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ARTIFICIAL PANCREAS' – A GAME CHANGER

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ABSTRACT

Type 1 DM is a metabolic disorder characterized by lack of insulin due to complete autoimmune destruction of the pancreas. Hence people with T1DM require intensive insulin therapy as well as glucose monitoring. Obtaining near-normal values of glucose is the main aim of T1DM treatment which still remains unachieved in most of the people with type 1 diabetes in spite of other therapies. Recent research in the field of type 1 diabetes medicinal devices has focused on improving glucose monitoring and insulin delivery devices with the goal of combining them into an artificial pancreas, closed-loop insulin administration system. Artificial pancreas system is a recent medical innovation, which helps to keep glucose levels in check, tackles hypoglycemia and is also said to be effective when compared to other devices. The employment of a control algorithm that controls insulin administration based on real-time sensor glucose readings distinguishes this unique technique from traditional pump therapy. This review is aimed to provide a detailed description about the APS system, it's working, benefits as well as its downsides.

KEYWORDS: Artificial pancreas, Diabetes Mellitus, Closed-loop systems, Continuous glucose monitoring, Controller, Insulin pumps.

INTRODUCTION

Technological advancements in diabetes have resulted in substantial advances in the quality of life and treatment provided to diabetic patients. Despite this, the barrier of hypoglycemia makes it difficult to achieve tight glucose control even with rigorous insulin therapy and contemporary insulin regimen.[1] Type 1 diabetes is a chronic, autoimmune, metabolic

disorder. Normally, the beta cells of the pancreas release insulin in response to increased serum glucose levels. But, in case of people with Type 1 DM, there is insulin deficiency due to the autoimmune destruction of beta cells of pancreas. Hence, in order to keep the BG concentration within the normal limit (70-140 mg/dl) they are led to life-long insulin replacement therapy in which insulin is administered by means of external routes to mimic the actions of bodily produced insulin. Technological innovations continue to benefit the management of T1DM. With the weight of self-management bestowed on the patient, automated insulin delivery devices that can automatically adjust insulin delivery rates to help maintain blood glucose in an optimal range lessened the burden of routine-self management. These kinds of devices are known as 'artificial pancreatic systems (APS)' or 'closed loop (CL) system'.[2]

DIABETES

Diabetes is a group of metabolic diseases distinguished by elevated levels of blood glucose due to faults in insulin secretion, insulin action, or both. Several pathogenic processes are involved in the development of diabetes. These extend from destruction of the pancreatic β-cells by body's self-antibodies following insulin inadequacy to abnormalities which causes resistance to the actions of insulin. The insufficient insulin action on the target tissues accounts for irregular metabolism of carbohydrate, fat, and protein in diabetes. This lack of insulin action is due to insufficient secretion of insulin and/or low response of the tissues to insulin.[3] When the glucose levels in the blood falls below 70 mg/dl it is said to be, hypoglycemia. It should be treated right-away because hypoglycemia can produce dizziness, unconsciousness, coma and in some cases even death. Likewise, blood glucose level over the range of 180mg/dl is termed as hyperglycemia. Hyperglycemia in the long-run may give rise to chronic disease conditions such as retinopathy, neuropathy and nephropathy.[4]

CLASSIFICATION OF DIABETES

The American Diabetes Association (ADA) in the year 1997 classified diabetes as type 1 diabetes, type 2 diabetes, other types, and gestational diabetes mellitus (GDM) which is up-to-date the most accepted classification and adopted by ADA.[2]

DM1

Type 1 diabetes mellitus comprises 5%-10% of people diagnosed with diabetes[5] and add up to 80%-90% of diabetes in children as well as adolescents.[6,7] In type 1 diabetes, the pancreatic β cells is destroyed by body's autoimmune system through T-cell mediated

inflammatory response (insulitis) and humoral (B cell) response leading to deficient insulin secretion.[8] Lack of insulin production is characteristic feature of DM1 and is predominant in children as well as adolescent group.[9] The action of autoantibodies against the islet cells of the pancreas is the specific trait of type 1 diabetes, but the part of these antibodies in the disease pathogenesis are not yet clear. Autoantibodies such as islet cell autoantibodies, and autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), protein tyrosine phosphatase (IA2 and IA2β) and zinc transporter protein (ZnT8A) are aimed against the pancreatic beta cells.[10] These pancreatic autoantibodies could be noticed in the patient's serum even months or years before the beginning of the disease and are attributed to type 1 diabetes.[11] Type 1 diabetes often progresses straight away and give rise to symptoms such as polydipsia (increased thirst), polyuria (excessive urination), enuresis (loss of bladder control or bed-wetting), lack of energy, fatigue (extreme tiredness), polyphagia (excessive eating because of increased hunger), sudden weight loss, decreased wound-healing, recurrent infections and blurred vision[9] with severe dehydration and diabetic ketoacidosis in children and adolescents. When compared to adults, the symptoms are more severe in children.[2]

DM2

It is reported that more than 90%-95% of diabetes patients belong to the type 2 diabetes category and most of them are adults. This high prevalence of type 2 diabetes among youth is largely because of the changes in children's lifestyle in terms of increased sedentary life and low healthy food intake. One of the major reasons for insulin resistance in type 2 diabetes is obesity.[12,13] Hence, screening of overweight children and adolescence is suggested by the ADA to identify type 2 diabetes.[14,15] The need for insulin in insulin-target tissues is elevated due to resistance to insulin in type 2 diabetes. But, due to faults in the action of these cells this high demand for insulin could not be met by the beta cells of the pancreas.[16] On the contrary, because of the subtle destruction of beta cells, insulin production diminishes with the elevated need for insulin by time[17] which could transform some of the patients with type 2 diabetes from insulin independent to insulin dependent ones. Dependence on insulin is one of the major differences from type 1 diabetes because, majority of the people with type 2 diabetes are not insulin dependent where their insulin production goes on and depletion of insulin is rare. Other distinguishing features form type 1 diabetes are absence of ketoacidosis in most of the patients with type 2 diabetes and there is no incidence of autoimmune destruction of pancreatic beta cells. Genetic predisposition is associated in type 1 as well as

type 2 diabetes, however, it is stronger in type 2 but the genes are more characterized in type 1diabetes.[18]

ARTIFICIAL PANCREAS

Diabetes is a metabolic disorder marked by changes in the serum glucose levels because of utter insulin shortfall or defective flawed action of insulin or a mix of both.[19] Generally, in case of high glucose levels, a healthy pancreas would release insulin to counteract the glucose actions. But in people with DM1, the beta cells of the pancreas which are responsible for insulin production are destroyed resulting in lack of insulin thereby leading to a life-long dependency on insulin delivery to the body by means of external administration. Hence, in order to mimic the actions of pancreas for a diabetic patient, basal insulin is delivered to duplicate background insulin during fasting phases of the day and during mealtimes additional bolus insulin is given.[2]

With the weight of self-management bestowed on the patient, there is an increasing requirement for devices that can continuously keep track of these BGLs and then adjust the insulin delivery rates automatically thereby keeping the blood glucose in an adequate range. These kinds of devices are known as 'artificial pancreatic systems (APSs)' or 'closed-loop (CL) system'. When these instruments are augmented with precise and authentic continuous glucose monitors, they can control glucose levels and also provides better control of a patient's glycemic status.[2]

APS – COMPONENTS AND WORKING

'Artificial Pancreatic Systems' comprises of a continuous glucose monitor, controller and an insulin pump to deliver insulin in a glucose responsive manner.

- A continuous glucose monitor (CGM) that keeps track of the glucose level in the blood and send signals to the insulin pump via the sensor inserted under the skin.
- The controller estimates the insulin levels from the CGB and perform a series of mathematic calculations by executing algorithm. Based on these calculations, the controller then sends the dosing instructions to the infusion pump.
- The insulin infusion pumps are then used to deliver insulin to the body based on the instructions received from the controller.[20]

Artificial pancreas can automatically adjust the amount of insulin entering the body by sensing the levels of glucose in the blood. Hence these are said to be more efficient when compared with other devices such as insulin pumps or sensor augmented pumps.[21]

CGM

Familiarly, Self-monitoring of blood glucose (SMBG) were used to verify any case of hypo/hyperglycemia by detecting the blood glucose levels (BGLs).[22] But, innovations in medical devices led to the transition of glucose recording from SMBG to CGM which helps the patients to monitor their BGLs throughout the day according to the estimations taken at definite amount of time. An electrode sensor that is inserted subcutaneously, a transmitter, and a receiver were included in the CGM device. BGLs are detected by the sensor through electrochemical detection of glucose.[23] The glucose levels in the interstitial fluid are computed by the sensor which is fixed to a transmitter that delivers the information to the receiver. These vital data have contributed towards better management of diabetes. Besides, a better understanding on user's glucose levels regarding the effect that other factors like food, physical activity, stress or any medical condition are obtained from CGM data.[24] On comparing SMBG with CGM through Self-Randomized, multicentre clinical trials, adults with DM1 who were using CGM devices reported to show improved control of glucose levels as well as decrease in the time spent in hypoglycemia with concomitant improvement in A1C.[25]

CONTROLLER

A controller is a software algorithm in a Closed-loop system. It regulates the amount of bolus and basal insulin required in response to deliberate variations in glucose levels between meals and rapid hike in glucose values at mealtimes.[26] The primary reason of a controller being applied into a closed-loop system is for safe and effective glucose control in patients with type 1 diabetes. Moreover, in case of any hypoglycemic events, the controller should be able to tackle it as well. The BG sensor passes the desired blood glucose value to the controller. The controller then transfers the required insulin value to the pump, which may be either SC or IP and delivers insulin to the patient. This required insulin value is determined by the control algorithm incorporated in the CL.[2]

Below mentioned are the various control algorithms used in Aps.[2]

1) Proportional-Integrated-Derivative (PID) controller

2) Model Predictive Control (MPC)

3) Fuzzy logic controller

The two main control algorithms employed in closed-loop clinical studies are, the classic feedback proportional-integral-derivative (PID) controller and the model predictive controller (MPC).[27]

The PID controller modulates insulin supply by analysing glucose excursions from three perspectives: egress from target glucose, area-under-curve between ambient and targeted glucose, and ambient glucose change.[28] PID controllers have been used with intravascular and subcutaneous glucose sensing and insulin delivery[29], as well as during intraperitoneal insulin delivery.[30] Recent researches focus on the MPC technique since it can more readily account for insulin absorption latencies as well as meal ingestion and prandial insulin boluses. A mathematical model that relates insulin administration and meal consumption to glucose excursions is a crucial element of the MPC.[31] To minimise the discrepancy between both the model predicted glucose concentration and the goal glucose concentration, the MPC technique compares the model predicted glucose levels with the actual glucose levels, updates the model, and predicts future insulin infusion rates. Fuzzy logic, which modulates insulin supply based on approximation principles and may be essential to reflect empirical data gleaned by diabetes practitioners, is yet another clinically tested control mechanism. Algorithms may include a safety module to constrain insulin delivery limiting the amount of insulin on board, or the maximum rate of insulin delivery, or suspending insulin delivery when glucose levels are low or decreasing.[32,33,34]

INSULIN PUMPS

Insulin pump employed in an APS normally deliver rapid-acting insulin analogues.[35] Based on the instructions received from the controller the insulin pumps are used to deliver insulin to the body. A portable electromechanical pump is incorporated in insulin pump therapy to mimic nondiabetic delivery of insulin. Insulin is infused at preselected rates via the pump - normally a slow fasting glucose rate with patient-activated boosts at mealtime.[36]

The majority of current insulin pumps are the size of a pager. They include an insulin reservoir, a small battery-operated motor, and a subcutaneous infusion set coupled to a computerised control mechanism (cannula and tubing system). Sensor-enhanced insulin pumps, such as the MiniMed Paradigm Veo® (Medtronic MiniMed, Northridge, CA, USA) and VibeTM (Animas, West Chester, PA, USA), integrate with a continuous glucose monitor

that has been shown to minimize HbA1c numbers.[37] The patch pump (the Omnipod, Insulet, MA, USA) is a new innovation in pump design that features a reservoir unit that adheres directly to the patient's skin and holds an integrated infusion set and automated inserter, making it "tubing-free".[38] Modern smart pumps have a configurable bolus calculator and an "insulin on board" sensor to help avoid insulin stacking.[39]

TYPES OF ARTIFICAL PANCREAS

APS can be categorized into two type which includes[20]

1. Dual-hormone systems
2. Insulin-only systems

1. DUAL HORMONE SYSTEMS:

These devices exert their action by subcutaneous infusion of two hormones – insulin and glucagon in response the glucose values detected by the CBGs. Insulin is released in case of elevated blood glucose levels to lower it whereas, glucagon is released as small bolus to tackle hypoglycemia by elevating the blood glucose. Together they imitate the physiological functions of pancreas in people without Type 1 DM and are more efficient than insulin-only systems.[20,40] Also, a study conducted to assess the use of dual hormone system versus insulin pump therapy concluded dual- hormone pancreas as more efficient when compared with conventional and sensor-mediated insulin pump therapy. Dual-hormone pancreas achieved superior glucose control without even counting the carbohydrates.[41] However, addition of glucagon has the potentiality to increase the device's complexity.[2]

2. INSULIN-ONLY SYSTEMS

Depending upon the CGM values, these insulin-only systems maintain the insulin level within the range by either increasing or decreasing the levels.[20] These systems can either be a hybrid system which only adjusts the basal blood glucose level or a closed loop system which not only adjusts the basal insulin but also provides insulin for meals. Single-hormone APS could be adequate for hypoglycemia-free overnight glycemic control.[2] Moreover, a study conducted to determine the safety of this device showed that there were no episodes of severe hypoglycemia or ketoacidosis.[42]

Sachit Kapil et.al, in their study concluded that, single-hormone and dual-hormone APSs are more efficient in controlling the glycaemic levels than conventional insulin pump therapy.[2]

BENEFITS OF USING CL SYSTEMS

According to data from various clinical research studies, CL systems are beneficial by offering better glycemic outcomes and lowering hypoglycemia, and have favourable user-end acceptability in children, adolescents, adults, and pregnant women with T1DM.[43]

When a person is asleep, their blood sugar levels can drop to extreme low ranges making them more prone to hypoglycemia. Therefore, to tackle the risk of hypoglycemia, a special safety module is present in Aps which provides intensified control overnight and thus helps in attaining near-normal blood sugar range every morning.[44]

Management of DM1 at any age is a challenging factor, but it is further complicated in young children. This is due to higher variability in insulin necessity and increased insulin sensitivity in young children than older children and adults. Not to mention, hypoglycaemia often occurs without any symptoms and can be extended specially at night time ensuing in high management burden. With the use of closed loop insulin systems, better control of blood glucose level at night time is obtained. This helps to alleviate the user's burden as well as provides better quality of life.[45]

Exercise intensity is said to be a prime factor impacting the blood glucose management. Even at low intensities, exercise will elevate glucose disposal through insulin mediated as well as non-insulin mediated mechanisms for numerous hours especially when there is depletion of glycogen stores giving rise to the risk of delayed, mostly nocturnal hypoglycaemia.[46,47] In patients with type 1 diabetes, physical activities can result in extensive sensitivity to insulin leading to hypoglycemic episodes.[48] The closed-loop delivery systems were proven to be efficient and safe in transporting required insulin even in cases of any unannounced physical activities without creating any risk of hypoglycemia during as well as after unannounced physical activities.[49] CL system aids in quick administration of insulin and also automatically adjusts the insulin level based upon the concentration of serum glucose in the blood resulting from physical activity and/or carbohydrate level. Thereby, APSs lessens the burden of self-management as well as tackles the risk of hypoglycaemia and improves the patient's health overall.[50] In case of fully automated CLS which are entirely reactive, there is no need of providing information regarding the physical activities or meal into the algorithm manually. As such it gives the benefit of relieving the patient from interceding.[51]

Usage of AP system were proven to show improvements in short-term control of glucose levels without any elevation in hypoglycemia following missed insulin for food in adolescents. Thus, AP partly makes up for missed insulin boluses for food which is a regular incident in adolescent diabetes management.[52]

Achievement of lower mean glucose, and decreased time spent with hypoglycemia as well as hyperglycemia were related to the use of Closed-loop delivery of insulin. This instant effect was achieved through overnight delivery of insulin automatically, correction doses given automatically during the day and adjustment in insulin delivery automatically to lower hypoglycemia. Usage of CLC was especially effectual at elevating time in range (TIR) overnight, accordance with the CLC algorithm design, which strengthens overnight control[53]. A clinical oriented randomised multicentre trial assessing the new artificial pancreas system reported that when compared to other present treatments closed-loop systems were found to be more efficacious at controlling the blood glucose of DM1 patients. Additionally, through the study they observed better control of blood glucose levels in the participants throughout day as well as night.[44]

LIMITATIONS AND CHALLENGES ON AP

Even though artificial pancreas has given impressive results, there are still some crucial challenges as well as limitations that have to be dealt with in order to obtain the ideal AP.

In case of dual hormone closed loop systems Glucagon in addition with insulin is a promising method, but the poor stability of glucagon formulations and the need to replace it with of freshly reconstituted glucagon every day is one of the important limiting factors for long-term use of it.[54] Therefore, at first, stable formulations and long-term safety evaluation of chronic glucagon use should be attained. In several exercise conditions, AP systems outperformed CSII or SAP, while total hypoglycemia prevention has yet to be attained. AP system capacity can also be extended by incorporating biometric variables to locate and recognize the kind, intensity, and energy expenditure of physical activities.[55]

Qualitative research in teens uncovered concerns regarding calibration issues, disrupted sleep due to alerts, and problems managing several devices.[56] Additional challenges include technical issues, an alert feature that is too obtrusive, the equipment's cumbersome size, inadequate device connectivity, and the inconvenient integration of CL systems into daily activities like exercise and bathing.[2]

A major determinant of sensor accuracy is the physiological time delay of glucose transport from the intravascular to the subcutaneous interstitial space. In adults with type 1 diabetes, this time delay is roughly 7 to 8 minutes as in overnight fasted state.[57] Understanding the physiological principles underpinning CGM technology, such as glucose transit time lag, allows CLS prediction algorithms to be fine-tuned.

For a variety of reasons, a continuous sensor implanted in the body may fail. These are some of them: 1) drift in calibration, 2) gap between arterial blood glucose and interstitial fluid glucose values at times of rapid changes 3) Inflammatory problems in the immediate area. As a result, practically all continuous glucose sensors in use or in research necessitate regular blood glucose tests to ensure appropriate calibration.[25]

Strategies to minimize hypoglycemic risk around exercise exists but it remains challenging.

CONCLUSION

For a person with DM1, Artificial pancreas system can bring a world of difference in their everyday life. As a bridge to cure, the artificial pancreas might improve type 1 diabetes care and improve overall health. According to data from various clinical research studies, CL systems are beneficial by offering better glycemic outcomes and lowering hypoglycemia, and have favourable user-end acceptability in children, adolescents, adults, and pregnant women with T1DM. Future research should emphasize on implementing technology to alleviate the pressure of diabetes management and improve efficacy, with the goal of informing system reimbursement and promoting greater access among diabetic population.

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ABBREVIATIONS

T1DM, DM1 – Type 1 diabetes mellitus

APS – Artificial pancreas

CL – Closed-loop system

BG – Blood glucose level

ADA – American Diabetes Association

A1C – Glycated hemoglobin

CGM – Continuous glucose monitoring

SMBG – Self monitoring of blood glucose

PID – Proportional-integrated-derivative

MPC – Model predictive control

CBG – Capillary blood glucose

CSII – Continuous subcutaneous insulin infusion

SAP – Sensor augmented insulin pump