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Future Directions for Closed Loop Insulin Delivery Systems

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Abstract

Closed loop insulin systems use a glucose sensor and insulin delivery system to maintain the blood glucose levels in an automated manner. These devices show great promise as a potential treatment option more importantly for Diabetes Mellitus Type 1 but also, Diabetes Mellitus Type 2. However these devices face many problems and these need to be solved before a truly clinically applicable form of the device is commercially introduced. Their efficacy also needs to be improved in certain groups such as children and pregnant women. The literature search was done on two indexes, Google Scholar and PubMed, using mesh words 'closed loop insulin delivery in diabetes'. All the publications, by various authors, returning to this search, were critically reviewed, assimilated and summarized. This article presents this summary of the problems faced by these devices and suggests possible solutions for their improvement.

Introduction

Type 1 diabetes (T1D) is characterized by immune mediated pancreatic beta cell destruction, thus absolute insulin deficiency. It predominantly affects the youth, with an increasing rate in the last decades (1). Patients with T1D, their families and care providers face the challenge of maintaining blood glucose levels in the near to normal range over years,

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which has been proved to be important for prevention of long-term microvascular and macrovascular complications (2) and to avoid the acute complications of severe hypoglycemia (SH) and diabetic ketoacidosis.

Infusion of insulin during the treatment of DMT1 may lead to hypoglycemic episodes since continuous manual monitoring of the blood glucose levels and adjustment of insulin dose accordingly is not feasible (3). Variability resulting from differences in patient compliance may decrease the overall efficacy of the treatment regimens (4).

The never-ceasing challenge faced by diabetic patients and their caregivers has through the years inspired continuing efforts to find ways and means for achieving better control of blood glucose levels. The new modern advanced technologies of closed-loop devices aims to mimic the human pancreas by continuous measurement of blood glucose and releases the amount of insulin accordingly. Some devices are also capable of reversing hypoglycemia by infusing hyperglycemic solutions in place of insulin (5). Improved glycemic control and lower rates of hypoglycemia and nocturnal hypoglycemia have been reported with these devices (6).

Another, aspect of closed loop insulin-delivery comprises of real time continuous glucose monitoring (RT-CGM). Frequent blood glucose tests per day were shown to be an important factor related to metabolic control in patients with T1D (7). Standard use of glucose meters for self-monitoring of blood glucose (SMBG) provides only intermittent single blood glucose levels without illustrating the glucose variability during the 24 h. Therefore, the use of RT-CGM provides continuous glucose measurements which may have potential to increase the proportion oo patients who are able to maintain target HbA1c values, to decrease glucose excursions and to decrease the risk of SH.

This paper reviews current research into the development of a closed loop insulin delivery system, with particular emphasis on creating a system emulating the physiological properties of the beta-cell.

Discussion: Limitations, and Future Directions

An artificial Beta-cell requires a glucose sensor, an insulin-delivery pump, and an algorithm for calculating insulin delivery. Technological and scientific advances have made sensors

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and pumps available, but linking the two as a “closed loop” has been challenging (8). Lingering questions remain regarding the suitability of different glucose-sensing sites (subcutaneous versus intravascular), insulin-delivery sites (subcutaneous versus intravascular versus intraperitoneal), and sensor reliability. In addition, no one algorithm has been universally accepted as optimal for insulin delivery (9).

Most of the currently available devices employ a single sensor for blood glucose monitoring. A single sensor has a high risk of inaccuracy resulting from calibration error or current drift (10). Use of two blood glucose monitors decreases the chance of such errors. Other limitations of the devices include physiological time lag and interference of the sensors with non-glucose substances and thus giving false results (11).

Corticosteroids especially have a tendency to interfere with the functioning of the device by reducing insulin sensitivity and causing stress-induced hyperglycemia. A similar hyperglycemic state is also observed in acute infections occurring in patients with diabetes.

The physiological time lag is one of the greatest challenges to these devices. Even the fastest acting insulin analogs available today are not fast enough to remove this barrier. New pharmacological developments are required to either increase the rate of absorption of insulin analogs or develop insulin analogs that can bring an effect even faster than current insulin analogs (12). Otherwise an intraperitoneal insulin delivery system may be used. Insulin delivered via intraperitoneal route may reduce the physiological time lag to a quarter (13). However catheter related complications may develop with this route of insulin delivery. If such developments do come into existence, these devices will lead to a more optimal blood glucose control.

Unpredictable eating and exercise patterns in patients, especially children, pose a risk for hypoglycemia (14). Until better sensors are developed and the problem of physiological time lag countered, it might be more prudent to use semi-automatic devices that may be switched off at will. Such inclusions are necessary to prevent hypoglycemic episodes especially at night and after exercise.

The above mentioned two problems of physiological time lag and haphazard food habits can be dealt effectively with closed loop delivery systems that continuously sense blood glucose levels (RT-CGM) and accordingly alter the dose of insulin injected.

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The sensors on current devices use the subcutaneous interstitial space to measure the glucose levels (15). This method is not only comparatively inaccurate but also contributes to the time lag. Therefore current devices require manual adjustment of the dose of insulin when the intrinsic body insulin or glucose load changes rapidly such as in times of food intake and stress.

As compared to the effects of these devices of non-pregnant individuals with DMT1, the efficacy of these systems in pregnant women is not well-established. Some studies have shown these systems to be safe and effective during pregnancy (16). However due to certain physiological changes in pregnancy, such as changes in the production and metabolism of glucose and insulin, the efficacy of these devices in pregnant women remains lower as compared to that in non-pregnant individuals (16, 17). More work is needed to eliminate the periods of hyperglycemia seen during pregnancy and to achieve optimal postprandial glucose levels comparable to that seen without pregnancy.

Also, these devices, especially those based on continuous subcutaneous insulin infusion lead to extensive insulin regimens and thus increase the Total Daily Dose (TDD) of insulin. (18)

The patient needs to be advised against rough sports, especially contact sports, and other activities which may physically damage the device. Wearing the device at all times may also be seen by many patients as uncomfortable. Combining insulin delivery and continuous glucose sensing into a single device is likely to increase device acceptability and hence compliance with wear. Work on devices that can be implanted subcutaneously with non-invasive procedures of refilling the insulin and glucagon stores is being done.

All large scale clinical studies performed to assess the safety and efficacy of such systems have been in highly controlled environment (19). Studies in such highly controlled environments are only poorly applicable to the daily environment of patients. Therefore long term safety and efficacy trials should be conducted in a range of patients in uncontrolled environments.

It is known earlier that diabetes increases one's risk for depression (20); therefore, targeting depression would seem to be a vital psychosocial variable to include in future such device

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assessments. Other areas of psychosocial functioning that are important to assess include measurements of self-management (21–23), quality of life (24), family functioning (25), and patient-provider relationships (26). Recently it has been shown that patient acceptance of future use of a closed-loop system is likely to be positive based on qualitative evaluation in adult patients (27), and caregivers of children with type 1 diabetes (28).

Before the currently available devices can be used commercially, it is imperative that the overall cost of manufacturing and the size of the device be adjusted to suit the users. If that can be achieved, we can hypothesize that the coming generation might not see DMT1 as a lifelong disease which severely affects the quality of life but as a simple curable disease requiring only the installation of an easy to operate, cost effective device.

In the last 3 years, it has been demonstrated that telemedicine may play an increasing role in closed-loop systems, enabling remote monitoring and logging of data. A prototype closed loop device equipped with global positioning system technology has been proposed as a way of alerting family and medical personnel of the location of patients in the event of severe or impending hypoglycemia (29).

Prior to employment of closed-loop systems in clinical practice, strict safety checks by regulatory bodies are essential. Ongoing safety monitoring in addition to robust infrastructure to manage technical issues will be necessary.

Conclusion

The ‘artificial pancreas’ or the closed – loop delivery system may offer a more convenient and superior mode of insulin delivery. They can potentially help us achieve near – normal and even physiological glucose profiles. Introduction of closed-loop insulin delivery into clinical practice is likely to be gradual. Just as it has taken a long time to reach the stage where we can actually foresee the development of a clinically applicable closed loop device, there is still a long time to go before these devices can be commercialized and be offered to patients as a routine treatment option.

Further research is required to address the current hurdles of physiological time lag, hypoglycemic episodes, sub-optimal blood glucose control in children and pregnant women, encountered in closed loop device functioning, including refinement of control algorithms to

cope with variability in insulin requirements and development of more accurate glucose sensors.

Large scale trials in uncontrolled, home-based locations are also necessary to assess whether the safety and efficacy of these devices is consistent outside of the hospital settings.

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