An analysis of the glycemic control of hybrid closed loop insulin systems compared with open loop insulin systems

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Background

Diabetes technology is an ever-growing field in bio-medical engineering and is continually striving to enhance the quality of life of those living with diabetes. Improved glycemic control is a primary outcome of these technologies and is an important factor when evaluating these devices. This paper will introduce the standard technologies available today, as well as research further into their comparable glycemic outcomes.

What is Diabetes

Type 1 diabetes (T1D) is an autoimmune disease affecting approximately 42.2 million individuals worldwide, with a statistical yearly increase of 3-5% (World Health Organization, 2021). This disease results in the damage or destruction of pancreatic beta cells, leading to insulin deficiency. Insulin breaks down glucose released from the liver, typically as part of the digestive process, thus patients with diabetes must self-monitor their blood glucose levels and provide insulin accordingly, known as intensive insulin therapy (INT). Improper insulin management is a common struggle among individuals living with diabetes and introduces many high-risk factors. (Allen & Gupta, 2019).

Glycemic control is one of these many serious risk factors people living with diabetes face. Hyperglycemia is denoted by high blood glucose levels of over 180 mg/dL, typically caused by an inefficient amount of insulin supplied (American Diabetes Association, 2021). Hypoglycemia is denoted by low blood glucose levels of under 70 mg/dL, typically caused by a surplus of insulin supplementation. When people with diabetes enter these ranges of blood glucose levels, they experience unpleasant physical reactions, and extended durations without treatment can be life-threatening (American Diabetes Association, 2021).

Insulin requirements have many confounding factors, such as time of day, hormones, illness, etc., thus the management can oftentimes be very unpredictable even to the most educated and self-aware diabetics. Therefore, glycemic control is an imminent factor and is a strong motivator for technologies to relieve this management fatigue, often denoted as "diabetes burnout" (McAuley et al., 2020).

Insulin Therapy Methods

Multiple daily injections (MDI) is a type of INT where users calculate their own required insulin and manually give injections. Blood glucose levels, measured through a blood glucose meter, are used in conjunction with carbohydrate intake to calculate the needed insulin (Allen & Gupta, 2019).

The popular alternative to MDI is insulin pump therapy (IPT), a device that intakes the blood glucose and carbohydrate variables, calculates the insulin and then automatically delivers it through the attached pump site (Allen & Gupta, 2019).

Basal-bolus insulin therapy is typically combined with the above methods. Basal insulin is taken daily, and acts as a long-lasting, background insulin. Bolus insulin is taken during meals, and has a more powerful, but shorter-lived effect on blood sugar. Insulin pumps typically come with an inbuilt bolus calculator, while MDI users can use blood glucose meters with an inbuilt bolus calculator to then supply the correct amount of insulin (Railton, 2019).

Sensor technology tracks blood glucose levels through an attached site on the user. There are two main types of sensors, flash glucose monitoring (FGM) and continuous glucose monitoring (CGM). FGM sensors output the blood glucose level when the user scans the sensor, while CGM sensors continuously outputs the blood glucose levels, typically to a CGM monitor.

CGM systems alert users when there are drastic changes in their glucose levels, such as eminent highs or lows (Allen & Gupta, 2019).

Sensor augmented pumps (SAP) use CGM sensors to continuously monitor the data, and adjust the basal rate, or give a correction bolus when the user is out of range. These pumps are not predictive, or preventive of glycemic changes, but can provide aid when needed (Allen & Gupta, 2019).

Hybrid closed loop (HCL) systems also monitor CGM sensor data, but use this data to predict insulin needs, thus requiring minimal interaction and glucose monitoring from the user. The glucose levels of the user are fed into an algorithm that controls insulin infusion. As the device is used more, the algorithms accuracy to the user increases, and the pump will be able to accurately predict major glycemic changes and implement the adjustments to prevent the major glycemic variations completely. It is recommended to give these devices at least three months to fully optimize the algorithm (Allen & Gupta, 2019).

Open-loop systems includes MDI and IPT, including SAP methods. The key difference with closed-loop systems is its ability to "learn" the patterns of the user's insulin requirements, and predictively adjust insulin infusion (Allen & Gupta, 2019).

Measuring Glycemic Control

The hemoglobin A1c (HbA1c) test displays the average level of blood glucose levels over a 3-month period. Though this is an important measure of blood glucose levels, it can be misleading and overall unhelpful when determining glucose variation. As it is an overall average, someone with spikes of high and low blood sugars can even out to an excellent HbA1c, as a

result they may be suffering physically and mentally, but they may think their blood sugars are not the cause (American Diabetes Association, 2021).

However, HbA1c is still an important indicator of long-term glycemic control, particularly as a predictor of developing long-term complications. A better metric for testing glycemic variability is time in range, a measure of the time spent in target blood sugar levels, which is typically between 70 – 180 mg/dL. Both measures are important for receiving an unbiased view of the user's glycemic control (American Diabetes Association, 2021).

Considering the importance of glycemic control to diabetes management, and the improvements to diabetes technology, it is imperative to test these improvements and compare the real-world outcomes of their glycemic control. Through this information the following PICO formatted question was developed:

Do people with type 1 diabetes who are 18 years or older experience improved glycemic control when using hybrid closed loop systems for at least three months compared with open loop insulin systems?

Search Criteria

The following research was conducted to further expand on this question. PubMed was searched with the following terms: ((Closed loop system) OR (HCL)) AND ((T1D) OR (type 1 diabetes)) AND (glycemic control). Sources searched were peer-reviewed and published between the years 2016-2021. The eligibility criteria included research with adults aged 18 or older with T1D, and the use of a HCL system compared with another INT method, that included the glycemic control of the systems. The study was required to be at least 3 months to allow for optimization of the HCL algorithm. As well, for sufficient glycemic control comparison, the

study was required to include at least both time-in-range and HbA1c measurements. Articles surrounding elderly, pregnant and adolescent diabetics were all eliminated.

With these criteria, two articles remained, a randomized control trial (RCT) and a cohort study. A further search on Google Scholars, with the same search terms, was conducted to find an applicable systematic review, however no such article was found.

The RCT is second to systematic reviews on the pyramid of evidence, as they have a powerful research design, their influence can be substantial to healthcare practices (Walden University, 2021). This RCT evaluated over 100 adults for a period of 6 months, thus was taken in for appraisal. Though cohort studies are low on the pyramid of evidence, this cohort examined over 300 adults for over a year, thus was deemed acceptable to further critically appraise.

Research appraisal is imperative to assess the performed study design, methodology and applicability to real-world practice. Critical appraisal of research involves determining a study's strengths and weaknesses to assess its validity and practicality for real-world use (Critically Appraisal Skills Program [CASP], 2020). Articles were reviewed using appraisal checklists for RCTs and Cohort studies as per CASP.

Randomized Control Trial – Appraisal #1 (McAuley et al., 2020)

A 2020 Australian RCT was conducted to investigate glycemic and psychosocial outcomes with HCL versus standard insulin dosing methods in adults with T1D. The standard insulin dosing methods included were MDI and IPT, denoted as the standard therapy for adults with T1D. The primary outcome of this study was masked CGM time in range during the final three weeks of the study.

Study Design

120 participants were recruited from several tertiary hospitals across Australia. Noted eligibility criteria included adults over 25 or older, with T1D for over a year, and individuals who have not used a CGM sensor before. This was an excellent asset to the study, as HCL systems require the CGM to "get to know" the patient, the data from this study reflects the learning growth of the algorithm.

To reduce human error, participants were given diabetes management training outlining carbohydrate counting for correct insulin supplementation. This is a strength, as the data will reflect the insulin therapy methods glycemic control ability, with less variation due to poor insulin management. Training was also done pre-randomization to eliminate bias, as well throughout the study all participants were given equal 24-hour management support.

Randomization was done with three variables, time-in-target, attended study center, and initial insulin delivery method. Randomization was performed by an independent group of statisticians, to equally distribute these variables into two separate groups. This method eliminates investigator bias, and ensures the data has equal variation, maintaining its applicability to all T1D adults.

Study Method

After randomization, a 5-week intervention period took place, which included more management training, and respective device training. Both groups had a total of 16 study visits, which included management support and adherence to study protocols, and 3 data collection periods of 3 weeks, 2 weeks, and 3 weeks, respectively.

During data collection, both groups wore the same masked CGM sensor, blinding the participants of their blood glucose readings. As HCL requires a sensor for operation, this group wore an additional sensor for data collection, thus could still see their readings from their usual sensor.

All participants used the same blood glucose meter to record their blood sugar levels at least 4 times daily. MDI participants were instructed to use this meter throughout the full duration of the study, and to use its inbuilt bolus calculator, further decreasing the likelihood of human error. Data was deemed invalid unless the sensor was available for at least 70% of the time, otherwise the user would have to provide an additional week of data.

These criteria greatly strengthen the data, as instrumental error due to variation was eliminated and the quality of data was ensured over the testing period. During data analysis, investigators were blinded to the originating group of the data, further decreasing investigator bias.

Study Results

The results showed an increase of 14.8% (±11) for HCL groups time in range compared to the standard therapy group. As well, the HCL group displayed time in hypoglycemia 2.0% (±2.5) less than the standard group, and time in hyperglycemia 12.0 (±16.1%) less than the standard group (p-value<0.001).

A minor decrease of 0.4% was found in the average HbA1c of the HCL group. The HbA1c was only provided through an average of the groups combined tests, instead of a standard deviation, which is a flaw of the study. The initial HbA1c of the HCL group had a range of 5.7% to 10.4%, which is broad and inclusive, but becomes an average of 7.7%, which is in target and

exclusive. The final average of the HbA1c tells us little about the actual changes made to HbA1c, such as if the range became smaller.

The HbA1c is also plotted over the course of the study. This plot shows the steady nature of the control groups HbA1c, while the HCL groups steadily declines to its minimum, 3 months into the study, and then remains there until the end. This further validates the 3-month recommendation of HCL technologies, for the algorithm to adjust accordingly.

Strengths to this study include unbiased randomization of the group, making the data applicable to all adults with type 1 diabetes. The study minimized human error through training sessions with the participants, gathered their results in an unbiased manner, and eliminated environmental variations by ensuring all participants utilized the same technology.

Through its study design, methodology and results analysis, this study has high-quality evidence that is applicable to adults with T1D that can conclude the use of HCL systems increases glycemic control after 3 months of use.

Cross-sectional design study – Appraisal 2 (Beato-Vibora et al., 2021)

This 2021 study aimed to evaluate the glycemic control achieved through sensor specific diabetes technology for real-life clinical practice.

Study Design

302 T1D adults were recruited from January 2019 to March 2020. There is selection bias present, as the participants were all recruited from the same Endocrinology Department. To further prove this bias, the initial HbA1c of the participants was 7.28 (±0.84%). Inclusive of the deviation, this is a target HbA1c and exclusive to most T1D adults.

Four groups were created, comparing MDI with CGM or FMG, a SAP group and a HCL group, with an equal division between age, gender and diabetes duration, which maintains variability between groups. All participants received the same training for insulin management to reduce human error.

Study Method

Patients' data was downloaded a total of 5 times throughout the year, which is an unbiased approach. The article does not mention the length of time the data was collected from, or the number of required blood glucose readings taken throughout the day. This creates very unreliable data since blood glucose readings vary substantially throughout the day and a single reading would not represent the data accurately. As well, an insufficient length of time the data is downloaded from can reflect an unnaturally bad day, further misrepresenting the data.

The results demonstrate glycemic outcomes of the study, but do not indicate whether these results are the average of the 5 data downloads, or only the final data, which creates inconclusive results. As HCL systems are growing, learning machines, displaying the progressive data would be most beneficial to this area of research.

Study Results

This study concluded that HCL had the highest time in range of 71 (±10%), which is 13 (±15%) higher than Group 2 (FGM + MDI), the lowest time in range group. The estimated HbA1c changes were very minute, with the HCL group decreasing by 0.28%. HCL was superior in all glycemic outcomes, however the SAP group was a very close contender.

The results from this cross-sectional study are not applicable to the local population, as there was bias in selection of individuals, and an average target HbA1c which is unapplicable.

As well, since the data extraction methodology is unclear, very little can reliably be concluded from this study.

Conclusion

Based on the critically appraised randomized control trial, it is concluded that people with type 1 diabetes 18 years or older experience improved glycemic control when using HCL systems for at least 3 months compared with other insulin delivery methods. HCL showed a total of 14.8 (±11%) increase in time in range, and a total average decrease of 0.4% for HbA1c (McAuley et al., 2020).

Though the results for the RCT are reliable, it is interesting to note the incongruity of the HbA1c outcome. The average decrease of HbA1c appears very minute, however instead comparing the decrease in its deviation range may provide greater results. This is an example of how HbA1c can lead to invalid results, as without the time-in-range outcome, the glycemic control of the HCL system would appear very minor.

Little can be concluded from the cohort study however it allows for the emergence of related questions. The cohort displayed very minimal differences between the HCL and SAP groups glycemic control. If this proves true with more concrete data, a comparison of these systems quality of life would give a complete overview of the benefits and disadvantages of the two methods.

The cohort group included only in-target individuals, and through inconclusive data showed minor improvements. Comparatively, there is evidence from a 2020 longitudinal qualitative study comparing the quality of life of patients transitioning to a HCL system, compared to their previous therapy method. This study came to similar conclusions that HCL has

the greatest impact on those who have poor glycemic control, but expectedly little impact on those already in target. Patients with excellent diabetes management and steady glycemic control actually found decreased quality of life due to heightened expectations, alert fatigue and micromanagement issues with the machine. Patients struggling the most with glycemic control described the most dramatic benefits, which challenges commonly held assumptions about the "ideal" patient for these types of studies (Wang et al., 2021).

To complete this line of research, a comparison of the quality of life of these different INT methods would create a whole perspective on choosing an appropriate insulin delivery method, based on various individuals' glycemic control, diet, exercise and overall lifestyle.

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