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Efficacy of *Insulclock* in patients with poorly controlled type 1 diabetes mellitus: a pilot, randomized clinical trial

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ABSTRACT

Insulclock is an electronic device designed to improve treatment adherence and insulin injection tracking. This randomized, single-center, pilot study assessed the clinical impact of *Insulclock* on glycemic control and variability, treatment adherence and satisfaction in patients with uncontrolled Type 1 diabetes mellitus (T1DM). We also compared these outcomes between the Active and Masked groups (with or without receiving reminders and app alerts). Sixteen patients completed the study: ten in the Active group and six in the Masked group. Insulclock use was associated with a decrease in mean glucose (-27.0 mg/dL [1.5 mmol/L]; p = 0.013), glucose standard deviation (SD) (-14.4 mg/dL [0.8 mmol/L]; p = 0.003), and time above range (TAR) (-12.5%, p = 0.0026), and an increase in time in range (TIR) (+7%; p = 0.038) in the overall population. The use of app information and alerts in the Active group was associated with an increase in TIR (+8%; p = 0.026). We observed a -3.9 (p = 0.1352) and -5.4 (p = 0.032) reduction per month in the number of missed and mistimed insulin doses in the overall population, respectively. Most of the items of The Insulin Treatment Satisfaction Questionnaire (ITSQ) improved after four weeks of *Insulclock* use. This pilot study points out an improvement in glycemic levels, adherence and satisfaction in T1DM patients, supporting the development of clinical trials powered to confirm these effects.

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INTRODUCTION

Despite the recognized potential of intensive insulin therapy for controlling glycemic levels and delaying the onset of diabetes-associated complications,[1] many people with type 1 diabetes mellitus (T1DM) do not meet nor maintain glycemic targets.[2] Treatment compliance with the prescribed regimen and incorrect injection techniques are among the leading barriers to achieving optimal glycemic levels.[3,4]

Mobile Health (mHealth) technology is a tool with increasing popularity aiming to facilitate the self-management of chronic diseases including diabetes, comprising recent advancements such as pens with memory function or electronic pen caps.[7–9] Alongside with these interventions, health applications (apps) have been developed for data log and review or educational purposes.[10,11] However, to date, these devices and apps have been mainly intended to monitor disease outcomes without targeting the optimal performance of insulin injections.

Insulclock® is a small electronic device developed to facilitate the optimal administration of insulin. This device works as an add-on module of commercially available insulin pens and monitors the date, time and dose of injections, the type of insulin injected, the duration of injections and insulin temperature. The *Insulclock* app allows automatic data logging, report generation and reminder settings, among other functions. We recently described the main capabilities and tests carried out to optimize *Insulclock* performance.[12] In this pilot study, we present the clinical impact of *Insulclock* on glycemic indices, treatment compliance, and treatment satisfaction in patients with persistent poorly controlled T1DM.

METHODS

Study design

This single-center, randomized, prospective, open-label, pilot study was conducted at the General Hospital of Segovia, after classification by the Spanish Agency for Medicines and Health Products (AEMPS) and ethical approval by the Ethics Review Committee of the General Hospital of Segovia. The study was conducted in compliance with the ethical

principles of the Declaration of Helsinki. Each participant provided written informed consent before inclusion in the study.

The study was scheduled across five visits. At Visit 1 (screening, Week -1), patients started with masked *Insulclock* for a one-week run-in period. A patient diary was provided to record study variables. At Visit 2 (baseline, week 0), demographic and clinical information was collected, concomitant medications were registered, and patients completed the Insulin Treatment Satisfaction Questionnaire (ITSQ). Participants were randomized 1:1 to the Active *Insulclock* group or the Masked *Insulclock* group. At Visit 3 (week 1), the masked FreeStyle Libre Pro™ CGM device (professional use) was applied by a healthcare professional in the upper arm to all the participants. At Visit 4 (week 3), the FreeStyle Libre Pro was removed. At Visit 5 (end of study, week 4) participants completed the ITSQ (**Supplementary Fig. 1**).

Study population

We included patients aged 18-80 years with uncontrolled T1DM, defined as glycated hemoglobin (HbA_{1C}) levels ≥8% for at least one year, and/or variations ≥1% in HbA_{1C} within the previous two years and attending regular (≥4 per year) follow-up visits at the Endocrinology department. We excluded pregnant or breastfeeding women, individuals with a history of or current alcohol or drug abuse, acute infection, cognitive decline or dementia, or any medical condition that may compromise the use of the device or study participation.

Study outcomes

The primary aim of the study was to assess the effect of *Insulclock* on glycemic control and variability, treatment adherence, and treatment satisfaction. The secondary objective was to compare these outcomes between patients in the Active and Masked *Insulclock* groups.

Glycemic variability indices were monitored according to international recommendations[13,14] with the FreeStyle Libre Pro™ and included glucose standard deviation (SD), time in range (TIR), time above range (TAR), and time below range (TBR).

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A late meal bolus (mistimed) was considered when *Insulclock* detected the insulin injection ≥30 minutes after a glucose rise in the CGM and a missed dose when no injection was detected ≥2 hours after a glucose rise in the CGM. We used the Glucose Rate Increase Detector (GRID) algorithm to identify meal glucose excursions.[15]

Participants completed the ITSQ, which comprises 22 items scored on a 7-point Likert scale ranging from 1 (extremely satisfied) to 7 (extremely dissatisfied).[16]

Study devices

Participants self-administered rapid insulin with Humalog Kwikpen® pens coupled with *Insulclock* and according to routine clinical practice. By means of acoustic and visual alarms, participants received information for a correct injection technique or to prevent stacking insulin.

In the Active group, participants received acoustic and visual alarms and had access to the *Insulclock* app with integrated information regarding insulin doses, glucose levels and injection time reminders. In the Masked group, participants knew the dose, time and duration of injections, but they did not receive any reminder and were masked to the *Insulclock* app.

Participants wore the masked Freestyle Libre Pro (Abbott Diabetes Care, Witney, Oxon, UK) for 14 days, which automatically records glucose data every 15 minutes.

Statistical analyses

Continuous variables were described by the mean and standard deviation (SD), median, interquartile range (IQR) and extremes (Min, Max). Categorical variables were described by number and percentage. Comparisons between two independent groups were performed using the Student's *t*-test for unpaired data for continuous variables or the Chi-square test for categorical variables. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SAS software for Windows, version 9.2 (SAS Institute, Cary, SC, USA).

RESULTS

Among the 21 participants included, one dropped out in the Active group and four in the Masked group: one because of mobile phone incompatibility with the device and four because of patients' decision. Sixteen patients were analyzed: ten in the Active *Insulclock* group and six in the Masked *Insulclock* group. Mean age (SD) in the overall population was 40.1 (13.9) years, and 56.3% were men (**Table 1)**.

Glycemic control and treatment adherence

Mean glucose concentration decreased in the overall population, Active and Masked groups, with significant differences in the overall population (p = 0.013) (**Fig. 1A**).

TIR increased in both groups after 14 days, with significant differences in the overall population (+7%, p = 0.038) and in the Active *Insulclock* group (+8%, p = 0.026) (**Fig. 1B**). We observed a numerical increase in TBR in the overall population (+5.3%, p = 0.0826) (**Fig. 1C**). Significant differences were observed in the overall population for TAR (-12.5%, p = 0.0026) (**Fig. 1D**).

Mean SD significantly decreased in the overall population (-14.4 mg/dL [0.8 mmol/L]; p = 0.003) and in the Masked group (-18.5 mg/dL [1.0 mmol/L]; p = 0.037) (**Fig. 1E**).

No significant differences were observed in the reduction of mean HbA_{1C} for any comparison (**Fig. 1F**).

The number of missed and mistimed insulin doses decreased per month in the overall population by -3.9 (p = 0.135) and -5.4 (p = 0.032), respectively. (**Fig. 1G,H**).

Individual trends are depicted in **Supplementary Fig. 2**.

Treatment satisfaction

We observed that most of the items of the ITSQ improved after four weeks of *Insulclock* use. Significant differences were observed in the perception of insulin treatment

interference in work/school activities and in the item assessing the potential of current insulin treatment for avoiding severe hypoglycemic episodes (**Supplementary Fig. 3**).

DISCUSSION

This prospective, pilot study showed that the *Insulclock* device contributes to improving mean glucose and variability indices, adherence to insulin treatment, and treatment satisfaction in poorly controlled T1DM patients.

The use of *Insulclock* was associated with an overall improvement in glycemic control, although only some variables reached statistical significance. This could be expected in the context of a pilot study with a limited sample size, which makes it difficult to establish reliable conclusions. In our case, it could be also related to the chosen target population with significant adherence problems since, as previously shown, engagement with mHealth technologies is more difficult in non-adherent patients.[17] In spite of this, the significant improvement in TIR (+8%) in the Active group, and the decrease in mean glucose (-27.0 mg/dL), glucose variability (SD -14.4 mg/dL) and TAR (-12.5%, p = 0.0026) and the increase in TIR (+7%) in the overall population are of remarkable importance. Although glycemic indices were still not optimal at Visit 4[14,18] and differences did not reach statistical significance for some variables, they trended in the right direction with the use of *Insulclock*.

Previous studies assessing the effectiveness of mHealth technology have provided conflicting results.[19,20] The authors hypothesized that telemedicine might not be suitable for all patient populations, particularly for those with persistent non-compliance issues.[21] Therefore, the improvements observed in our study in patients with persistent poorly controlled glycemic levels seem promising.

In line with the improvement observed in glycemic indices, the mean number of missed and mistimed doses was reduced by -3.9 and -5.4 per month, respectively. This reduction is particularly important, since a previous study showed that two missed mealtime injections per week correlated with a 0.5% increase in HbA_{1C} levels.[22] Although omissions and late injections were still high at Visit 4, the reduction observed may represent an important achievement with a positive impact on glycemic control in this complex

population. These results agree with recent data showing a decrease from 25% to 14% in missed bolus dose injections after six months of treatment with a smart insulin pen.[23]

Individual trends revealed dramatic improvements in specific patients in the Active *Insulclock* group. Understanding what motivated these patients to change compliance habits would require further investigation. It is worth mentioning that the patient with the greatest glucose improvement during the study period was the only one using a tutor from the *Insulclock* app. Although we cannot obtain reliable conclusions from a single patient, it would be interesting to study the effect of reinforcing this role.

In agreement with the results observed for glycemic variability, ITSQ items related to hypoglycemia control showed the most considerable improvements. However, only two items reached statistical significance, which could indicate that achieving substantial changes in quality of life requires longer time of follow-up and more pronounced clinical improvements.

This is the first clinical study assessing the effect of an insulin pen cap on clinical outcomes, treatment adherence and satisfaction. One of the main strengths is that it targeted patients with persistent uncontrolled glycemic levels, a particularly vulnerable population with a high risk for complications.

The main limitations of this study are the reduced sample size and follow-up time, as usual in pilot studies. In addition, we observed a considerable drop-out rate (23.8%), which could be explained considering the particularly challenging population analyzed.

In conclusion, this pilot study points out an improvement in glycemic levels, adherence and quality of life in T1DM patients, supporting the development of future clinical trials to confirm such clinical benefit.

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AUTHOR DISCLOSURE STATEMENT

Fernando Gómez-Peralta has taken part in advisory panels for Sanofi and Novo Nordisk; has received research support from Sanofi, Novo Nordisk, Boehringer Ingelheim Pharmaceuticals and Lilly; and has acted as a speaker for Sanofi, Novo Nordisk, Boehringer Ingelheim Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Co. and Lilly. Cristina Abreu has received research support from Sanofi, Novo Nordisk, Boehringer Ingelheim Pharmaceuticals and Lilly and has acted as a speaker for Sanofi, Novo Nordisk, Boehringer Ingelheim Pharmaceuticals, AstraZeneca Pharmaceuticals LP and Bristol- Myers Squibb Co. Sara Gómez-Rodriguez, Margarita Cruz-Bravo, Cristina María-Sanchez and Gema Poza have nothing to disclose. Luis Ruiz is an Insulcloud S.L. employee.

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TABLES

Table 1. Demographic and clinic characteristics of patients at baseline.

	Total	**Active Insulclock**	**Masked Insulclock**	***P*-value**
Age (years)	40.1 (13.9)	43.1 (13.8)	35.2 (13.8)	0.285
Sex (male), n (%)	9 (56.3%)	5 (50.0%)	4 (66.7%)	0.515
Duration of diabetes	20.4 (11.9)	20.9 (12.5)	19.5 (11.9)	0.828
Weight (kg)	69.4 (10.6)	65.2 (9.5)	75.1 (10.1)	0.085
BMI (kg/m^2)	24.8 (3.9)	23.2 (3.0)	27.0 (4.2)	0.070
Microvascular				
Retinopathy	6 (37.5)	4 (40.0)	2 (33.3)	
Nephropathy	2 (12.5)	2 (20.0)	0 (0)	
Neuropathy	5 (31.3)	3 (30.0)	2 (33.3)	
SBP (mmHg)	121.9 (18.4)	118.0 (8.3)	126.8 (27.5)	0.515
DBP (mmHg)	75.0 (10.3)	72.4 (9.7)	78.3 (11.5)	0.434
Insulin (IU/kg)				
Long-acting	0.39 (0.21)	0.31 (0.09)	0.50 (0.27)	
Rapid-acting	0.41 (0.22)	0.34 (0.13)	0.50 (0.27)	

Data are expressed as mean (SD), except for sex and microvascular complications (%).

BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPM, beats per minute; IU, international units.

Statistical significance between groups was determined using either the Student's t-test or the Chi-square test for continuous or categorical variables, respectively.

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FIGURE LEGENDS

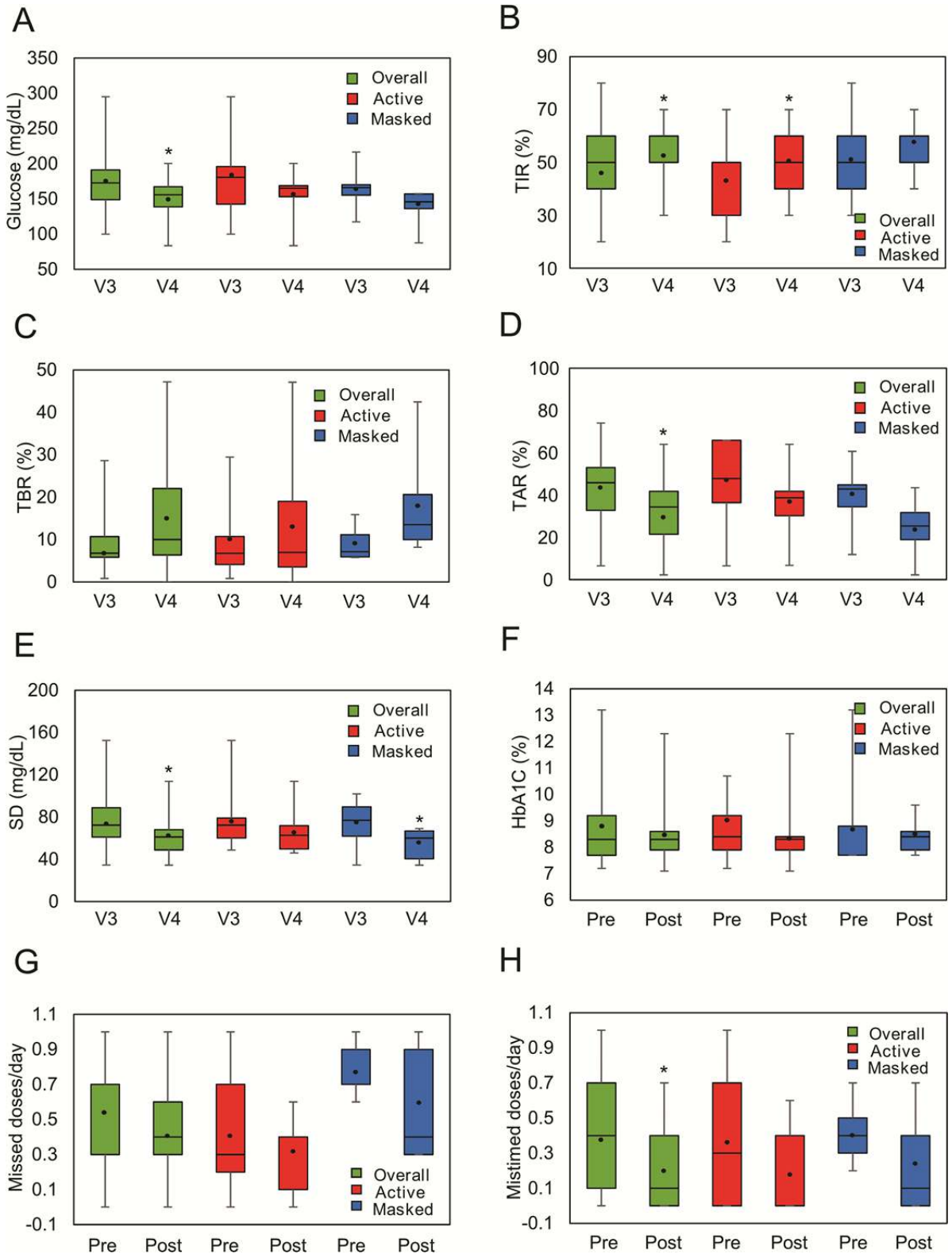

FIG. 1. Effect of *Insulclock* on glycemic control, variability and treatment adherence. The box-plots show median, Q1, Q3, Min and Max values for (A) glucose, (B) time in range

(TIR), (C) time below range (TBR), (D) time above range (TAR) and (E) standard deviation (SD) at Visit 3 (V3) and Visit 4 (V4), and (F) $HbA1_C$, (G) missed and (H) mistimed insulin doses at baseline (pre) and Visit 5 (post). Black dots indicate the mean.* indicates $p < 0.05$ from baseline (Student's t-test).

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This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

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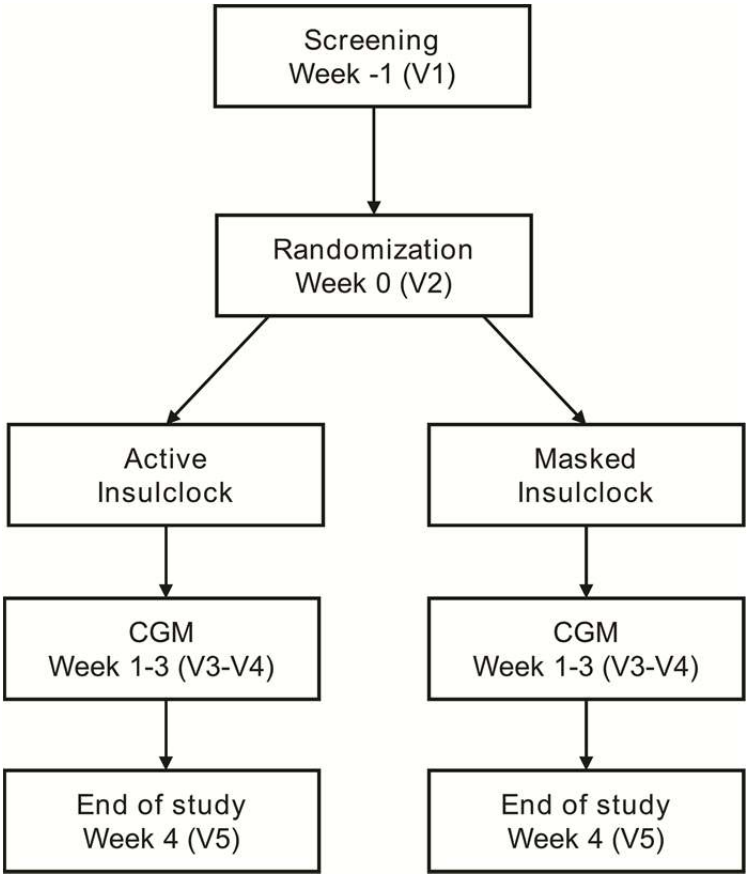

Supplementary FIG. 1. Flowchart showing the study design.

CGM, continuous glucose monitoring.

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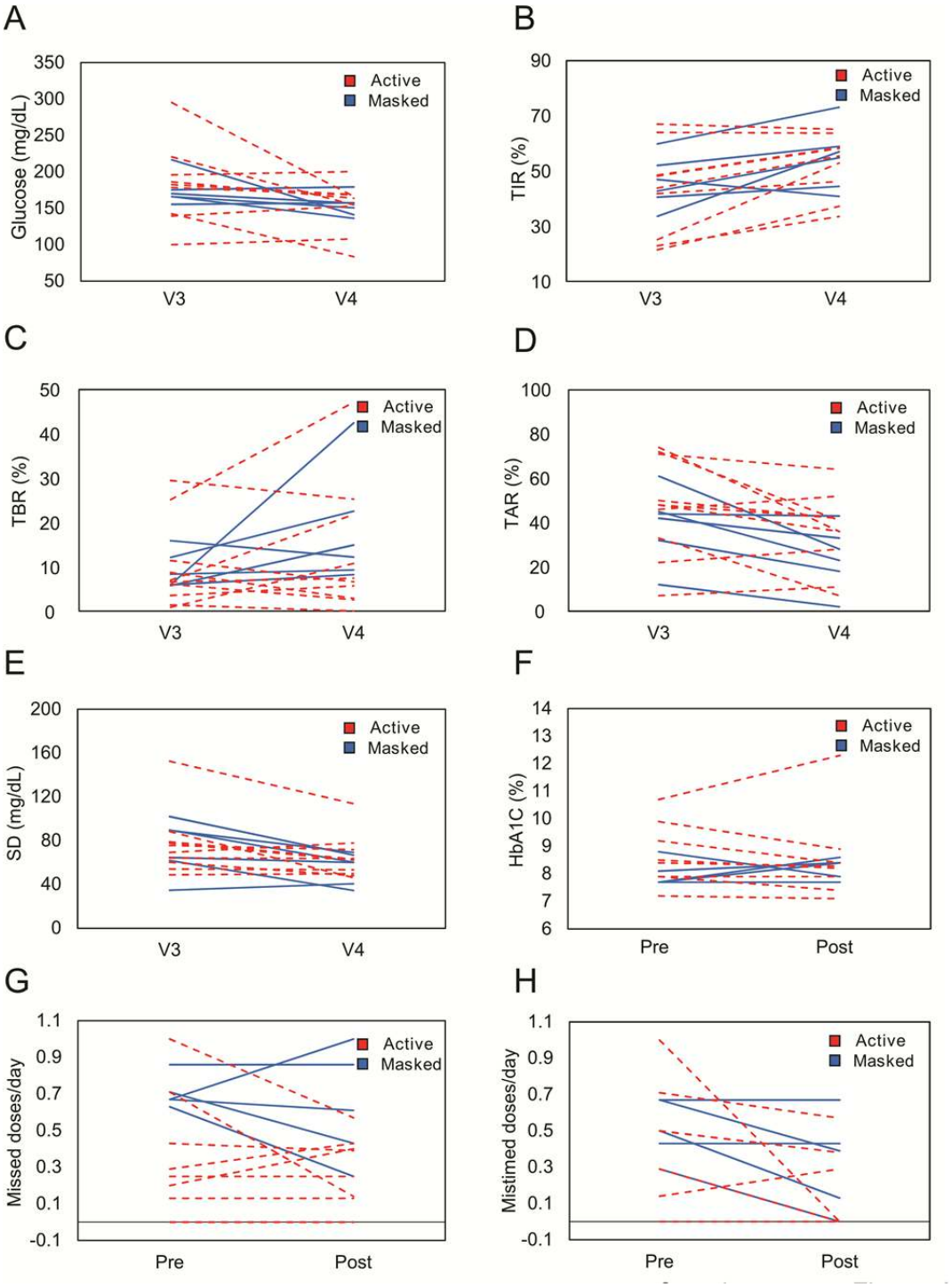
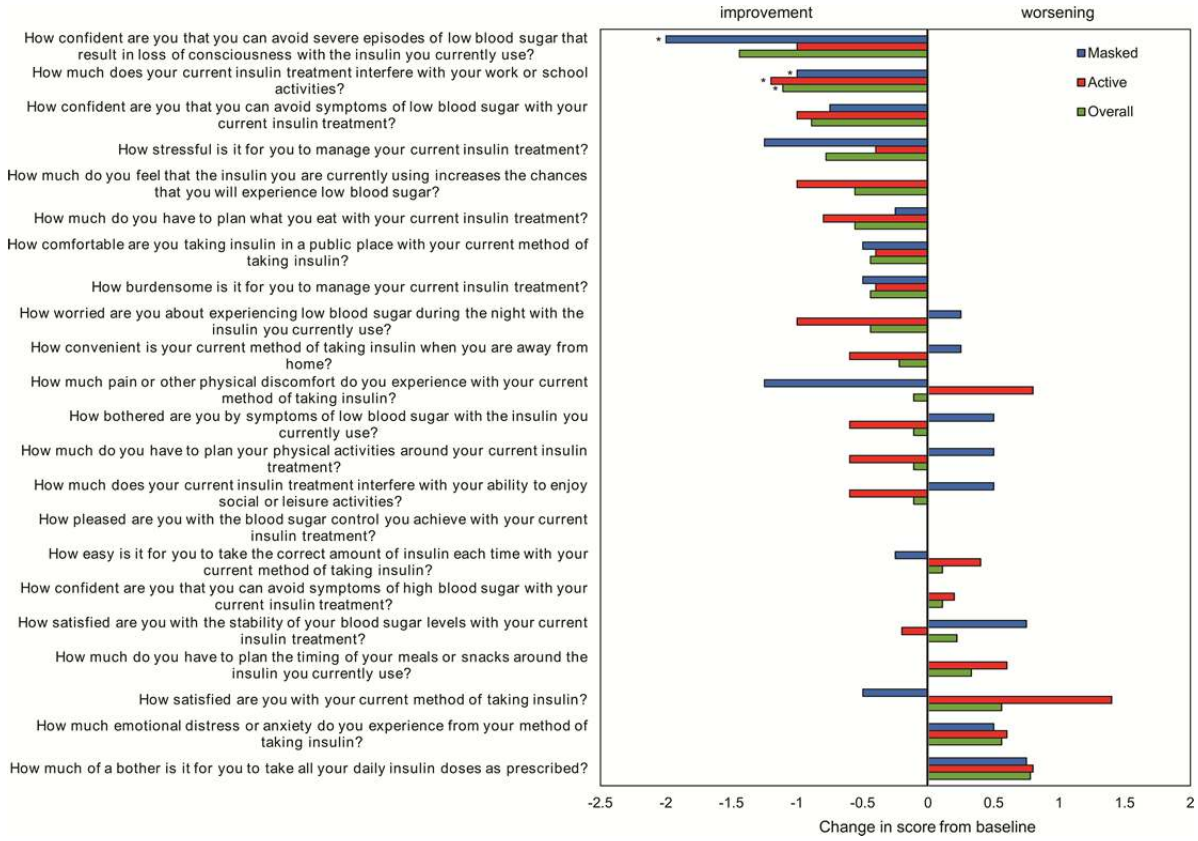


Supplementary FIG. 2. Effect of *Insulclock* on individual trends. Line graphs show individual trends for (A) glucose, (B) time in range (TIR), (C) time below range (TBR), (D) time above range (TAR) and (E) standard deviation (SD) at Visit 3 (V3) and Visit 4 (V4), and (F) $HbA1_C$, (G) missed and (H) mistimed insulin doses at baseline (pre) and Visit 5 (post).



Supplementary FIG. 3. Effect of *Insulclock* on treatment satisfaction. The bar graphs show the change in mean scores for each item of The Insulin Treatment Satisfaction Questionnaire (ITSQ) from baseline to Visit 5. * indicates $p < 0.05$ (Student's t-test).

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