Journal of Medical and Health Studies (JMHS)
ISSN: 2710-1452
DOI: 10.32996/jmhs
Journal Homepage: www.al-kindipublisher.com/index.php/jmhs

JMHS
AL-KINDI CENTER FOR RESEARCH AND DEVELOPMENT

| RESEARCH ARTICLE

Exploring Use of Closed-Loop Insulin Delivery System for Hospital-at Home: A Meta-analysis of Randomized Controlled Trials on Closed-Loop Insulin Delivery System in Type 2 Diabetes

Tay Priscilla[1]✉ and See Qin Yong[2]
[1]MN, RN, Advanced Practice Nursing Department, Changi General Hospital, Singapore
[2]MBBS, MMed (Family Medicine), FCFP, Head, Service of Acute and Rehabilitative Care at Home, Changi General Hospital, Singapore
Corresponding Author: Tay Priscilla, **E-mail**: priscilla_tay@cgh.com.sg

| ABSTRACT

This meta-analysis aims to evaluate the use of closed-loop insulin delivery system (CLS), compared to regular insulin therapy, in controlling glucose levels in adults with type 2 diabetes mellitus (T2DM). This is to explore the use of CLS for optimal glucose management in Hospital-at-Home (HaH). HaH is a programme that brings monitoring and treatment to patients houses, instead of requiring them to stay in the hospital. Patients under HaH are commonly treated for infections, with a large percentage with T2DM. Fluctuations of glucose during acute illness call for frequent monitoring and titration of insulin. CLS has proven efficacy in glucose management for Type 1 diabetes. However, there were no articles reporting the use of CLS in HaH. This meta-analysis aims to evaluate Randomized Controlled Trials (RCTs) done for CLS in T2DM, to analyse its feasibility in HaH. RCTs that investigated adults >18 years old, diagnosed with T2DM, comparing CLS and regular insulin therapy. The search was performed on CINAHL, Embase and PubMed on 11 January 2023. A search was limited to 2012 to 2022, and language was not limited in the search. Two researchers independently screened for selection, extracted data, and appraised included articles. Of 398 articles identified from the 3 databases, 5 RCTs were selected and included in the review with a total sample size of 302 and an average age of 67.2 years. Studies were done in both hospitals and home. The quality of studies was high. Meta-analysis results show a significantly longer proportion of time within target glucose range in the intervention group, measuring a mean difference of 21.15 (95%CI, 17.33, 24.96). CLS showed efficacy in managing blood glucose in T2DM, regardless of their current medical conditions, pre-existing comorbidities, meals, or activity levels. There is potential CLS to be used for the remote monitoring and active titration of insulin for patients under HaH. However, as included studies had small sample sizes, more high quality RCTs, on larger sample sizes are warranted to ascertain its efficacy.

| KEYWORDS

Artificial Pancreas; Closed-loop Insulin Delivery; Diabetes; Hospital-at-Home

| ARTICLE INFORMATION

ACCEPTED: 10 January 2025 **PUBLISHED:** 11 February 2025 **DOI:** 10.32996/jmhs.2025.6.1.13

1. Introduction

Hospital-at-Home (HaH) is a care model that allows inpatient treatment to be done at home instead of the hospitals. The quality and safety of care with Hospital-at-Home depends greatly on remote patient monitoring (RPM) that patients and/ or their caregivers must do by themselves. RPM can be Bluetooth-enable devices or wearables that allow intermittent or continuous collection of biometric data such as vital signs and heart rhythm (Cafazzo & Seto, n.d.; Kanagala et al., 2023; Whitehead & Conley, 2023).

Common conditions treated under the programme are infections requiring intravenous antibiotics (Kanagala et al., 2023; Patel & West, 2021),and a large percentage of these patients have comorbidities such as Type 2 diabetes (T2DM).

During acute illnesses, body glucose concentrations usually increase, contributed by immune responses that trigger insulin resistance and hepatic gluconeogenesis. Insulin therapy is usually initiated for patients with diabetes during acute illness to avoid hyperglycaemia (blood glucose concentrations >10.0mol/L) as it is associated with worse clinical outcomes and increased mortality. However, insulin increases risk of hypoglycaemia (blood glucose concentrations <4.0mmol/L) and the fluctuations of blood glucose levels between hyperglycaemia and hypoglycemia, especially when critically ill, have shown to increase mortality in septic patients (Eslami et al., 2011; UpToDate, 2024). Therefore, patients, especially those with diabetes, will have frequent fingerpicks for point-of-care (POC) monitoring of capillary blood glucose to dose insulin (Egi et al., 2017; Wensveen et al., 2021).

The frequent fingerpicks and close titration of insulin bring about discomfort for patients and inconvenience to patients and their family and/or caregivers under HaH. Population who are frail, have poor health literacy or non-communicative will be at high risk for undetected hypoglycaemia episodes, especially if it happens overnight. Therefore, frequent monitoring of glucose is very important in HaH. Continuous glucose monitoring (CGM) is a technology that allows glucose measurements every 5-15 minutes via a sensor (Suresh Rama Chandran, 2023). This reduces the need for frequent finger-pricks for frequent monitoring, but the challenge remains to the frequent titration of insulin. There is a need to increase the efficacy of remote monitoring and treatment of glucose control by HaH. Closed-loop insulin delivery system (CLS) consists of continuous interstitial glucose monitoring and insulin pump with an algorithm that calculates and delivers insulin needed. Many large trials have shown safety and feasibility of the CLS in Type 1 diabetes (Fuchs & Hovorka, 2020; Templer, 2022). However, to our current knowledge and literature search, no studies were done on the use of CLS in HaH. It may be postulated that patients require closer monitoring and titration of medications when critically ill. The current RPM may not be able to accommodate that level and limits the acuity of patients that HaH is able to manage. Therefore, this meta-analysis aims to evaluate the use of closed-loop insulin delivery system (CLS), compared to regular insulin therapy, in controlling glucose levels in adults >18 years old with T2DM. Setting was not limited in this search to explore the possibility of the use of CLS in T2DM patients during illness in all settings, inpatient or community.

2. Inclusion Criteria

The following criteria were used in selecting studies for inclusion:

- Participants: Adults >18 years old, diagnosed with type 2 diabetes mellitus.
- Intervention(s): CLS
- Comparator(s): Regular basal and/or prandial insulin therapy.
- Outcomes: Time in normal blood glucose levels range
- Types of studies: Randomized Controlled Trials (RCTs) published in English.

3. Method

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were referred to (Figure 1) for systematic reporting of results (Page et al., 2021).

3.1 Search Strategy

The search was performed on the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica database (Embase) and PubMed. The search terms used in all text were: ("closed-loop insulin" or "closed loop insulin" or "artificial pancreas" or "insulin infusion pump" or "insulin infusion system" or "closed loop control" or "closed-loop control") and ("type 2 diabetes mellitus" or "T2DM" or "non-insulin-dependent diabetes mellitus" or "type 2 diabetes" or "type II diabetes mellitus" or "adult-onset diabetes" or "adult onset diabetes"). Search was limited to 2012 to 2022 as there were rapid advancements of development and research of the fully closed-loop system in the past decade (Shah et al., 2016). Language was not limited in the search.

Initial search was done on PubMed to generate search terms for the key concepts of T2DM and CLS. A full search strategy was then formulated (Table 1). The last search was done on 11 January 2023 (Appendix 1). Titles and abstracts for all the search results were screened for eligibility. Only RCTs on human subjects were included. Reviews, conference proceedings, case reports and retrospective studies were rejected. Full text articles were retrieved for included studies. Hand search of the reference list of retrieved studies was done to find relevant articles missed by electronic search on the databases.

A.	B. Concept 1 /Population/Problem	C. Concept2 /Intervention
D. Key concepts E.	F. People with Type 2 diabetes mellitus	G. Closed-loop insulin delivery system
H. Search terms I.	J. "Type 2 Diabetes Mellitus" OR "T2DM "OR "Non-Insulin-Dependent Diabetes Mellitus" OR "Type 2 diabetes" OR "Type II diabetes mellitus" OR "adult-onset diabetes" OR "adult onset diabetes"	K. "Closed-loop insulin" OR "closed loop insulin" OR "Artificial pancreas" OR "insulin infusion pump" OR "insulin infusion system" OR "closed loop control" OR "closed-loop control" L. M.

Table 1: Search strategy

3.2 Study Selection

Two investigators selected full studies that met the inclusion criteria and rejected those that did not. Disagreements were resolved through discussion or with a third investigator till a consensus was met. 323 articles were excluded.

3.3 Assessment of Methodological Quality

The Joanna Briggs Institute (JBI) critical appraisal tool for Randomized Controlled Trials was used to assess the quality of selected studies. JBI scores of 60% and above were considered as high quality. Two reviewers appraised each study independently and a third review was involved if discrepancies arose.

3.4 Data Extraction

Data was extracted individually by different investigators into a standardized table (Appendix 2) including specific details of publication year, number of participants, characteristics of enrolled patients, duration of diabetes, study design, details of intervention, outcome measure of time duration that glucose concentration was in target glucose range. Authors were contacted for any vagueness and/ or missing data.

3.5 Data Synthesis

An outline of the characteristics of each included study was summarized in Appendix 2. Meta-analysis of standardized mean difference for continuous outcome was done using the Review Manager (RevMan) version 5.4, comparing the duration of time in the target glucose range. I2 was used to assess heterogeneity of studies with a statistically significant level (P value) set at 1.0.

4. Results

The search generated 430 articles from 3 databases. After the removal of duplicates, titles and abstracts of 398 articles were screened, of which full text was retrieved and reviewed for 26 articles. 19 articles were rejected as they were not RCTs, and 7 articles remained in the review. Study selection process is illustrated in Figure 1.

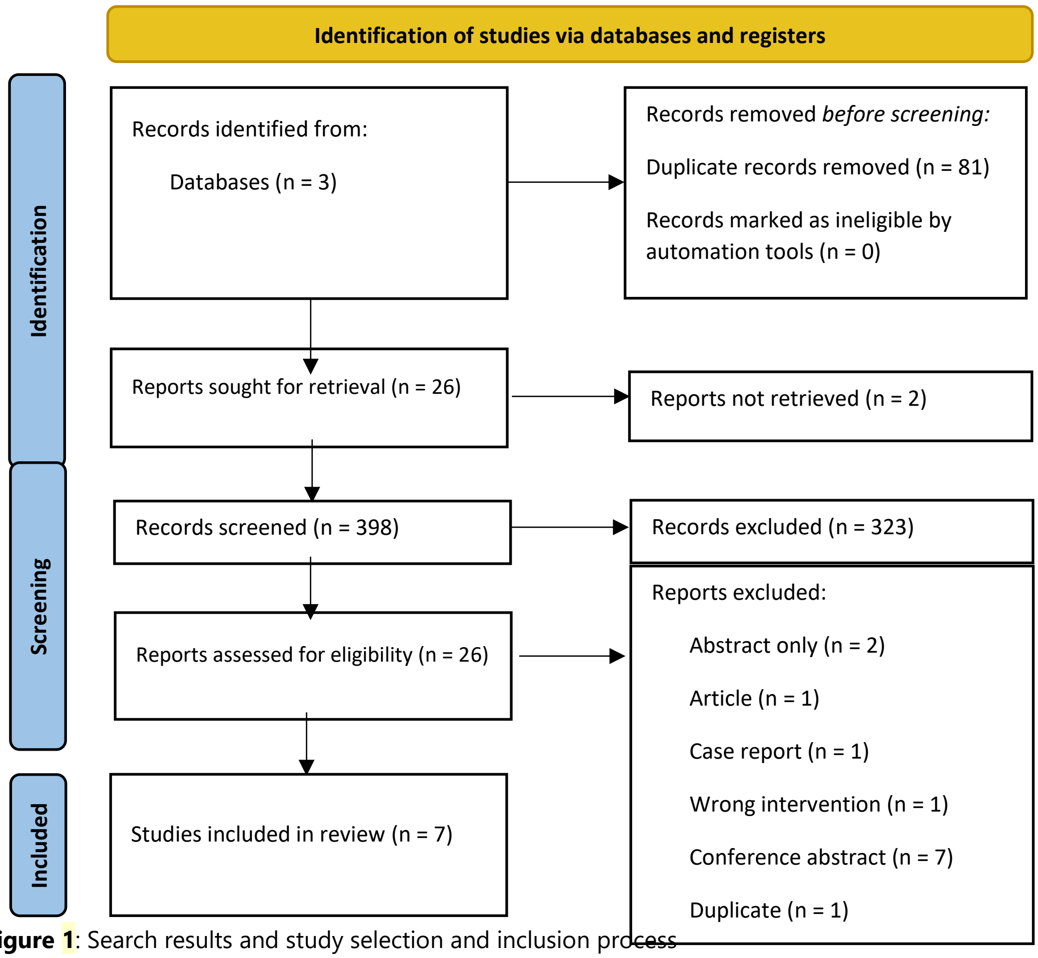

Figure 1: Search results and study selection and inclusion process

4.1 Characteristics of Included Studies

All studies included were RCTs, 4 were conducted in Europe, 1 in Canada. 2 out of 5 studies were crossover trials, 1 of which had an average washout period of 17 days, while the other had at least 3 days. All studies have sample sizes ranging from 30 to 136 with an average age of 67.2 years.

Participants of all studies had an average HbA1c of 7.9% and BMI of 31.9. 1 study included participants for elective surgeries, 2 included participants in general inpatient wards, 1 study included outpatient participants requiring dialysis and another 1 investigated outpatient participants without dialysis.

CLS consists of continuous glucose monitoring, rapid-acting insulin delivery systems that are regulated by algorithms. For continuous glucose monitoring, 2 of the studies used Freestyle Navigator II, another 3 used Dexcom. Dana Diabecare was used in 4 studies for insulin delivery, while 1 used Accu-Check Combo. 2 studies used the CamAPS HX closed-loop application which uses the Cambridge adaptive model predictive control algorithm while the other 3 studies used model predictive control algorithm (version 0.3.65 and 0.3.70). Intervention period ranged from 24 hours up to 20 days.

The 5 studies had a total sample size of 302, investigating the proportion of time participants had their glucose within the target range. A significantly longer proportion of time within the range was observed in the intervention group, measuring a mean difference of 21.15 (95%CI, 17.33, 24.96). No statistical heterogeneity was present (I2 = 0%, P = 0.43).

	Intervention			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Bally 2018	65.8	16.8	70	41.5	16.9	66	45.4%	24.30 [18.63, 29.97]
Boughton 2021	52.8	12.5	26	37.7	20.5	26	17.1%	15.10 [5.87, 24.33]
Herzig 2022	76.7	10.1	22	54.7	20.8	22	15.6%	22.00 [12.34, 31.66]
Taleb 2019	52.8	12.5	15	37.7	20.5	15	9.9%	15.10 [2.95, 27.25]
Thabit 2017	59.8	18.7	20	38.1	16.7	20	12.1%	21.70 [10.71, 32.69]
Total (95% CI)			153			149	100.0%	21.15 [17.33, 24.96]

Heterogeneity: $Chi^2 = 3.83$, $df = 4$ ($P = 0.43$); $I^2 = 0\%$
Test for overall effect: $Z = 10.86$ ($P < 0.00001$)

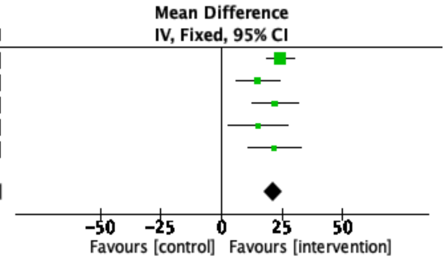

Figure 2: Forest plot of comparison of the mean proportion of time in target glucose range. Intervention: CLS

5. Discussion

In general, RCTs evaluated in the meta-analysis suggest that CLS can be an effective and safe mode of glucose management for T2DM.

All studies used the proportion of time in target glucose range (5.6 – 10mmol/L) as their outcome measure, which enabled comparison among all studies. Results unanimously showed larger proportion of time in the target glucose range in the intervention group compared to their usual care, with low number of hypoglycaemic events. This was similar to the studies investigating CLS in Type 1 diabetes (Boughton et al., 2023; Elleri et al., 2011; Toschi et al., 2022).

Profiles of participants in both the control and intervention group were similar, particularly Hba1c, which represents their average control of glucose at the point of study. Only 2 studies reported participants' regular glucose-lowering therapy including oral hypoglycaemic agents (OHGAs), basal and bolus insulin (Herzig et al., 2022; Thabit et al., 2017). There was an imbalanced distribution of participants with higher number of insulin naïve in the intervention group, and a higher number with basal insulin therapy in the control group (Herzig et al., 2022). The glucose lowering effect in insulin naïve participants is usually more significant with increased risk of hypoglycaemia. The imbalanced distribution may contribute to the larger proportion of time spent in the target glucose range in the intervention group. Despite the differences in distribution and reporting, the similar results of a larger proportion of time in the target glucose range in all studies supported that CLS can improve glucose management regardless of the therapies that participants had.

Poorly controlled diabetes indicated by Hba1c >7% is associated with poorer outcomes in sepsis such as mortality (Wang et al., 2006). Hba1c in participants for all the 5 studies ranged from 7.5 – 9%. Results from the 5 studies propose that CLS can maintain glucose within the target range. It is reasonable to propose that CLS can improve outcomes for poorly controlled diabetes during illness.

The study by Bally et al. (2018) has the largest sample size among all studies evaluated and was conducted in 2 tertiary hospitals in the United Kingdom and Switzerland. The other 4 studies had small sample sizes ranging from 15-45 and may not be sufficient to represent the population, considering the prevalence of T2DM worldwide. Also, 4 studies were conducted in Europe, 1 in Canada. Asians, compared to Caucasians, have different genetic predispositions, pathophysiology of diabetes (Cho, 2017; Loh et al., 2022). Results, therefore may not reflect the effect of CLS in the Asian population. More larger-scale studies, especially in Asian populations will be recommended.

2 of the studies were crossover trials that allow higher accuracy in study results by minimizing subject variability. One study reported an average washout period using rapid-acting insulin Aspart to be 17±5 days (Boughton C K et al., 2021) while the other at least 3 days. Although exact insulin was not reported in the other study(Taleb et al., 2019) , rapid-acting insulin is usually used in all insulin delivery pumps for titration. The average half-life of Aspart is about 66 minutes (Rubin et al., 2024) so effect of washout period of 3 to 17 days is sufficient to totally eradicate any effect of treatment. Although there may be a sufficient washout period in between the intervention and control for the 2 crossover trials, patients' regular regime, such as long-acting insulin may have had effects on the results. The study by Taleb et al. (2019) failed to report the participants' regular regime and the study period was only over 24 hours. Any remaining effects of their regular regime may have affected the glucose readings in the next 24 hours. This may have resulted in smaller effect size with MD 7.1% (P-value 0.046) as compared to the crossover trial by Boughton C K et al. (2021) of MD 15.1% (P-value <0.001), despite a larger range of target glucose range (4 – 10mmol/L) in the study by Taleb et al. (2017), and target glucose range (5.6 – 10mmol/L) in the study by Boughton C K et al. (2021). The true effect of CLS may be less

represented in the study by Taleb et al. (2019) and both crossover trials studied had a small sample size. Larger sized trials will be recommended to ascertain the effect.

The effect size of glucose control was similar in the 3 studies conducted in the general wards that investigated patients admitted for acute illnesses, predominantly sepsis(Bally et al., 2018), infected foot ulcer (Thabit et al., 2017), or receiving elective surgery (Herzig et al., 2022). The effect size was similar in the 2 studies conducted in the outpatient setting (Boughton C K et al., 2021; Taleb et al., 2019) and smaller than that conducted inpatient. Blood sugar fluctuations is likely be higher when patients are more acutely ill, so it is reasonable to deduced that CLS adapts better to the fluctuations, resulting in a larger effect size in the inpatient group.

Of the studies conducted outpatient, Boughton C K et al. (2021) had the study period over 20 days of unrestricted living in a population requiring dialysis. Taleb et al. (2019) excluded those with a creatinine clearance <30mL/min but participants adhered to a controlled meal and activity plan over a 24-hour period. The larger effect size observed despite unrestricted living and dialysis suggests that CLS can effectively control glucose levels regardless of patient's pre-existing health conditions, meal intake or activity levels. This observation suggests that CLS is suitable for patients under HaH who often have multiple co-morbidities and where healthcare providers have limited control over their diet and activity.

6. Conclusion

CLS showed efficacy in managing blood glucose in T2DM, regardless of their current medical conditions, pre-existing comorbidities, meals, or activity levels. Considering the unique need for remote patient monitoring and treatment for patients under HaH, CLS show potential to provide safe and efficient glucose management for patients with T2DM, that may experience greater fluctuations in their glucose than usual when having an infection and receiving treatment at home. Future research into using CLS for HaH is recommended. Comparison of the different models and algorithms will be needed to compare the safety and efficacy. Finally, cost effective analysis comparing CLS to the current standard of frequent POC finger-prick tests and insulin injections would provide deeper insights into optimizing resources in patient management as well.

Funding: This research received no external funding.
Conflicts of Interest: The authors declare no conflict of interest.
ORCID iD: Tay Priscilla (0000-0002-3331-3885), See Qin Yong (0009-0000-3195-194X)

References

[1] Bally, L., Thabit, H., Hartnell, S., Andereggen, E., Ruan, Y., Wilinska, M. E., Evans, M. L., Wertli, M. M., Coll, A. P., Stettler, C. & Hovorka, R. (2018). Closed-loop insulin delivery for glycemic control in noncritical care. New England Journal of Medicine, 379(6), 547–556. https://doi.org/10.1056/NEJMoa1805233

[2] Boughton, C. K., Hartnell, S., Lakshman, R., Nwokolo, M., Wilinska, M. E., Ware, J., Allen, J. M., Evans, M. L. & Hovorka, R. (2023). Fully Closed-Loop Glucose Control Compared With Insulin Pump Therapy With Continuous Glucose Monitoring in Adults With Type 1 Diabetes and Suboptimal Glycemic Control: A Single-Center, Randomized, Crossover Study. https://doi.org/10.2337/dc23-0728

[3] Boughton C K, Tripyla A, Hartnell S, Daly A, Herzig D, Wilinska M E, Czerlau C, Fry A, Bally L & Hovorka R. (2021). Fully automated closed-loop glucose control compared with standard insulin therapy in adults with type 2 diabetes requiring dialysis: an open-label, randomized crossover trial. Nature Medicine, 27(8), 1471–1476. https://doi.org/10.1038/s41591-021-01453-z

[4] Cafazzo, J. A. & Seto, E. (n.d.). ConneCtivity and Remote monitoRing Remote Monitoring for Chronic Disease Self-Management The Hospital at Home: Advances in Remote Patient Monitoring.

[5] Cho, Y. M. (2017). Characteristics of the pathophysiology of type 2 diabetes in Asians. Annals of Laparoscopic and Endoscopic Surgery, 2(2), 14–14. https://doi.org/10.21037/ALES.2017.01.03

[6] Egi, M., Furushima, N., Makino, S. & Mizobuchi, S. (2017). Glycemic control in acute illness. Korean Journal of Anesthesiology, 70(6), 591. https://doi.org/10.4097/KJAE.2017.70.6.591

[7] Elleri, D., Dunger, D. B. & Hovorka, R. (2011). Closed-loop insulin delivery for treatment of type 1 diabetes. BMC Medicine, 9(1), 1–9. https://doi.org/10.1186/1741-7015-9-120/TABLES/3

[8] Eslami, S., Taherzadeh, Z., Schultz, M. J. & Abu-Hanna, A. (2011). Glucose variability measures and their effect on mortality: A systematic review. Intensive Care Medicine, 37(4), 583–593. https://doi.org/10.1007/S00134-010-2129-5/TABLES/2

[9] Fuchs, J. & Hovorka, R. (2020). Closed-loop control in insulin pumps for type-1 diabetes mellitus: safety and efficacy. Expert Review of Medical Devices, 707–720. https://doi.org/10.1080/17434440.2020.1784724

[10] Herzig, D., Suhner, S., Roos, J., Schurch, D., Cecchini, L., Nakas, C. T., Weiss, S., Kadner, A., Kocher, G. J., Guensch, D. P., Wilinska, M. E., Raabe, A., Siebenrock, K. A., Beldi, G., Gloor, B., Hovorka, R., Vogt, A. P. & Bally, L. (2022). Perioperative Fully Closed-Loop Insulin Delivery in Patients Undergoing Elective Surgery: An Open-Label, Randomized Controlled Trial. Diabetes Care, 45(9), 2076–2083. https://doi.org/10.2337/DC22-0438

[11] Kanagala, S. G., Gupta, V., Kumawat, S., Anamika, F., McGillen, B. & Jain, R. (2023). Hospital at home: emergence of a high-value model of care delivery. The Egyptian Journal of Internal Medicine, 35(1), 21. https://doi.org/10.1186/S43162-023-00206-3

[12] Loh, M., Zhang, W., Ng, H. K., Schmid, K., Lamri, A., Tong, L., Ahmad, M., Lee, J. J., Ng, M. C. Y., Petty, L. E., Spracklen, C. N., Takeuchi, F., Islam, M. T., Jasmine, F., Kasturiratne, A., Kibriya, M., Mohlke, K. L., Paré, G., Prasad, G., … Chambers, J. C. (2022). Identification of genetic effects underlying type 2 diabetes in South Asian and European populations. Communications Biology 2022 5:1, 5(1), 1–10. https://doi.org/10.1038/s42003-022-03248-5

[13] Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj, 372, n71. https://doi.org/10.1136/bmj.n71

[14] Patel, H. Y. & West, D. J. (2021). Hospital at Home: An Evolving Model for Comprehensive Healthcare. Global Journal on Quality and Safety in Healthcare, 4(4), 141–146. https://doi.org/10.36401/JQSH-21-4

[15] Rubin, R., Khanna, N. R. & McIver, L. A. (2024). Aspart Insulin. XPharm: The Comprehensive Pharmacology Reference, 1–5. https://doi.org/10.1016/B978-008055232-3.63717-1

[16] Shah, R. B., Patel, M., Maahs, D. M. & Shah, V. N. (2016). Insulin delivery methods: Past, present and future. International Journal of Pharmaceutical Investigation, 6(1), 1–9. https://doi.org/10.4103/2230-973X.176456

[17] Suresh Rama Chandran. (2023). Continuous Glucose Monitoring: A Useful Tool for Diabetes Management in Primary Care - SingHealth. https://www.singhealth.com.sg/news/defining-med/continuous-glucose-monitoring

[18] Taleb, N., Carpentier, A. C., Messier, V., Ladouceur, M., Haidar, A. & Rabasa-Lhoret, R. (2019). Efficacy of artificial pancreas use in patients with type 2 diabetes using intensive insulin therapy: A randomized crossover pilot trial. Diabetes Care, 42(7), E107–E109. https://doi.org/10.2337/dc18-2406

[19] Taleb, N., Carpentier, A., Rene, J., Messier, V., Morais, J., Haidar, A. & Rabasa-Lhoret, R. (2017). The efficacy of single-hormone artificial pancreas at controlling glucose levels in insulin-treated patients with type 2 diabetes: A randomized crossover trial. Diabetes, 66, A277. https://www.embase.com/search/results?subaction=viewrecord&id=L616961275&from=export

[20] Templer, S. (2022). Closed-Loop Insulin Delivery Systems: Past, Present, and Future Directions. Frontiers in Endocrinology, 13, 919942. https://doi.org/10.3389/FENDO.2022.919942/BIBTEX

[21] Thabit, H., Hartnell, S., Allen, J. M., Lake, A., Wilinska, M. E., Ruan, Y., Evans, M. L., Coll, A. P. & Hovorka, R. (2017). Closed-loop insulin delivery in inpatients with type 2 diabetes: a randomised, parallel-group trial. The Lancet Diabetes and Endocrinology, 5(2), 117–124. https://doi.org/10.1016/S2213-8587(16)30280-7

[22] Toschi, E., Atakov-Castillo, A., Slyne, C. & Munshi, M. (2022). Closed-Loop Insulin Therapy in Older Adults with Type 1 Diabetes: Real-World Data. Diabetes Technology and Therapeutics, 24(2), 140–142. https://doi.org/10.1089/dia.2021.0311

[23] UpToDate. (2024). Glycemic control in critically ill adult and pediatric patients - UpToDate. https://www.uptodate.com/contents/glycemic-control-in-critically-ill-adult-and-pediatric-patients

[24] Wang, X., Calzia, E., Bassi, G., Nguyen, C., Radermacher, P., Hauser, B., Asfar, P., Ploner, F., Barth, E. & Matejovic, M. (2006). Hemoglobin A1c predicts outcome of sepsis in patients with diabetes. Critical Care, 10(Suppl 1), P251. https://doi.org/10.1186/CC4598

[25] Wensveen, F. M., Šestan, M., Turk Wensveen, T. & Polić, B. (2021). Blood glucose regulation in context of infection. Vitamins and Hormones, 117, 253–318. https://doi.org/10.1016/BS.VH.2021.06.009

[26] Whitehead, D. & Conley, J. (2023). The Next Frontier of Remote Patient Monitoring: Hospital at Home. Journal of Medical Internet Research, 25(1), e42335. https://doi.org/10.2196/42335