Internet-based algorithm-guided insulin titration system improves glycemia in people with insulin-treated type 2 diabetes

Nishanth Thiagarajan, Hong Chang Tan, Suresh Rama Chandran, Phong Ching Lee, Yun Ann Chin, Wanling Zeng, Emily Tse Lin Ho, David Carmody, Su-Yen Goh, Yong Mong Bee

Submitted to: JMIR Formative Research
on: November 17, 2024

Table of Contents

Internet-based algorithm-guided insulin titration system improves glycemia in people with insulin-treated type 2 diabetes

Nishanth Thiagarajan[1] MBBS; Hong Chang Tan[2] MBBS; Suresh Rama Chandran[2] MBBS; Phong Ching Lee[2] MBChB; Yun Ann Chin[2] MBBS; Wanling Zeng[2] MD; Emily Tse Lin Ho[2] MBBS; David Carmody[2] MBChB; Su-Yen Goh[2] MBBS; Yong Mong Bee[2] MBBS

[1]Singapore General Hospital Singapore SG
[2]Department of Endocrinology Singapore General Hospital Singapore SG

Corresponding Author:
Nishanth Thiagarajan MBBS
Singapore General Hospital
20 College Road, Academia, Singapore General Hospital, Singapore. 169856
Singapore
SG

Abstract

Background: Self-monitoring of blood glucose (SMBG) using online diabetes management platforms has shown promise in type 2 diabetes (T2D) management.

Objective: This study aimed to assess the effect of the ALRT Telehealth Solution, an FDA-cleared online platform incorporating SMBG with algorithm-guided insulin titration recommendations, on the hemoglobin A1c (HbA1c) in insulin-treated T2D.

Methods: Adults with T2D on twice-daily premixed insulin, HbA1c ?7.5% (58 mmol/mol) and <10% (86 mmol/mol), and BMI ?40 kg/m² were enrolled. They measured blood glucose twice-daily and uploaded glucometer data weekly using the ALRT mobile-phone application, which then alerted physicians with algorithm-guided insulin titration recommendations. These were communicated back to participants via the app weekly. HbA1c and fasting plasma glucose (FPG) were measured at baseline, weeks 12 and 24.

Results: We enrolled 25 adults (44.0% female, 52.0% Chinese), mean age 58.9 years. Adherence to twice-daily SMBG regimen was 97.4%. Over 24 weeks, mean total daily insulin dose increased from 0.73 to 0.79 units/kg/day. This led to a significant reduction in HbA1c from an average of 8.6% (70 mmol/mol) to 7.4% (57 mmol/mol) and FPG from an average of 8.7 to 7.1 mmol/L (both p<0.01). Most hypoglycemia events were mild (88.5%) (3.0-3.9 mmol/L), and the prevalence of hypoglycemia (<4.0 mmol/L) at 48.0% was similar to the self-reported baseline of 44.9%. There were more hypoglycemia episodes during the final 12 weeks of the study (72) than the first 12 weeks (25).

Conclusions: An internet-based glucose monitoring system with structured SMBG and algorithm-guided insulin titrations significantly improved glycemia in individuals with insulin-treated T2D without increasing hypoglycemia.

(JMIR Preprints 17/11/2024:68914)
DOI: https://doi.org/10.2196/preprints.68914

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

Original Paper:

Internet-based algorithm-guided insulin titration system improves glycemia in people with insulin-treated type 2 diabetes

Nishanth Thiagarajan, MBBS; Hong Chang Tan, MBBS; Suresh Rama Chandran, MBBS; Phong Ching Lee, MBChB; Yun Ann Chin, MBBS; Wanling Zeng, MD; Emily Tse Lin Ho, MBBS; David Carmody, MBChB; Su-Yen Goh, MBBS; Yong Mong Bee, MBBS

Department of Endocrinology, Singapore General Hospital

Corresponding Author:

Dr Nishanth Thiagarajan

Department of Endocrinology, Singapore General Hospital

20 College Road, Academia, Singapore General Hospital, Singapore. 169856

Email: nishanth.thiagarajan@mohh.com.sg

Word count (manuscript): 2220

Word count (abstract): 251

Abstract

Background: Self-monitoring of blood glucose (SMBG) using online diabetes management platforms has shown promise in type 2 diabetes (T2D) management. This study aimed to assess the effect of the ALRT Telehealth Solution, an FDA-cleared online platform incorporating SMBG with algorithm-guided insulin titration recommendations, on the hemoglobin A1c (HbA1c) in insulin-treated T2D.

Methods: Adults with T2D on twice-daily premixed insulin, HbA1c ≥7.5% (58 mmol/mol) and <10% (86 mmol/mol), and BMI ≤40 kg/m² were enrolled. They measured blood glucose twice-daily and uploaded glucometer data weekly using the ALRT mobile-phone application, which then alerted physicians with algorithm-guided insulin titration recommendations. These were communicated back to participants via the app weekly. HbA1c and fasting plasma glucose (FPG) were measured at baseline, weeks 12 and 24.

Results: We enrolled 25 adults (44.0% female, 52.0% Chinese), mean age 58.9 years. Adherence to twice-daily SMBG regimen was 97.4%. Over 24 weeks, mean total daily insulin dose increased from 0.73 to 0.79 units/kg/day. This led to a significant reduction in HbA1c from an average of 8.6% (70 mmol/mol) to 7.4% (57 mmol/mol) and FPG from an average of 8.7 to 7.1 mmol/L (both $p<0.01$). Most hypoglycemia events were mild (88.5%) (3.0-3.9 mmol/L), and the prevalence of hypoglycemia (<4.0 mmol/L) at 48.0% was similar to the self-reported baseline of 44.9%. There were more hypoglycemia episodes during the final 12 weeks of the study (72) than the first 12 weeks (25).

Conclusion: An internet-based glucose monitoring system with structured SMBG and algorithm-guided insulin titrations significantly improved glycemia in individuals with insulin-treated T2D without increasing hypoglycemia.

Keywords: Diabetes; Insulin; Monitoring; Technology; Mobile; Application; Intervention

Introduction

The global prevalence of diabetes mellitus has risen dramatically, with projections estimating that over 1.3 billion people will be affected by 2050(1). This chronic disease profoundly impacts both quality of life(2)and healthcare expenditure(3), and has driven significant efforts toward early detection and treatment.

Effective glycemic control remains the corner stone of diabetes management, correlating with improved long-term outcomes (4–6). Despite rapid advances in pharmacotherapy, up to two-thirds of patients fail to achieve their glycemic targets (7). Self-monitoring of blood glucose (SMBG) is a pivotal component of diabetes management(8), enhancing patient engagement and glycemic control(9). The benefits of SMBG are most pronounced(10–12) when a structured approach is taken. Ideally, blood glucose readings should be collected at specified intervals and returned to healthcare providers for interpretation. In this regard, a safe and consistent dose adjustment regimen will be needed if any treatment modification is required. Finally, patients need to be promptly informed of the necessary changes. Thus, structured SMBG's effectiveness is contingent on regular, frequent physician reviews and adjustments of therapy(13,14).

However, having frequent in-person clinic visits to review SMBG and adjust insulin doses is impractical, given the massive patient load and long waiting time of many diabetes clinics. Furthermore, a vast amount of SMBG data needs to be reviewed and interpreted by the physician during the limited allocated clinic time. This process is laborious and time-consuming, yet decision-making for insulin dose adjustments need to be rapid. Providers with less clinical experience will find this especially challenging. Consequently, the SMBG data is often not fully capitalised to improve a patient’s diabetes management.

Several online programmes and mobile applications have been developed to overcome some of the abovementioned challenges. Instead of manual recording and feedback of SMBG to their provider in person, these programmes allow patients to record and transmit SMBG data directly via the application, reducing the frequency of face-to-face visits (15–17). In an earlier study, we demonstrated the ability of an online blood glucose monitoring system to optimise insulin dosages for patients receiving a basal-plus or basal-bolus insulin regimen. Importantly, glycemic control improved without increasing hypoglycemia rates (18). However, although this approach reduced the

need for face-to-face visits for insulin titration, physicians still need to review a large number of SMBG data before recommending any insulin dose adjustment. In addition, insulin doses are adjusted based on the physician's discretion and experience. Such an approach is manpower-resource intensive and is unlikely to solve the real-world problem of delays in treatment optimisation. One potential solution is to utilise an automated insulin dose adjustment system that could interpret SMBG data and provide dose adjustment recommendations based on a pre-programmed algorithm. Studies have demonstrated the superiority of such systems in improving glycemic control compared to physician-dependent adjustments alone(19). However, such programmes have not been studied in an Asian cohort.

We thus designed the Glucose Monitoring and Intervention in Insulin-treated Type 2 Diabetes Patients (GEMINI-T2D) study to examine the efficacy and safety of an online platform that incorporates monitoring and insulin titration recommendations based on an in-built algorithm in insulin-treated patients.

Methods

Study Design: The GEMINI-T2D study was a prospective, single-site, single-group, pre-post interventional study.

Study participants: All subjects were recruited from the Singapore General Hospital's Diabetes & Metabolism Centre from September 2020 to May 2022. The SingHealth Institutional Review Board (CIRB) reviewed and approved the study (Ref. No 2019/2874).

Inclusion criteria: We recruited adults (≥21 years old) with T2D of more than six months duration on twice-daily premixed insulin regimen for ≥3 months. The total daily dose (TDD) of insulin must be <1 unit/kg, hemoglobin A1c (HbA1c) between 7.5% (58 mmol/mol) to 9.9 % (86 mmol/mol), and

body mass index (BMI) ≤40 kg/m². We chose to study patients on premixed insulin as it represents a common and preferred insulin formulation in Asia (20,21). Subjects were required to have experience performing SMBG and own a compatible smartphone capable of weekly data uploads via the study app.

Exclusion Criteria: We excluded individuals with hypoglycemia unawareness (Gold score ≥4) to limit the risk of severe hypoglycemia during treatment. Pregnant or breastfeeding women, those with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m²), hemoglobinopathies, systemic corticosteroid use, and medical disease with a life expectancy of less than one year were excluded.

Intervention: Eligible participants were given a glucometer and instructed to perform SMBG twice daily. They were trained to use the ALRT System, an FDA-cleared diabetes management system, and asked to upload their SMBG data to the ALRT application weekly for the next 24-weeks. Participants were also educated on hypoglycemia recognition and management and instructed to perform SMBG when experiencing symptoms suggestive of hypoglycemia.

Insulin Dose Adjustment: The ALRT System analysed uploaded SMBG data every seven days. When capillary blood glucose (CBG) readings consistently fell outside the pre-defined range of 4 – 8 mmol/L, a predefined algorithm adjusted the pre-breakfast and/or pre-dinner insulin doses, implementing an increment or decrement of up to 15-20% as necessary (details of the algorithm are in Appendix 1). The treating physician was notified via a web-based user interface with the recommended insulin dose adjustments and was required to accept or decline the recommendation. Subsequently, the adjusted insulin doses were communicated to the participants via the ALRT application every seven days, or more frequently in the event of hypoglycemia. Participants were required to acknowledge the recommended dose adjustments via the app.

Baseline and Follow-up Assessments: Medical history, vital signs, body measurements, and laboratory measurements were collected at baseline. HbA1c and fasting plasma glucose (FPG) were measured at baseline, week 12, and week 24.

Outcome Measures: The primary outcome measure was the change in HbA1c at the end of 24 weeks relative to baseline. Secondary outcome measures included the number of hypoglycemia episodes and the adherence to the prescribed SMBG regimen. Hypoglycemia episodes were classified as follows:

- **Level 1:** Glucose value of 3.0-3.9 mmol/L.
- **Level 2:** Glucose value of <3.0 mmol/L.
- **Level 3:** Severe hypoglycemia causing altered mentation requiring external assistance for recovery.

Adherence to the SMBG regimen was defined as the proportion of the prescribed twice-daily SMBG that the participant successfully completed and uploaded to the ALRT platform. The incidence of hypoglycemia was defined as the number of hypoglycemia episodes that occurred during each 12-week period of the study.

Statistical Analysis: Continuous data were presented as mean (standard deviation) and categorical data as numbers (percentages). We compared the variables at baseline, week 12 and week 24 using Repeated measures ANOVA for normally distributed variables with post-hoc Tukey’s Method, and Friedman's ANOVA for non-normally distributed variables with post-hoc Wilcoxon Signed-Rank Tests with Bonferroni correction. Statistical analyses were performed using R version 4.1.1.

Results

25 subjects were recruited and followed up over 24 weeks. The baseline demographic and clinical characteristics are summarised in Table 1. The study cohort had a mean age of 58.9 (7.0) years, comprised 56.0% males, and had a mean BMI of 29.0 (3.6) kg/m^2.

Table 1. Baseline characteristics of study participants

Age, years, mean (SD)	58.9 (7.0)
Gender, n (%)	
Male	14 (56.0)
Female	11 (44.0)
Ethnicity, n (%)	
Chinese	13 (52.0)
Malay	4 (16.0)
Indian	6 (24.0)
Others	2 (8.0)
BMI, kg/m^2, mean (SD)	29.0 (3.6)
HbA1c, %, mean (SD)	8.6 (0.7)
HbA1c, mmol/mol (SD)	70.4 (7.7)
Fasting plasma glucose, mmol/L, mean (SD)	8.7 (2.0)

Duration of diabetes, years (SD)	18.9 (6.7)
Duration of insulin use, years (SD)	6.3 (3.5)
Total daily dose of insulin (TDD), units/day	57.3 (24.4)
Total daily dose of insulin (TDD), units/kg/day	0.73 (0.31)
Hypertension, n (%)	22 (88.0)
Hyperlipidemia, n (%)	23 (92.0)
Ischemic heart disease, n (%)	3 (12.0)
Stroke, n (%)	1 (4.0)
Retinopathy, n (%)	12 (48.0)
Neuropathy, n (%)	4 (16.0)
Nephropathy, n (%)	6 (24.0)
Peripheral vascular disease, n (%)	2 (8.0)

HbA1c and other glycemic variables (Table 2)

Mean baseline HbA1c and fasting plasma glucose were 8.6 (0.7) % and 8.7 (2.0) mmol/L, respectively. The mean baseline TDD of insulin was 57.3 (24.4) units/day or 0.73 (0.31) units/kg/day. All 25 participants experienced a reduction in HbA1c of ≥ 0.4 mmol/l at 24 weeks. Mean HbA1c decreased by 1.2% over 24 weeks, from 8.6 (0.7) % to 7.4 (0.6) % ($p<0.01$, Figure 1). From 0-12 weeks HbA1c decreased by 0.8% ($p <0.01$) and from 13-24 weeks HbA1c decreased by 0.4% ($p <0.01$). Individuals with a higher baseline HbA1c experienced a greater absolute decrease in HbA1c over 24 weeks ($p <0.01$, Figure 1).

Mean fasting plasma glucose (FPG) also decreased by 1.6 mmol/L over 4 weeks, from 8.7 (2.0) mmol/L to 7.1 (1.4) mmol/L ($p<0.01$, Figure 1). From 0-12 weeks FPG decreased by 1.3 mmol/L ($p =0.02$) and from 13-24 weeks FPG decreased by 0.3 mmol/L ($p =1$).

The mean TDD of insulin increased from 0.73 (0.31) to 0.79 (0.34) units/kg/day ($p<0.01$, Figure 1). From 0-12 weeks TDD of insulin increased by 0.05 units/kg/day ($p=0.02$) and from 13-24 weeks TDD of insulin increased by 0.01 units/kg/day ($p =1$). Body mass index (BMI) rose from 29.0 kg/m^2 to 29.5 kg/m^2 over 24 weeks ($p=0.03$).

Table 2. Key outcomes from baseline to week 12 and week 24.

Variable	Baseline	Week 12	Week 24	p-value for trend
HbA1c, %	8.6 (0.7)	7.8 (0.6)	7.4 (0.6)	<0.01
HbA1c, mmol/mol	70.4 (7.7)	61.4 (7.0)	57.3 (6.7)	<0.01
Fasting plasma glucose, mmol/L	8.7 (2.0)	7.4(1.9)	7.1(1.4)	<0.01
Total daily dose of insulin (units/day)	57.3 (24.4)	61.3 (25.7)	62.1 (25.4)	<0.01
Total daily dose of insulin (units/kg/day)	0.73 (0.31)	0.78 (0.33)	0.79 (0.34)	<0.01
Body mass index, kg/m^2	29.0 (3.6)	29.3 (3.6)	29.5 (3.6)	0.03

All data reported as mean (SD).

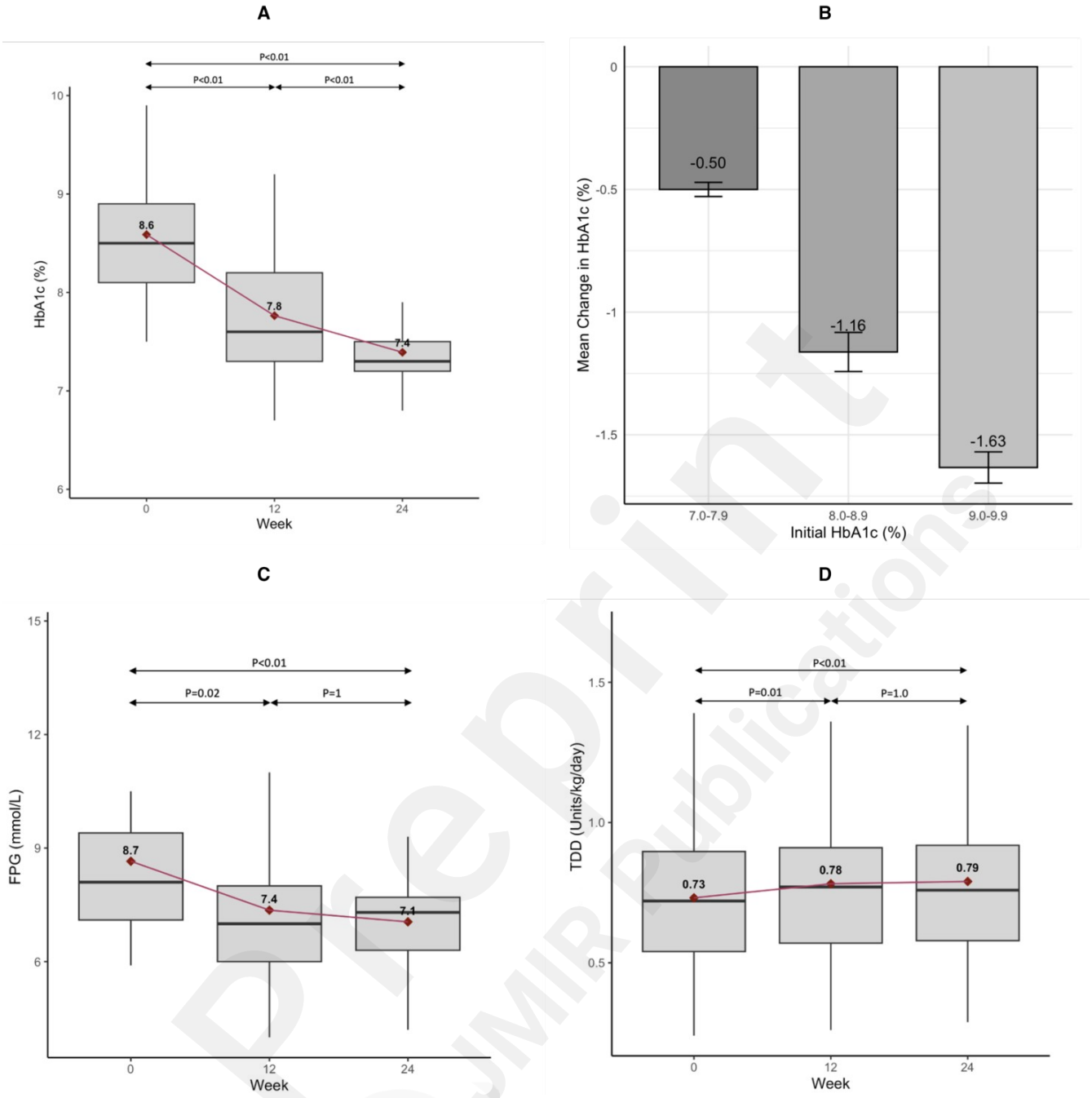


Figure 1. Change in (A) HbA1c (B) HbA1c stratified by baseline HbA1c (C) Fasting plasma glucose (D) Total daily dose of insulin (units/kg/day) over 24 weeks.

Hypoglycemia and adherence to self-monitoring of blood glucose

At baseline, 44.0% of participants reported at least 1 hypoglycemia episode in the preceding month. During our study, 48.0% of participants experienced at least one episode of hypoglycemia. In total, 24 episodes of hypoglycemia occurred in weeks 0-12, while 72 episodes occurred in weeks 13-24.

The hypoglycemia episodes were predominantly confined to level 1 (blood glucose 3.0 - 3.9 mmol/L), with 85 out of 96 episodes falling in this category (Figure 2). There were no level 3 hypoglycemia episodes reported during the study. Adherence to the prescribed SMBG frequency was 98.2% for weeks 0-12 and 96.5% for weeks 12-24.

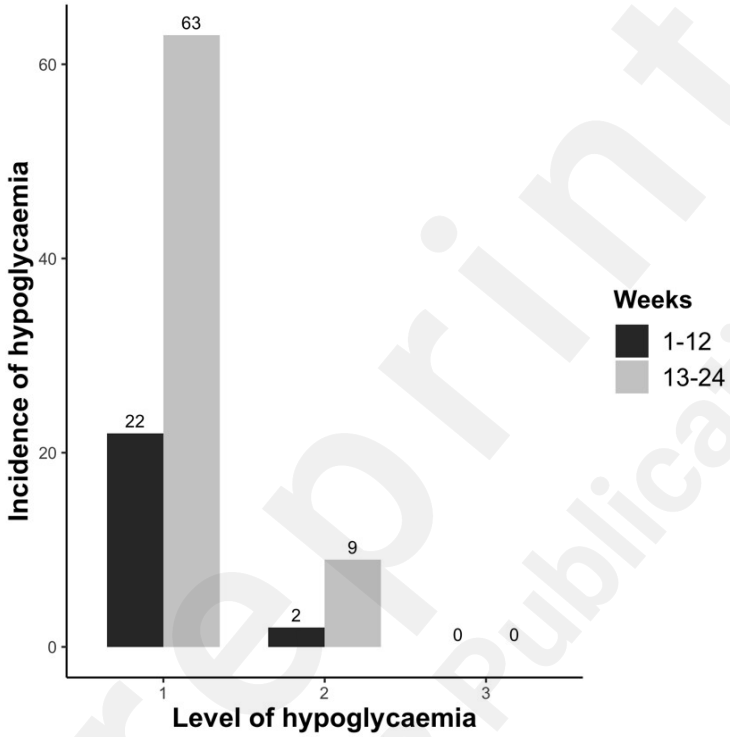


Figure 2. Incidence of hypoglycemia episodes per 12-week period, classified by level of hypoglycemia.

Discussion

The GEMINI-T2D study demonstrated that remote monitoring of SMBG data via a glucose management platform, coupled with algorithm-guided insulin titration, effectively improved

glycemic control in insulin-treated T2D subjects. To the best of our knowledge, this is the first study an integrated mobile phone-based solution in an Asian cohort with insulin-treated diabetes. The degree of HbA1c improvement in our study was comparable to studies on smartphone-based diabetes management platforms (15,22) and a larger trial on an automated insulin titration system(19).

Several key factors likely contributed to the improvement in glycemic control in our cohort. The ALRT system empowered participants to participate in structured SMBG, through a platform that allowed for ease of upload of blood glucose readings directly from glucometer. It also provided a convenient way to store, visualise and communicate the data with their physicians with timely feedback. The excellent adherence to the prescribed SMBG regimens in our study group was noteworthy, and higher than described in literature(23). The weekly review of data followed by insulin dose adjustments also tightened the feedback loop between patients and their physicians, enabling more prompt insulin dose adjustments than usually possible in a clinic setting. Physicians are also likely to have been empowered by the algorithm-guided insulin dose recommendations, eliminating the need for guesswork and providing a framework to base their therapeutic decisions upon. In addition, we also found that improvement in HbA1c in the first half of the study continued during the second half, demonstrating sustained benefits from the intervention. Interestingly, although the average increase in TDD of insulin was only 0.05 u/kg/day or 3 units/day for a 60 kg person, HbA1c decreased by 1.7%. Such a modest increase in insulin dose is unlikely to explain this degree of improvement in glycemia. Hence, we speculate that the “outsized” improvement in glycemia may be explained by a more optimal redistribution of insulin doses guided by a structured SMBG.

The fear of developing hypoglycemia (24) is a well-described barrier faced by physicians in the management of insulin therapy. It is likely that our intervention, through facilitating more frequent SMBG review and insulin dose titration than traditionally possible in the clinic setting, provided

physicians with greater confidence to make insulin dose adjustments with less hypoglycemia fear. Additionally, twice-daily SMBG and weekly feedback from physicians could have empowered the participants in their diabetes care. Enhanced patient engagement has consistently been identified(25,26) as a crucial component in managing chronic diseases such as diabetes, and our intervention encourages this.

With regard to the safety of our intervention, while an increase in mild hypoglycemia episodes occurred with tighter glycemic control, we found a low rate of level 2 hypoglycemia episodes with no level 3 severe hypoglycemia episodes. This safety signal was likely contributed by a few measures, such as patient education on hypoglycemia recognition and management at the time of enrolment, along with automated alerts with algorithm-guided insulin dosing suggestions to the treating physician via the ALRT application in event of hypoglycemia, prompting timely adjustment of insulin doses ahead of the scheduled weekly SMBG reviews. The safety profile aligns with a US-based randomised controlled trial(19) that showed similar hypoglycemia rates with automated insulin titration guidance compared to standard care.

This intervention holds promise for closing the titration gap for people on insulin therapy, offering dynamic and frequent adjustments based on data, while assisting busy physicians in delivering necessary care safely and conveniently. Moving forward, it is also fathomable that artificial intelligence may allow for yet larger scales of SMBG data management and analysis, and provide more personalised insulin dosing recommendations that take into account factors beyond glycemic trend such as diet, lifestyle, and general health.

Our study's limitations include a small sample size, potential selection bias from our strict recruitment process, and the lack of a control arm. Although the pre-post intervention design suggests effectiveness compared to prior standard care, a longer study with a larger sample size would be warranted to evaluate the long-term effectiveness and scalability of such an online platform

in diabetes care. A comparison arm with similar selection criteria of would also provide valuable insights on the performance of our intervention compared to usual care. Finally, understanding physicians' experiences from using this intervention in patient care may provide insights on how best this technology can be incorporated in clinical practice at a larger scale.

In conclusion, our study demonstrated that an internet-based glucose monitoring system with algorithm-guided dosing recommendations improved glycemic control in insulin-treated T2D subjects.

Declarations

No generative artificial intelligence (AI) or AI-assisted technologies were used in this study. This research was supported by A*STAR, Singapore under its Industry Alignment Pre-Positioning Fund (Grant No. H19/01/a0/023 – Diabetes Clinic of the Future) and ALR Technologies. There are no conflicts of interest to be reported.

Abbreviations

SMBG: Self-monitoring of blood glucose

FPG: Fasting plasma glucose

T2D: Type 2 Diabetes

References

1. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023 Jul 15;402(10397):203–34.

2. Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life. World J Diabetes. 2017 Apr 15;8(4):120–9.

3. Magliano DJ, Boyko EJ, IDF Diabetes Atlas 10th edition scientific committee. Idf Diabetes Atlas. Brussels: International Diabetes Federation; 2021.

4. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med [Internet]. 1993 Sep 30 [cited 2023 May 7];329(14). Available from: https://pubmed.ncbi.nlm.nih.gov/8366922/

5. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract [Internet]. 1995 May [cited 2023 May 7];28(2). Available from: https://pubmed.ncbi.nlm.nih.gov/7587918/

6. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med [Internet]. 2008 Oct 9 [cited 2023 May 7];359(15). Available from: https://pubmed.ncbi.nlm.nih.gov/18784090/

7. Mannucci E, Monami M, Dicembrini I, Piselli A, Porta M. Achieving HbA1c targets in clinical trials and in the real world: a systematic review and meta-analysis. J Endocrinol Invest [Internet]. 2014 May [cited 2023 May 10];37(5). Available from: https://pubmed.ncbi.nlm.nih.gov/24699860/

8. Benjamin EM. Self-Monitoring of Blood Glucose: The Basics. Clin Diabetes. 2002 Jan 1;20(1):45–7.

9. Karter AJ, Ackerson LM, Darbinian JA, D'Agostino RB, Ferrara A, Liu J, et al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes registry. Am J Med [Internet]. 2001 Jul [cited 2024 Mar 12];111(1). Available from: https://pubmed.ncbi.nlm.nih.gov/11448654/

10. Polonsky WH, Fisher L, Schikman CH, Hinnen DA, Parkin CG, Jelsovsky Z, et al. Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes. Diabetes Care. 2011 Feb 1;34(2):262–7.

11. Parkin CG, Buskirk A, Hinnen DA, Axel-Schweitzer M. Results that matter: Structured vs. unstructured self-monitoring of blood glucose in type 2 diabetes. Diabetes Res Clin Pract. 2012

Jul;97(1):6–15.

12. Lalić NM, Lalić K, Jotić A, Stanojević D, Živojinović D, Janićijević A, et al. The impact of structured self-monitoring of blood glucose combined with intensive education on HbA1c levels, hospitalizations, and quality-of-life parameters in insulin-treated patients with diabetes at primary care in Serbia: The multicenter SPA-EDU study. J Diabetes Sci Technol. 2017 Jul;11(4):746–52.

13. Chow N, Shearer D, Plaa JA, Pottinger B, Pawlowska M, White A, et al. Blood glucose self-monitoring and internet diabetes management on A1C outcomes in patients with type 2 diabetes. BMJ Open Diabetes Research & Care [Internet]. 2016 [cited 2023 May 10];4(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4853800/

14. Chircop J, Sheffield D, Kotera Y. Systematic Review of Self-Monitoring of Blood Glucose in Patients With Type 2 Diabetes. Nurs Res [Internet]. 2021 Nov [cited 2023 May 10];70(6). Available from: https://pubmed.ncbi.nlm.nih.gov/34292228/

15. Yu Y, Yan Q, Li H, Li H, Wang L, Wang H, et al. Effects of mobile phone application combined with or without self-monitoring of blood glucose on glycemic control in patients with diabetes: A randomized controlled trial. J Diabetes Investig. 2019 Sep;10(5):1365.

16. Cui M, Wu X, Mao J, Wang X, Nie M. T2DM Self-Management via Smartphone Applications: A Systematic Review and Meta-Analysis. PLoS One [Internet]. 2016 Nov 18 [cited 2023 May 10];11(11). Available from: https://pubmed.ncbi.nlm.nih.gov/27861583/

17. Katalenich B, Shi L, Liu S, Shao H, McDuffie R, Carpio G, et al. Evaluation of a Remote Monitoring System for Diabetes Control. Clin Ther [Internet]. 2015 Jun 1 [cited 2023 May 10];37(6). Available from: https://pubmed.ncbi.nlm.nih.gov/25869625/

18. Rama Chandran S, Tan HC, Chen Q, Lee PC, Gardner DS-L, Chin YA, et al. Telemonitoring

with a connected glucose meter improves glycemia among people with insulin-treated type 2 diabetes. J Diabetes Sci Technol. 2023 Jul;17(4):909–15.

19. Bergenstal RM, Johnson M, Passi R, Bhargava A, Young N, Kruger DF, et al. Automated insulin dosing guidance to optimise insulin management in patients with type 2 diabetes: a multicentre, randomised controlled trial. Lancet. 2019 Mar 3;393(10176):1138–48.

20. Kalra S, Balhara YPS, Sahay BK, Ganapathy B, Das AK. Why is premixed insulin the preferred insulin? Novel answers to a decade-old question. J Assoc Physicians India. 2013 Jan;61(1 Suppl):9–11.

21. Chinese Elderly Type 2 Diabetes Prevention and Treatment of Clinical Guidelines Writing Group, Geriatric Endocrinology and Metabolism Branch of Chinese Geriatric Society, Geriatric Endocrinology and Metabolism Branch of Chinese Geriatric Health Care Society, Geriatric Professional Committee of Beijing Medical Award Foundation, National Clinical Medical Research Center for Geriatric Diseases (PLA General Hospital). Clinical guidelines for prevention and treatment of type 2 diabetes mellitus in the elderly in China (2022 edition). Zhonghua Nei Ke Za Zhi. 2022 Jan 1;61(1):12–50.

22. Zhou W, Chen M, Yuan J, Sun Y. Welltang - A smart phone-based diabetes management application - Improves blood glucose control in Chinese people with diabetes. Diabetes Res Clin Pract [Internet]. 2016 Jun [cited 2024 Mar 12];116. Available from: https://pubmed.ncbi.nlm.nih.gov/27321324/

23. Hu ZD, Zhang KP, Huang Y, Zhu S. Compliance to self-monitoring of blood glucose among patients with type 2 diabetes mellitus and its influential factors: a real-world cross-sectional study based on the Tencent TDF-I blood glucose monitoring platform. mHealth [Internet]. 2017 Jun 27 [cited 2024 Mar 13];3. Available from: https://pubmed.ncbi.nlm.nih.gov/28736734/

24. Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. Diabetes Obes Metab. 2016 Apr;18(4):401–9.

25. Barello S, Graffigna G, Vegni E. Patient engagement as an emerging challenge for healthcare services: Mapping the literature. Nurs Res Pract. 2012;2012:1–7.

26. Forbat L, Cayless S, Knighting K, Cornwell J, Kearney N. Engaging patients in health care: An empirical study of the role of engagement on attitudes and action. Patient Educ Couns. 2009 Jan;74(1):84–90.

Appendix 1: Insulin dose titration algorithm

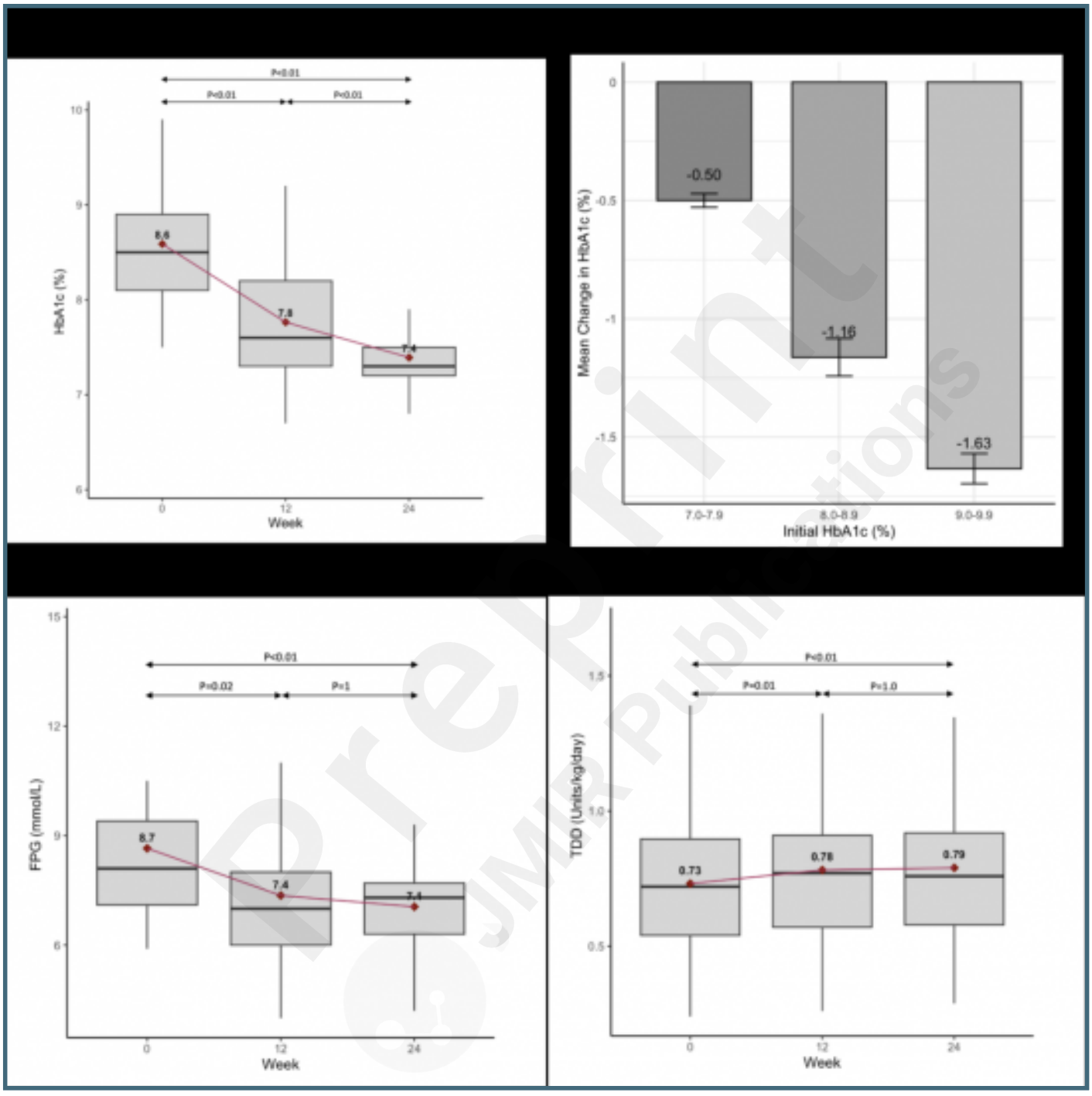
- Dose titration algorithm for twice daily premixed insulin
    - Capillary blood glucose (CBG) monitoring frequency:
        - At least twice a day and up to 4 times a day

        - Pre-breakfast and pre-dinner (optional: pre-lunch or bedtime)
        - Study subjects will upload CBG data from their glucometer to the ALRT system every seven (7) days using the study app
- CBG targets
    - Pre-prandial CBG: 4 – 8 mmol/L
- Dose titration algorithm
    - Premixed insulin dose titration will be based on pre-breakfast and pre-dinner CBG readings
    - Hyperglycemia: increase corresponding dose by 10-15% or 1-2 units (whichever is lower)
        - E.g. Pre-breakfast dose: increase by 10-15% or 1-2 units if the lowest pre-dinner CBG on the preceding 7 nights was >8.0 mmol/L
        - E.g. Pre-dinner dose: increase by 10-15% or 1-2 units if the lowest pre-breakfast CBG on the preceding 7 mornings was >8.0 mmol/L
    - Hypoglycemia: decrease corresponding dose by 10-20% or 2-4 units whichever is higher
        - If sleeping hypoglycemia occurs, reduce pre-dinner dose
        - If daytime hypoglycemia occurs between meals (post-breakfast, pre-lunch, post-lunch, pre-dinner), reduce pre-breakfast dose.
        - For safety reason, all study subjects will be counselled on hypoglycemia recognition and appropriate rescue measures.
        - All study subjects will be advised to upload CBG data from their glucometer to the study App after a hypoglycemic episode is confirmed via finger-prick testing.

Supplementary Files

Figures

Change in (A) HbA1c (B) HbA1c stratified by baseline HbA1c (C) Fasting plasma glucose (D) Total daily dose of insulin (units/kg/day) over 24 weeks.



Incidence of hypoglycemia episodes per 12-week period, classified by level of hypoglycemia.