HbA1c Reduction with Digital Health Devices in Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials

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INTRODUCTION

- Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by chronic hyperglycemia due to impaired insulin production and secretion.
- As of 2021, 537 million adults are living with diabetes, and this number is projected to increase to 783 million by 2045.[1]
- Many patients struggle to achieve glycemic control, putting them at risk of microvascular (e.g., retinopathy, nephropathy) and macrovascular complications (e.g., coronary heart disease, cardiomyopathy).[2]
- Glucose monitoring devices, such as self-measured blood glucose (SMBG) and continuous glucose monitoring (CGM), can help patients to achieve and maintain glycemic control.[2]
- In addition, evidence shows that patients need assistance and coaching for building awareness of their daily health-related behaviors.[3] This helps in bridging the gap between glucose awareness and behavioral change.

OBJECTIVE

To compare the efficacy of digital T2DM interventions, defined as SMBG or CGM combined with a coaching component, in reducing HbA1c compared to usual care.

METHODS

Systematic Literature Review

- A systematic review was conducted using standard methodologies from Cochrane. Details have been previously described,[4] briefly:
  - MEDLINE®, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from database inception to April 5, 2022. Searches were limited to the English language.
  - Included articles were comparative observational and clinical trials on adults (>18 years old) with T2DM who received a digital intervention (containing both human coaching and digital glucose monitoring components) or usual care.
  - The primary outcome of interest was change in HbA1c.

Meta-Analysis

- Randomized controlled trials (RCTs) were eligible for the meta-analysis (MA).
- If a study had more than one control or intervention arm, then the arms were pooled by taking the sample size-weighted average of mean change in HbA1c, and if a study reported HbA1c at more than one timepoint then the final measurement was used.
- MAs were conducted using the metafor package (v3.0-2)[5] for R (v4.1.1),[6] using the random effects model (restricted maximum likelihood method).
- The primary analysis was restricted to studies that reported lab measured HbA1c.
- In a secondary analysis, meta-regression was performed with intensity of coaching in the digital intervention (high, medium, or low) as a categorical covariate. Intensity was defined as follows:
  - **High intensity:** Patient data is uploaded automatically and regularly. Communication with dedicated staff occurs at least once per week, with personalized encouragement/goal-setting and education about the disease, behavioral strategies, and psychological coping.
  - **Medium intensity:** Patient data is uploaded manually. Communication is initiated ad-hoc by staff and includes non-behavioral advice and education on the disease and the digital device.
  - **Low-intensity:** Data sharing is limited. Communication is delayed, feedback is generic, and there is no education component.
- We also conducted sensitivity analyses (1) including studies which did not measure HbA1c in a lab, (2) excluding studies which were judged to have a high risk of bias according to the Cochrane risk of bias tool,[4] and (3) excluding studies which used CGM.
- We evaluated heterogeneity using tau, the Cochran's Q test, and the I^2 statistic.

RESULTS

Study Selection

- Of 6,288 records screened, 23 RCTs were eligible for the MA (See **Figure 1** for the PRISMA diagram and **Table 1** for list of included studies).
- Across the included studies, the median age was 55.6 years (range: 47.2 to 63.1 years), and the median proportion of female patients was 50.7% (29.0% to 72.6%). At baseline, the median HbA1c was 8.5% (7.0% to 10.9%), and the median BMI was 31.5 kg/m^2 (24.0 to 40.8 kg/m^2).
- Three studies did not measure HbA1c in a lab, and so were excluded from the primary analysis but included in a sensitivity analysis: Guo (2021), Pimazoni-Netto (2011), and Welch (2015).[7-9]
- Two studies used CGM and were excluded in a sensitivity analysis: Allen (2011) and Lee (2019).[10,11]
- Four studies were judged high risk of bias and were excluded in a sensitivity analysis: Allen (2011), Azelton (2021), and Kim (2003) because they did not employ double-blinding,[10,12,13] and Jeong (2018) because it did not adequately report how HbA1c was collected.[14]

Meta-Analysis

Primary Analysis

- The primary analysis estimated -0.31% (95% confidence interval [CI]: -0.45, -0.16; $p = 2.38 \times 10^{-5}$) greater reduction with a digital intervention compared to usual care (**Figure 2**).
- Heterogeneity was statistically significant ($Q = 57.64$, df = 19, $p = 9.09 \times 10^{-6}$), with an estimated τ of 0.21 (95% CI: 0.12, 0.61) and I^2 of 67.54% (95% CI: 41.2, 94.48).

Meta-Regression Analysis

- When digital intervention intensity was included as a categorical covariate, the following meta-regression equation was estimated:

$$\widehat{\mathrm{MD}} = -0.43 + 0.18(\text{intensity=low}) + 0.20(\text{intensity=medium}),$$

  where $\widehat{\mathrm{MD}}$ is the predicted mean difference (MD) of change in HbA1c, "intensity=low" is 1 if the digital intervention being predicted is low intensity and 0 otherwise, and "intensity=medium" is 1 if the digital intervention being predicted is medium intensity and 0 otherwise.
- This predicts an MD of -0.43% (95% CI: -0.74, -0.11; $p = 0.0084$) for high intensity interventions, -0.22% (95% CI: -0.38, -0.06; $p = 0.0055$) for medium intensity interventions, and -0.25% (95% CI: -0.57, 0.07; $p = 0.13$) for low intensity interventions (**Figure 1**).
- The low ($p = 0.44$) and medium ($p = 0.26$) intensity coefficients were not statistically significant.
- Heterogeneity was statistically significant ($Q = 43.60$, df = 19, $p = 0.000393$), with an estimated τ of 0.18 (95% CI: 0.11, 0.70) and I^2 of 54.45% (95% CI: 32.71, 94.90).

Figure 1: PRISMA Diagram

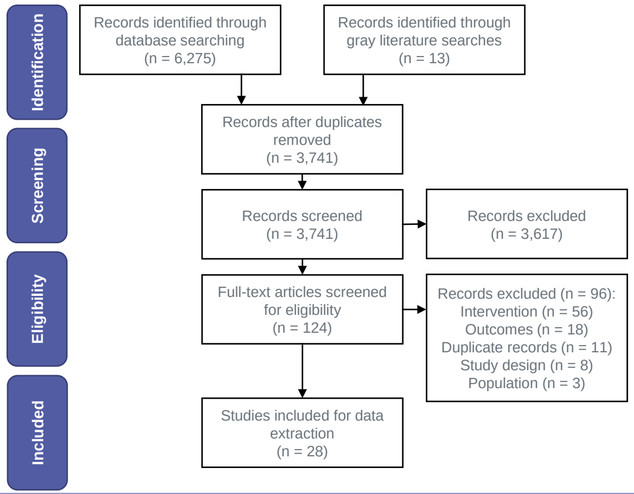
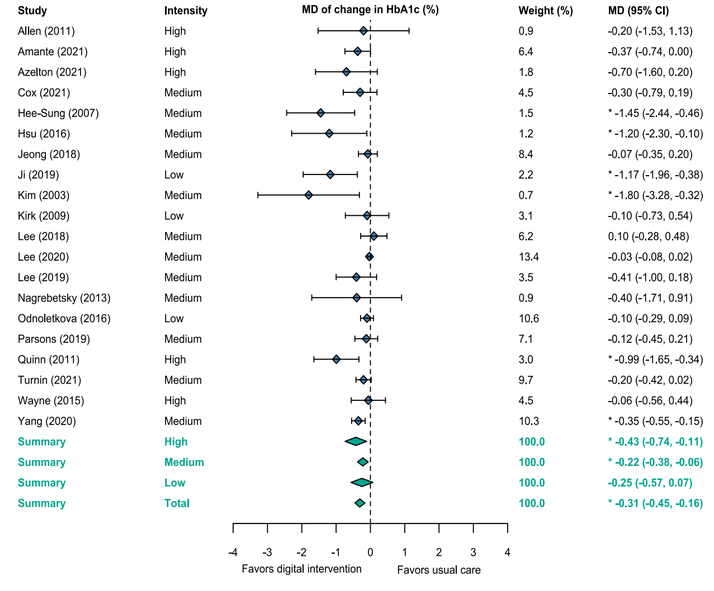


Table 1: Included Studies

Study	Continent	Sample size	Follow-up (months)
Allen (2011)[10]	North America	29	3
Amante (2021)[15]	North America	119	12
Azelton (2021)[12]	North America	45	3
Cox (2021)[16]	North America	172	13
Guo (2021)[7]	Asia	68	1
Hee-Sung (2007)[17]	Asia	60	3
Hsu (2016)[18]	North America	40	3
Jeong (2018)[14]	Asia	338	6
Ji (2019)[19]	Asia	100	6
Kim (2003)[13]	Asia	50	3
Kirk (2009)[20]	Europe	134	12
Lee (2018)[21]	Asia	148	12
Lee (2020)[22]	Asia	240	12
Lee (2019)[11]	Asia	63	6
Nagrebetsky (2013)[23]	Europe	17	6
Odnoletkova (2016)[24]	Europe	574	18
Parsons (2019)[25]	Europe	446	12
Pimazoni-Netto (2011)[8]	North America	63	3
Quinn (2011)[26]	North America	213	12
Turnin (2021[27]	Europe	282	12
Wayne (2015)[28]	North America	138	6
Welch (2015)[9]	North America	399	6
Yang (2020)[29]	Asia	247	3

Note: Follow-up is in months. N/R – Not Reported.

Figure 2: Primary and Meta-Regression Analysis Results



Note: The "Total" summary row is from the primary analysis, and the "High", "Medium", and "Low" summary rows are from the meta-regression analysis. * – A statistically significant comparison ($p \leq 0.05$). CI – Confidence Interval, MD – Mean Difference.

RESULTS (Continued)

Sensitivity Analyses

- When studies with non-lab measured HbA1c were included, the resulting MD was more favorable to the digital intervention (MD: -0.40%; 0.95% CI: -0.56, -0.24; $p = 7.64 \times 10^{-7}$).
- When CGM studies (MD: -0.31%; 0.95% CI: -0.47, -0.16; $p = 6.16 \times 10^{-5}$) and studies with high risk of bias (MD: -0.31%; 0.95% CI: -0.46, -0.15; $p = 8.41 \times 10^{-5}$) were excluded, the point estimate was the same as the primary analysis, but the CI was slightly wider.

CONCLUSIONS

- **This meta-analysis found significantly greater HbA1c reduction in T2DM patients on digital interventions compared to usual care.**
  - Including studies with non-lab measured HbA1c led to a more favorable result for the digital intervention.
  - Excluding CGM studies or those with high risk of bias led to similar results as compared with the primary analysis.
- Results support digital interventions as an effective addition to usual care.
- The association between digital intervention intensity and HbA1c reduction was not statistically significant, and further research is warranted to understand optimal intensity for digital interventions.

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DISCLOSURES

This study was funded by Sanofi and conducted by Evidinno Outcomes Research Inc. Felix Lee, Edward Han-Burgess, and Adee Kennedy are employees of Sanofi and may hold shares/stock in Sanofi. Paul Serafini, Mir-Masoud Pourrahmat, and Boris Breznen report employment with Evidinno Outcomes Research Inc. Authors report no other conflicts of interest.

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