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Review Article

Artificial pancreas: a game changer in the diabetic management

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ABSTRACT

Diabetes mellitus (DM) is one of the world's leading metabolic disorders, where extensive research on therapeutic management is going on. Artificial pancreas is an emerging novel therapeutic solution for diabetes mellitus based on the automatic insulin delivery system (AID). Medtronic's MiniMed 670G System (hybrid closed loop) was the first artificial pancreas approved by food and drug administration (FAD) and currently in clinical use. Efficiency, success rate, cost, and very less usage were few major barriers for an artificial pancreas. We described the basic structure, functions, limitations, and future of the artificial pancreas.

Keywords: Diabetes mellitus, Artificial pancreas, Insulin, Glucose

INTRODUCTION

Diabetes mellitus (DM) is the world's most common disease diagnosed by family physician.[1] DM is a metabolic, heterogeneous disorder presenting with a higher blood sugar level than normal due to lack of insulin.[2] When we see the statistics of diabetes patients, in 2019, 463 million people had diabetes worldwide and 4.2 million deaths approximately. These alarming rates indicate that there would be a continuous rise in the number of patients.[3] There are two types of diabetes: type 1 and type 2; type 1 is due to a defect in insulin production by the pancreas due to autoimmune destruction of beta cells, and in type 2, our body becomes resistant to its own insulin. In both cases, insulin must be injected occasionally with glucagon.[4] In severe cases, it may lead to the risk of early death in the patients.[5] The major goal of therapy is to maintain normal glucose levels and minimize risk of hypoglycemia and diabetic complications.[6] Treatment plan usually includes regular blood glucose measurement and individualized insulin regimen.[6] Many people suffering from diabetes fail to achieve proper glycemic control due to hypoglycemia. Unsafe management over the long term can lead to complications such as diabetes seizure, or diabetes ketoacidosis. The US search for diabetes in youth study reported that nearly 30% of youth with newly diagnosed type 1 diabetes age <20 years presented with diabetes ketoacidosis.[7]

Type 1 diabetic patients' therapeutic methods are intensive insulin therapy of multiple daily insulin injections or insulin pump therapy and frequent blood glucose measurements. Management of type 1 diabetes can be hindered by school and work schedules with varying dietary habits and constant glucose monitoring is required by the individuals.[6] Diabetes self-management remains complicated in adults and children's that they require devices that continuously monitor glucose concentrations and automatically adjust insulin delivery rates-the so

called "artificial pancreas".[8] In this system insulin is delivered in an glucose responsive manner whereby the patient levels can be varying throughout the day based on diet, metabolism and physical activity levels.[9] AP has been proven to reduce the burden for patients, improve their quality of life by better self-monitoring their T1D Several clinical studies have also shown that insulin dosing decision are better managed by an AP than human controlled decision making.[9,10] Its largest benefits include reduced risk of hypoglycemia, improved target glucose levels in patients both during daytime and night, avoidance of externally administered insulin and self-adjustments.[11]

In 2016, the largest outpatient setting trial using this AP among T1D population was published which showed efficacy of this model as well as safety.[12] This led to the recent US Food and Drug Administration approval of first AP system for T1D that is available in market.[13]

ARTIFICIAL PANCREAS

The futuristic man-made device is an integrated system used to mimics the functions of the original pancreas, i.e., monitoring blood glycemic index and injecting insulin when needed; it is officially referred to as Automatic insulin delivery system (AID), also known as the closed-loop system and autonomous system for glycemic control.[14] This artificial pancreas is an integrated system which makes the diabetic patients not to rely on the testing by fingerstick or continuous monitoring systems and separate, non-integrated delivery of insulin by shots or a pump.[15]

The principle involved in these APs are an intravenous route of glucose sensing and insulin infusion into the body, which is not suitable in an out-patient setup; they belong to class proportional-derivative controllers, which consider blood glucose level changes and calculate the amount of insulin to be infused in type 1 diabetes patients.[16] The only APs available for now approved by the food and drug administration (FAD) is the first hybrid closed loop Medtronic's MiniMed 670G system and control-IQ from tandem diabetes care. These were only marketed artificial pancreas for clinical use.[8] It is not a fully automated system; we can manually feed the amount of carbohydrate diet you have taken. The fully automatic one is under clinical trials.[17]

This closed-loop system is not a single device; it is a combination of a glucose sensor, a control algorithm, and an insulin infusion device.[18]

Glucose sensor

It is also called a blood glucose device (BGD)/ continuous glucose monitoring (CGM) device. It measures the blood sugar levels continuously by a sensor on the skin connected to the insulin infusion device.[14] It enables the patient to continuously monitor their blood glucose levels. For better management, i.e., increase or decrease in levels, it works with an insulin infusion device for better insulin therapy. A randomized study shows that CGM decreases hypoglycemia. The data collected by this CGM is shared with patient mobiles to be used for further treatment.[19]

Control algorithm

It is the "brain" of the artificial pancreas consists of an algorithm. An algorithm is software present in the controller. It receives signals from CGM crunches the numbers then signals the insulin infusion pump to infuse how much insulin is based on the threshold pre noted values. The controller algorithm for insulin is a proportional-integral-derivative (PID) controller, a model predictive controller (MPC), a Fuzzy logic controller, and an H-infinity controller.[4,14,19]

Insulin infusion device

It is also called continuous subcutaneous insulin infusion (CSII)/ Insulin pump. It works under the control algorithm and CGM and infuses insulin or sometimes glucagon into the body.[14]

MECHANISM OF WORKING OF AN ARTIFICIAL PANCREAS IS BY THE FOLLOWING STEPS

CGM monitors the rise in blood glycemic index and sends signals to the controller algorithm. Controller algorithm calculates the amount of insulin required and send signals to the insulin pump. An insulin pump delivers the required amount of insulin into the body. This artificial pancreas monitors not only hyperglycemia but also hypoglycemia.[20]

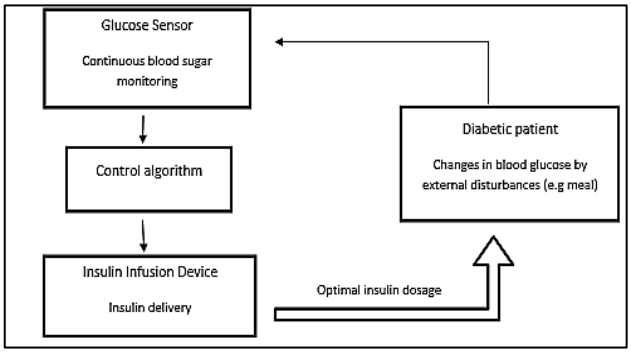

Figure 1: Artificial pancreas model- closed-loop system.

The three main types of artificial pancreas based on the functioning of the insulin pump by the readings of CGM were described below.

THRESHOLD SUSPEND DEVICE SYSTEM

It's also called an implanted artificial pancreas. Its main goal is to prevent hypoglycemia by temporarily stopping insulin infusion. Mainly it contains a gel that controls the insulin infusion; if there is hypoglycemia, it temporarily

stops insulin infusion; if it is hyperglycemia, it promotes insulin infusion. This system Is refilled with insulin on a regular basis.[4,21]

INSULIN-ONLY SYSTEM

The most commonly used system, and it has a single insulin pump that works on the signaling of CGM, it semi-automatic only adjust basal insulin, and the patient must take bolus insulin before a meal to cover it up.[4,21]

BI-HORMONAL CONTROL SYSTEM

It is also called the bionic pancreas, and it has 2 algorithms to send signals to the infusion pump to infuse insulin during hyperglycemia and glucagon during hypoglycemia. Its working principle is closely related to the normal functioning of the pancreas.[14] Hypoglycemia is the main problem faced by diabetic patients during insulin infusion in a normal functioning pancreas. Pramlintide is the hormone co hormone secreted with insulin but is absent in type 1 diabetes patients. So, co-formulation of Pramlintide along with insulin in the bionic pancreas shows promising results.[22]

Medtronic 670G artificial pancreas in the retail market is $7,000 to $8,000 the CGM costs $699 and the sensor costs $50 to $75.[14] Artificial pancreas treatment significantly improves glycemic control while reducing the burden of hypoglycemia in out-patients with type 1 diabetes. It is safe to use in children below the age of 4 years.[4,16,23] Usage of APs decreases the psychological burden on the patients. It improves overnight glucose control, due to this patient feeling reassurance and reduced anxiety, improved sleep, and confidence due to relaxed eating habits.[8]

LIMITATIONS

The main limitation of APs is the present research is not sufficient to tell the full efficiency of APs, because the research has small sample sizes, inconsistency in outcomes, and lack of follow-up in individual trials.[16] Integration of many devices, technical difficulties, lack of knowledge, alarm intrusiveness, and size of the equipment and variable trust and difficulties incorporating closed-loop systems into daily life activities are the psychological problems faced with this AP's usage.[8,24]

Human blood glucose levels tend to change for every 5 minutes, decreasing the accuracy of glucose sensors and causes the delivery of an inadequate amount of insulin to the body.[19] The usage of the artificial pancreas cannot completely cure hyper and hypoglycemia.[25] A lack of successful APs in the clinical field is a major setback.[16] In the bionic pancreas, two slots for two hormones made it complex. A serious limitation of this is the lack of additional skill to handle infusion sites' system and rotation while dealing with young patients.[19] Insulin delivery remains delayed by 2 hours after a meal. Subcutaneous insulin delivery causes a loss of the liver's physiological role, causing insulinemia. An insulin infusion pump is a major issue; if undetected, it may lead to ketoacidosis. The closed-loop system cannot compensate for the insulin need during mealtime.[18]

DO-IT-YOURSELF ARTIFICIAL PANCREAS SYSTEM (DIY APS)

#WEARENOTWAITING is the movement created to use DIYs. As commercial availability of APs is very less and cannot be affordable by all, so a community with technical knowledge formed and develops "Open-APS," "Loop," and "Android-APS." Open-APS developed on a Raspberry Pi controller connected to an insulin pump, and it works on the principle of insulin to carbohydrate ratios. Loops can be used with the iPhone, and at a particular time, if u want glucose value, it considers present and past 30 mins values. Android-APS are the most advantageous ones because they are used with all insulin pumps. In DIY'S algorithms used are not tested and not regulated, there would be high risk on users. Another challenge faced is the lack of interaction on the basis of the safety concerns of users. It is difficult for physicians to use to ethically in the clinical field.[19]

FUTURE DIRECTIONS OF ARTIFICIAL PANCREAS SYSTEM (APS)

Over so many years, enhancements of APS from the research field to clinical field are very successful. It requires many future advancements to be a safe system to use by all diabetic patients. The APS must be an interactive mode with patients, easy to use, less complicated, and must reduce the burden while using it.[8] APS must be made portable for children's usage by developing the advanced system, fast-acting insulin analogs, making it completely automatic, and reducing the burden.[23]

Control algorithms must be compatible with all the variations like physical exercise, meal composition, stress, illness, and circadian variations in insulin sensitivity. Remote supervision must be included. In the bionic pancreas, stable glucagon needs must be fulfilled.[23] In the future, training on the usage of APS to all the clinicians and the normal public must be done, and its usage must be an increase in the clinical field and daily usage. Flexibility in choosing the device for the user makes the system's seamless experience.[19]

CGM must reduce lag in measuring, be easy to wear, sensor stability, affordability, and life must be improved. In insulin pumps, delay in insulin absorption must be reduced. Machine learning, along with system strategies, enables one to know both fast and slow glucose dynamics.[19] 3D bioprinting of islets for the generation of a human-made pancreas may be a newly emerging field of study with a huge potential to enhance islet transplantation.[25]

CONCLUSION

An efficient artificial pancreas would be a path-breaking therapeutic choice for many people with diabetes mellitus. The artificial pancreas with affordable price can be a game-changer in diabetic management.

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