaneous tissue and hence requireno trans-skin communication.The enzyme glucose oxidase is coated on the sensor membrane in these devices which catalyzes a chemical reaction. This reaction is as follows [5]:

$$\text{glucose} + O_2 \Rightarrow \text{gluconic acid} + H_2O_2.$$

$H_2O_2$is hydrogen peroxide and the production of hydrogen peroxide is directly proportional to the concentration of blood glucose available in the blood. Early on sensors estimated hydrogen peroxide levelsby directly measuring the electrical current produced by its conversion into water. Hydrogen peroxide, however, rapidly degrades glucose oxidase and to overcome this alternative sensors work indirectly. They measure the consumption of blood oxygen in the reaction stated relative to the reference sensor. [6]

A representative fully implanted sensor consists ofa sensing electrode system, glucose oxidase laminated membrane, and a unit of radio-telemetry transmission. The weight of this unit is 27 g. The enzymatic sensor is powered by a tiny lithium battery. It has a lifespan of almost 1.5 years and the sensor transmits signals to an external computer.

These sensors are small sized, cost effective and have a relatively mature technology.Despite this implantable enzymatic sensors are not yet clinically applicable because of biocompatibility problems. Clinical research is necessary to cure the instances of chronic subcutaneous implantation and reduce local inflammation on glucose sensor implantation.

2. SUBCUTANEOUS GLUCOSE SENOR

The artificial pancreas can use subcutaneous insulin delivery from a portable pump. It is guided by a subcutaneous glucose sensor having encountered delays and variability of insulin absorption from the subcutaneous tissue fluid. A closed-loop intraperitoneal insulin infusion from an implanted pump driven by a subcutaneous glucose sensor has been tested. It is driven via a proportional-integral-derivative (PID) algorithm. This kind of device requires an external apparatus. A subcutaneous system might experience time lag for equilibration with blood glucose as the delay

required for subcutaneous glucose to achieve equilibrium after a change in blood glucose may be too long to allow a practical approach to an artificial pancreas. This serves as a major disadvantage for subcutaneous approach. [7]

3. INTRAVASCULAR BLOOD GLUCOSE SENSOR

Not much research has been done to study the effects of variable local inflammation at the site of sensor implantationbased on glucose concentration and transition time. Moreover, a patient showing sign of acute hypoglycemic activity requires a sensor that responds with a delay of not more than 12 minutes. These issues could be removed by direct intravascular insertion of an enzymatic sensor. This approach has been tested in dogs however it may not be applicable to humans in near future to the risks ofclotting, infection and bleeding. [8]

4. OPTICAL SENSORS

Optical sensor is an alternative for glucose sensing systems that has come to light recently. It simply shines a beam of light through a blood vessel, preferably a fingertip.The principle used is based on absorption pattern of near-infrared light (wavelength range- 700-1300 nm) which can be quantitatively associated to the glucose concentration. However, other substances such as plasma, protein, and hemoglobin and erythrocytes also absorb near-infrared light at these wavelengths which reduces the clarity producing a relatively weak glucose signal.Fundamental research is required to investigate the composite in-vivo factors that affect the measurement of glucose using optical sensors. As far as feasibility is concerned, an optical sensor can be made wearable, reliable and accurate, but it would create a challenge to create a small enough unit at a clinically applicable cost[6].

B. CONTROL SYSTEM

A miniature sized control system in an artificial pancreas system should be able to sample, filter, and interpret the data given by the glucose sensor. It should also be able to compare the reading with appropriate standard parameters and precisely order enough insulin so as to maintain normal glucose levels in the blood. This control process must operate properly all of the time, because inaccuracies could lead to severe hypoglycemia or hyperglycemia in a patient.Investigators and researchers have control algorithms for operating the required feedback loop anticipating the development of a glucose sensor to complete the artificial pancreas.No human interaction or interference is required in the development of a fully automated closed-loop and dual sensor multi hormonal artificial pancreas system. The system is comprised of mainly two sensors to measure glucose, two pumps for separate delivery of the hormones insulin and glucagon, and a microcontrollerfor the operation of a software application (custom-made) that controls the sensor gaining and required amount of insulin or glucagon delivery basedlevels of glucose values recorded. Two control algorithms are designed into the software:

(1)An algorithm used to deliver insulin and glucagon according to their proportional and derivative errors and proportional and derivative gains

(2) An adaptive algorithm that adjusts the gain factors based on thepatient's current insulin sensitivity by constructing a mathematical model. [8]

C. INSULIN INJECTION PUMP

An insulin pump is a device to deliver insulin, usually small about a size of a pager. It contains reservoir filled with insulin.A microcomputer will adjust the appropriate amount of insulin to be delivered.Insulin is pumped through an infusion line attached with a small plastic tube called a 'cannula'. It is inserted just under the skin usually on the stomachof the patient and then taped in place.The peristaltic metal pump is used for pumping the insulin. The main advantage is the simplicity of a 'peristaltic' style metering pump making it quitea reliable method for injecting a broad range of variety of chemicals into water treatment applications. Insulin will be pumped through an infusion line attached with a tiny plastic tube. Pump design could be based on a motorized syringe or miniature roller pump.[9]

Advantages of using an insulin pump are: (1) flexibility of meal and activity timing, (2) freedom from multiple daily injections, (3) precise insulin delivery pattern and (4) improved glycemic control. On the other hand, the limitations include possibility of skin infection due to attachment of a foreign device and the hassle of constantly wearing the device.

1. IMPLANTABLE INSULIN PUMP

There is also an implantable type insulin pump.Implantable pump could provide better comfort for patient since it is unobtrusive and no infection at skin catheter junction occurs. They can be used generally as implantable drugs infusion device. There can be numerous types of implantable insulin pumps like:

Electricity driven pumps

Pumping Mechanism: Some product uses electrically driven piston pumps (e.g. Minimed MIP 2001, Siemens Promedos ID 3). The displacement of piston draws insulin from a reservoir into piston chamber.When piston moves to the original position, insulin is forced through a free-floating catheter.The catheter is usually inserted into the peritoneal cavity.Electrical energy is required to operate the piston, piston chamber inlet and outlet valve and pump electronics.The advantages of Implantable Insulin Pump are

that they are safe and effective, refills are practical, it improvesthe metabolic control and hypoglycemic conditions in patients can be lessened to a considerable extent. However, the battery power in these devices is limited.

Gas powered pump:

Another type of pump (e.gInfusaid) is 'gas powered pump'.Freon gas is used to produce a positive pressure.The pressure will push insulin from reservoir into valve-type accumulator and into the catheter.Electrical energy is required to operate the accumulator inlet and outlet valves and the pump electronics.

Vapor pressure-pump mechanism: The driving force is generated by gas vapor (usually Freon). It consists of two chambers: stored insulin and vapor system. Vapor in a compartment will push against bellow chamber that contains insulin.Pressure against bellow is constant regardless of amount of insulin. The infusion rate is determined by an outflow restrictor. There are2 outflow restrictors in the pump.When the valve activated, one of the flow restrictors will be bypassed.If valve not activated, insulin will still flow out but infusion rate is restricted.Thus, insulin will be continuously delivered. The amount of insulin (i.e infusion rate) depends on outflow restrictor. The advantages of a vapor pressure pump mechanism are that no parts give rise to friction and there is no need of electrical energy for pumping.But care must be taken in the vapor pressure as pressure might rise due to ambient pressure and other factors.This might lead to uncontrollable infusion. [10]

2. INSULIN REFILL

The reservoir refilled 1-3 months according to patient's requirement, reservoir volume and concentration of insulin preparation. A hypodermic needle is used for insulin refill. It is inserted directly through the patient's skin into the pump's reservoir. Also, it removes any unused insulin and replaces it with a fresh supply. A hypodermic needle is a hollow needle commonly used with a syringe to inject substances into the body.

IV. FUTURE PROSPECTS

The development of an artificial pancreas system holds a lot of promise. The key advantage of customized artificial pancreas architecture is the opportunity for successive development, the possibility of clinical testing, and ambulatory acceptance of elements of the closed-loop system. An ideal AP should have separate interacting components responsible for prevention of hypoglycemia, administration of required boluses, postprandial insulin correction boluses as well as basal control rate control. [11]

A recent development of control system is of a MD-Logic Artificial Pancreas (MDLAP) System. It applies fuzzy logic theory to reproduce lines of reasoning which correlate to that of caregivers. It uses a combination of strategies which are control-to-range and control-to-target to spontaneously regulate the glycemic levels of diabetic patients. Feasible clinical studies were conducted on 7 adults suffering from type 1 diabetes in the age group of 19-30 years. [12]

Boris P. Kovatchev [et al.] proposed the concept of conducting clinical trials on out-patients (who do not have to be admitted to the hospital for monitoring). "Home-like" environment was given while implying specific protocols and system adaptations among which the introduction of remote monitoring was essential. A tool called DiAs Web Monitoring (DWM)was createdwhich was a web-based application that ensured reception, storage, and exhibit the information sent by the AP systems. Continuous glucose monitoring (CGM) and insulin delivery data were presented to facilitate convenient reading and interpretation. Several subjects can be monitored simultaneously on a screen, and alarms which could be triggered when events such as hypoglycemia or CGM failures were detected. This outpatient trial was of major significance in the process of commercializing artificial pancreas. [13].

Moreover, an organization called 'Pancreum Genesis Systems' is investigating to replace glucagon by cortisol and adrenalin. They aim to pass the data collected by the glucose sensing unit from the interstitial fluid to the controller (or smartphone) via a Bluetooth wireless link. The controller uses an algorithm to adapt to a patient's individual metabolic needs. [14]

In early 2016, two trials will be conducted at nine different sites in the USA and Europe by the National Institute of Health (NIH), a team of researchers from University of Virginia (UVA) School of Medicine and the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS). In the first trial would be conducted for a period of 6 months in which 240 patients suffering from Type 1 diabetes will test the safety and efficacy of the device. The device would be compared to a standard insulin pump that was developed by UVA in its tendencies to induce hypoglycemia. The second trial would continue for the consecutive 6 months where 180 of the patients from trial 1 will test the adaptive control algorithm of the device within an acceptable zone and monitor the variables that might cause it to fluctuate. [15]

V. CONCLUSION

During the last 5 years there have been massive developments in this field. There are two major system-level approaches used for achieving a closed-loop control of blood glucose in diabetic individuals. The uni-hormonal approach is just for using insulin to reduce the blood glucose levels. It relies heavily on complex safety algorithms to mitigate the risk of hypoglycemia. A bi-hormonal approach is also feasible which uses both insulin (lower blood

glucose) and glucagon (raise blood glucose) applying two separate delivery pumps and this relies on complex algorithms as well to provide safety to the user. Several major strategies are being developed for the design of control algorithms and also supervision control for application to the artificial pancreas which are proportional-integral-derivative, model predictive control, fuzzy logic, and safety supervision designs to name a few. Advancements in the field of artificial pancreas research between in the first decade of 21st century (2000-2010) were based on the ongoing computer revolution andmaking the technology as compact as possible. The introduction of modern smartphones uses android and Bluetooth technology as the centerpiece of artificial pancreas.With these advances, an artificial or bionic pancreas is within reach.

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