



A Smartphone Application to Deliver a Treat-to-Target Insulin Titration Algorithm in Insulin-Naive Patients With Type 2 Diabetes: A Pilot Randomized Controlled Trial

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An emerging trend in telemedicine has been the development of health applications (apps) for smartphones. Apps focusing on insulin dose calculators are widely available, but the majority of them may contribute to incorrect dose recommendations that put patients at risk for overdose or hypoglycemic events (1). Published data evaluating the effectiveness of using an app in purposely guiding insulin dose titration among patients with type 2 diabetes mellitus (T2DM) is scarce.

In this pilot study, we developed a smartphone app called “Diabetes Pal” and investigated its feasibility to deliver an insulin titration algorithm in insulin-naive T2DM patients. A 24-week, randomized, open-label, parallel-group trial was conducted at the Singapore General Hospital between March 2013 and March 2015. The study was approved by the ethics board of the Singapore Health Services and registered with ClinicalTrials.gov (NCT01950676).

Insulin-naive T2DM patients with sub-optimal glycemic control ($HbA_{1c} \geq 7.5\%$ [58 mmol/mol]) despite use of two or more oral glucose-lowering drugs were recruited and randomized in a 1:1 ratio into the intervention and control

groups. The randomization list was computer generated with a fixed block size of four within each of five endocrinologists. Treatment allocation codes were concealed in sequentially numbered envelopes that were opened each time a patient was enrolled. Participants received a one-time individual educational session with a diabetes nurse educator. Participants were instructed to start with 10 units of insulin detemir at bedtime, self-monitor fasting blood glucose (FBG) daily, and self-titrate insulin every 3 days using a prescribed algorithm to reach a target FBG of 72–126 mg/dL (4.0–7.0 mmol/L). The algorithm was based on the mean FBG (mFBG) over 3 days; +4 when mFBG exceeded 180 mg/dL (10 mmol/L) and +2 when mFBG was 126–180 mg/dL (7.0–10.0 mmol/L). If FBG was $<72 \text{ mg/dL}$ ($<4.0 \text{ mmol/L}$), the dose was reduced by 4 units. Uptitration of insulin dose was continued until the patient reached the target FBG or the predetermined maximum insulin dose (0.6 units/kg) allowed for self-titration (i.e., algorithm end point), whichever occurred first. The maximum dose was based on a previous study where the mean (\pm SD) dose for patients on insulin detemir was 0.4 (\pm 0.2) units/kg to

achieve the target FBG of $\leq 108 \text{ mg/dL}$ ($\leq 6.0 \text{ mmol/L}$) (2). Patients were assessed at weeks 6, 12, and 24.

Patients in the intervention group ($n = 33$) entered FBG readings into the app daily; the app responded with a suggested insulin dose. Each patient’s maximum dose was preset and locked in the app as a safety feature. The app had a “hypoglycemia guide” tab containing text instructions on recognizing and managing hypoglycemia. “Diabetes Pal” had an additional safety feature: an administrative module where the research staff could remotely monitor glucose readings submitted and flag issues to the endocrinologists. In contrast, patients in the control group ($n = 33$) used paper logbooks and written instructions.

A total of 66 patients were enrolled: 22 were women; age (mean \pm SD) was 53.3 ± 7.4 years; duration of diabetes was 12 ± 8 years; BMI was $27.5 \pm 4.69 \text{ kg/m}^2$; and HbA_{1c} was $9.9 \pm 1.8\%$ ($85 \pm 19.7 \text{ mmol/mol}$). Baseline characteristics by group were not statistically different. The linear mixed-effects model (group and time as fixed effects; subject and doctor as random effects) revealed a trend toward a reduction in mean HbA_{1c} in both groups; there was

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no statistically significant difference between groups ($P = 0.88$) (Fig. 1A). Reductions from baseline were numerically greater in the intervention group at all three follow-ups (Fig. 1B); mean reduction of HbA_{1c} from baseline, 0.39% (95% CI -0.30, 1.07), was numerically greater in the intervention group than the control group with no significant difference between groups ($P = 0.26$).

Reductions in fasting plasma glucose were observed in both groups; the decrease was prominent from baseline to week 6 but less marked thereafter (Fig. 1C). Likewise, patients were titrated more rapidly in the first 6 weeks of the study. Daily basal insulin dose increased more steeply in the intervention group. At week 24, the mean insulin doses were 33 units and 28 units ($P = 0.08$) for the intervention and control groups, respectively; after correction for body weight, the corresponding mean values were

0.43 units/kg and 0.36 units/kg ($P = 0.03$). At week 24, 10.3% (3/29) and 10.0% (3/30) of the intervention and control groups, respectively, reached the maximum dose. The Kaplan-Meier plot revealed a trend toward a shorter median time-to-event (reaching the algorithm end point) in the intervention group (27 days, 95% CI 18, 45) versus the control group (39 days, 95% CI 24, 51) ($P = 0.08$) (Fig. 1D).

There were no episodes of severe hypoglycemia. Although the intervention group had a higher proportion of patients who experienced at least one confirmed hypoglycemic event (27.3%) than the control group (21.2%), no difference between groups was found ($P = 0.57$).

This pilot study demonstrated feasibility for the app to improve glucose control without significantly increasing hypoglycemia rate. The earlier time-to-event seen in the intervention group suggests

that patients had more timely adjustments of insulin dose as the group reached the algorithm end point more rapidly. We conjecture that the app was able to create an immediate feedback mechanism that has influenced self-efficacy, prompting patients to adhere to the app's instructions.

Limitations of the study include design issues with "Diabetes Pal": patients were unable to edit typographical errors in their FBG inputs, a field for actual injected dose was not available, and the app, being a web app (versus native app), was not usable offline. Moreover, individual educational sessions with a nurse were given only once for both groups, with the control group performing self-titration without any subsequent support (e.g., regular phone calls) commonly done in trials. However, similar to the intervention group, patients from the control group were seen at weeks 6 and 12 by their doctors and nurse educators,

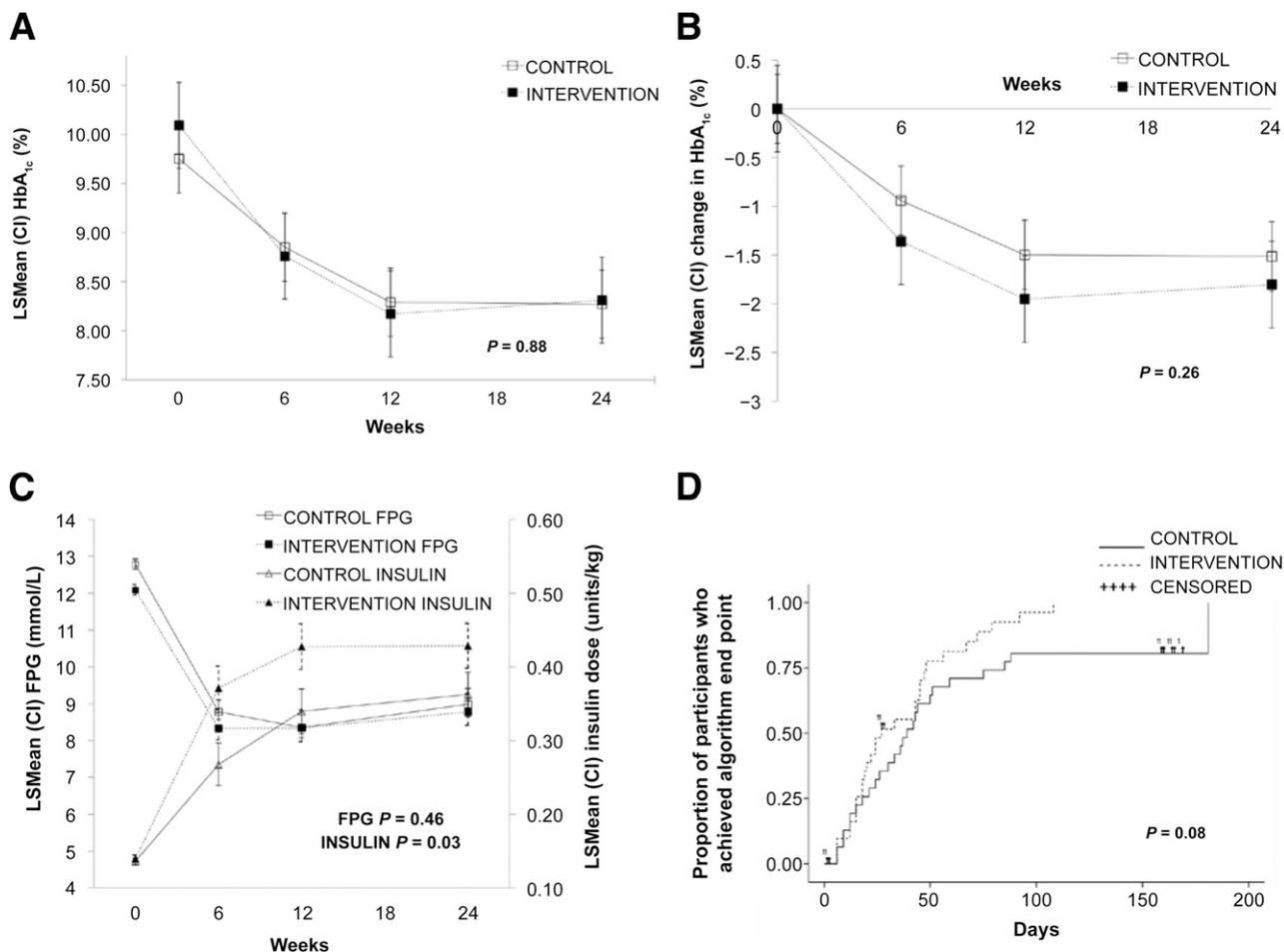


Figure 1—Clinical measures during treatment by visit time. A: Mean HbA_{1c}. B: Change in HbA_{1c} from baseline. C: Mean fasting plasma glucose (FPG) and mean insulin dose. D: Time-to-event (event is defined as reaching the algorithm end point, i.e., target blood glucose or maximum insulin dose, whichever occurred first). LS Mean, least squares mean.

which was usual care at our institution. Another limitation concerns the upper margin of the FBG target (<126 mg/dL), which was considerably higher than the usual target of <108 mg/dL. The higher FBG target was selected for safety considerations. This small-scale study showed statistically nonsignificant differences in the clinical outcomes between the two groups, which should be interpreted with caution.

Software improvements will be addressed in a planned update of the app. The lowest of three FBG readings (versus the mean) will be used as decision-making criterion to provide a greater safety margin. We also plan to develop a native app version of "Diabetes Pal" for patients to perform titration even without a network/wireless connection.

In conclusion, it is technically and clinically feasible to use an app for insulin self-titration in insulin-naive T2DM patients. While the results are promising, a larger

trial is recommended to fully understand the potential of the app for integration in diabetes-management workflow.

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of data. Y.K.D. and B.H. contributed to the study concept and design and reviewed/edited the manuscript. S.-Y.G., P.C.L., P.P.S.C., and E.T.L.H. were coinvestigators, acquired data, and reviewed/edited the manuscript. D.B.M. was the principal investigator and contributed to the study concept and design, trial execution, data interpretation, and critical revision of the manuscript. D.B.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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