Role of Continuous Glucose Monitoring in Non-Insulin-Requiring Type 2 Diabetes

Ronnie Aronson, MD, FRCPC

About the Author

Ronnie Aronson is an Endocrinologist and the founder of LMC Diabetes and Endocrinology (LMC), a practice groups of more than 60 Endocrinologists, providing care to over 45,000 people with diabetes, supported by diabetes educators, pharmacists, chiropodists and optometrists. Dr. Aronson's own research focus has centred on individuals who struggle to achieve optimal diabetes health outcomes. He has led projects that have defined their barriers, validated new devices, and developed novel tools and strategies to overcome these barriers. He has served as Principal Investigator in over 300 clinical trials in diabetes and its complications.

Affiliations: Chief Medical Officer, LMC Diabetes & Endocrinology

Introduction

Effective management of diabetes has always been contingent on our awareness of patients' glucose levels. There has been a slow evolution in glucose-measurement technology over the last century. Benedict's copper reagent test for urinary glucose became available in 1908, followed by the colorimetric technology of Dextrostix, patented in 1963 by Miles Laboratories Inc., and the electrochemical process of ExacTech introduced by Medisense in 1987, as examples.

Continuous glucose monitoring (CGM) systems have evolved more rapidly with a well-established evidence base documenting their value in individuals using insulin. Their potential impact among individuals with type 2 diabetes (T2D) who are not using insulin has been the subject of a series of studies in the past few years, culminating most recently in a key Canadian randomized controlled trial, the IMMEDIATE study.[1]

Reviewing first the major trials that used real-time CGM (rtCGM), we find a number of prospective trials that had initially explored mixed populations with T2D, where a significant proportion were non-insulin requiring. A Korean study of four hospital-based clinics, reported on 57 individuals with T2D, most not using insulin therapy (n=48).[2] Participants were randomized to a monthly series of 3-day Guardian RT wears, in comparison to continued self-monitor blood glucose (SMBG) alone, and showed a greater hemoglobin A1c (HbA1c) reduction of 0.7% (p=0.004) over the 3-month trial.

Also in 2008, a smaller pilot study (n=25) by a group of French hospital-based clinics found a similar trend of HbA1c reduction (0.3%, not statistically significant), following a single 48-hour wear of the GlucoDay CGM combined with physician counseling.[3]

In 2011, the Walter Reed Health Care System was the setting for a randomized controlled trial (RCT) comparing an early-generation Dexcom product, the SEVEN, to SMBG alone.[4] Among 100

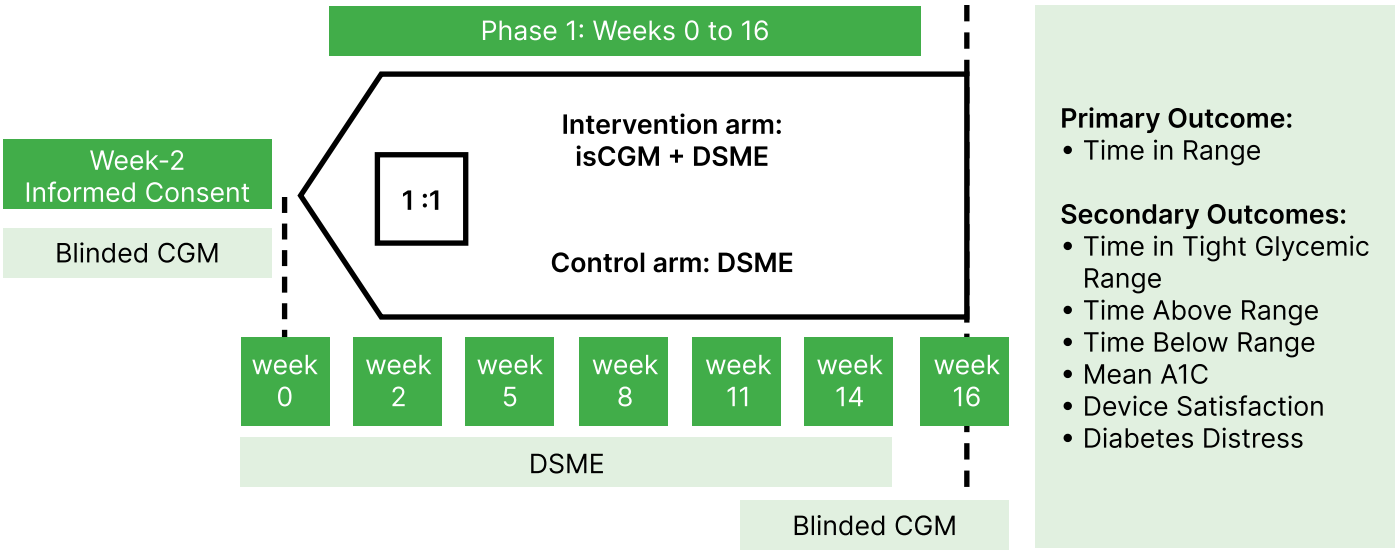


Figure 1: IMMEDIATE Study Design; courtesy of Ronnie Aronson, MD, FRCPC
Abbr: isCGM: intermittently scanned continuous glucose monitoring;
DSME: diabetes self-management education

randomized individuals with T2D, two-thirds were not insulin-requiring. Participants that wore CGM intermittently for four cycles showed a greater HbA1c reduction of 0.5% vs those continuing SMBG.

Most recently, the International Diabetes Center in Minnesota specifically compared CGM to frequent and structured SMBG[5] and found a trend to benefit with a non-significant 0.3% HbA1c difference between groups. The trial was comprised of subjects with uncontrolled T2D (A1c ≥7.0%) between the ages of 18 and 75 and who were being treated with one of the following three common therapies: **1.** sulfonylurea (SU) ± metformin (SU group), **2.** incretin (DPP4 inhibitor or GLP-1 agonist) ± metformin (incretin group), or **3.** insulin± metformin (insulin group).

The impact of rtCGM among individuals who were exclusively not insulin-requiring has been studied in only three trials, each using an episodic-wear approach.

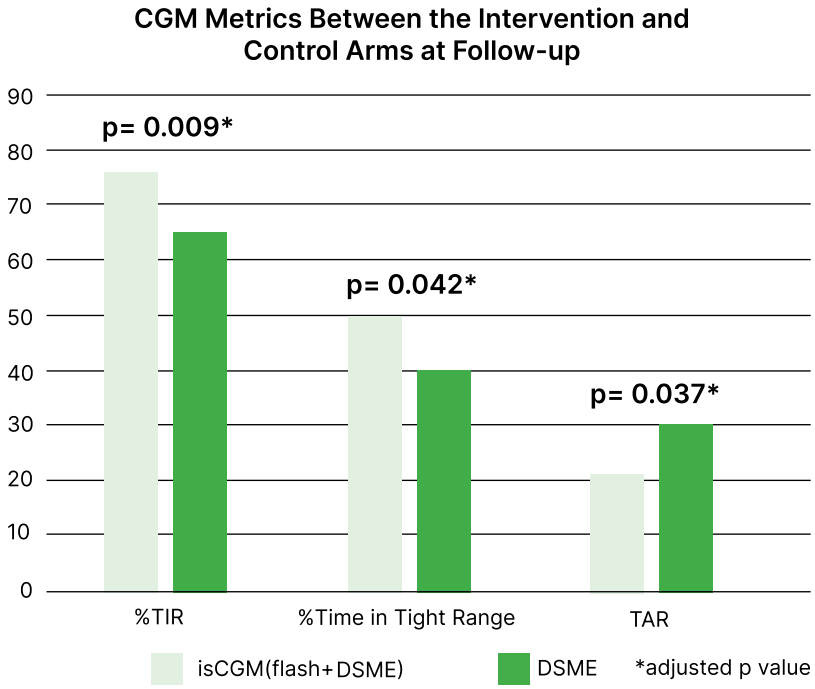
The Glycemic Excursion Management (GEM) initiative at the University of Virginia used the Dexcom G4 in one of its studies, along with considerable individualized specialist counselling.[6] In a randomized, controlled study of only 30 individuals, researchers found that using a Dexcom G4 along with extensive physician interaction was associated with a greater HbA1c reduction by 1.1% vs continued self-monitoring. Two subsequent trials used a similar design of episodic CGM versus SMBG. The COMMITED study found a non-significant trend to HbA1c reduction (0.2%) vs continued SMBG using the Dexcom G6 in three 10-day cycles.[7] A Korean study found a significantly larger HbA1c reduction of 0.7% ($p < 0.02$) using the Guardian Connect in three 7-day cycles.[8]

As with real-time CGM, intermittent-scanned CGM technology (isCGM) has been studied in both mixed populations with T2D and those not on insulin. Among mixed-population studies, the large, recently reported PDF trial in Seoul, South Korea, randomized 126 participants with T2D, of which 72.5% did not use insulin, to Freestyle Libre vs continued SMBG.[9] At 12 weeks, the researchers found a between-group difference in HbA1c of 0.5% in favour of CGM ($p<0.001$).

Studies of isCGM specifically in non-insulin-using individuals include several retrospective studies and real-world-evidence reports, all of which consistently show a benefit of CGM use on glycemic control. Three prospective trials in this population have also been published. In Japan, a group of five hospital-based practices randomized 100 individuals to 12 weeks of isCGM – in this case, Freestyle Libre – versus continued SMBG and found an HbA1c reduction of 0.3% versus that of the SMBG group that reached statistical significance at the end of the pre-planned 24-week extended period of observation.[10]

An uncontrolled, prospective pilot study led by William Polonsky in San Diego involving 35 non-insulin-requiring individuals with T2D showed an increase in time in range (TIR) of 19% (55–74%) over 3 months using isCGM with Freestyle Libre[11] with extensive personalized diabetes education.

To more definitively assess the efficacy of isCGM in adults with T2D using non-insulin therapies, a group of Canadian community-based diabetes clinics initiated the IMMEDIATE study.[12] The trial,



As compared to the DSME arm, at 16 weeks of follow-up the intervention arm had:

- Significantly greater mean TIR by 9.9% (2.4 hours)
- Significantly greater time in the tight glycaemic range by 8.5% (2.0 hours)
- Significantly less TAR by 8.1% (1.9 hours)

Figure 2: IMMEDIATE Study Results; courtesy of Ronnie Aronson, MD, FRCPC
Abbr: TIR: time in range; TAR; time above range

across six sites, used a randomized, controlled, open-label design. Participants were randomized to either 16 weeks of isCGM (Freestyle Libre) or continued daily SMBG, in a 1:1 ratio, stratified by use of glucagon-like peptide-1 receptor agonists (GLP-1 RA) **(Figure 1)**.

Outcome data in IMMEDIATE were based on 2-week periods of blinded CGM-wear at baseline and at 16 weeks. Because of potential confounding by individualized diabetes self-management education (DSME) on outcomes, we sought to control for that variable by providing a structured curriculum to all participants, with equal time provided to each group. Inclusion criteria were adults with T2D of more than 6 months duration and an HbA1c >7.5% who were taking more than one non-insulin antihyperglycemic therapy. All participants had no prior CGM use. TIR was the primary outcome, adjusted for baseline glycemic control. Secondary outcomes included HbA1c and several other CGM outcomes, such as time in tight glycemic range.

The study enrolled 116 participants, of which 63.8% were male, with a mean age of 58.4 years, with a BMI of 29.9 kg/m^2 and having a duration of diabetes of 10 years. Participants were using a mean of 2.4 antihyperglycemic agents, with nearly all using metformin. Approximately 30% were using GLP-1 RAs and approximately 39% were taking SGLT2 inhibitors.

The primary outcome of TIR was significantly higher in the CGM group at 76.3% vs the SMBG group at 65.6% (adjusted difference of 9.9%, p<0.001), indicating nearly 2.4 hours daily of additional TIR for this group **(Figure 2)**. Time in tight glycemic range (3.9 - 7.8 mmol/L) was higher by 8.5% (p = 0.04) and time above range was lower by 8.1% for the CGM group (p = 0.04) **(Figure 2)**.

In the IMMEDIATE trial, as in previous studies, HbA1c showed a greater improvement in the CGM group, in this case showing a difference of 0.3% (p<0.05). Hypoglycemia, whether measured by time below range or as clinical hypoglycemia events, was minimal and not different between groups. There were no events of severe hypoglycemia. TIR outcomes were not altered when stratified by mean number of therapies, GLP-1 RA use, diabetes duration, or isCGM scanning frequency. There was a greater treatment effect among participants with a baseline HbA1C above 9%. These individuals gained 20.4% of time in range, which translates to a mean of 4.9 hours per day.

Most patient-reported outcome measures improved equally in both groups over the course of the study, including important measures such as diabetes distress, which has sometimes increased among individuals adopting greater self-monitoring of any type. An exception was the Glucose Monitoring Satisfaction Survey (GMSS) mean score, which improved in the CGM arm and was unchanged among self-monitoring patients.

Finally, the IMMEDIATE trial showed that there was no change in mean number of therapies per person, nor adherence, as measured by the Adherence to Refills and Medications–Diabetes (ARMS-D) scale. There were also no significant differences in final weight or waist circumferences, although mean weight did decline by 1.4kg in the CGM group with no change in the SMBG group.

Two recent meta-analyses support the IMMEDIATE findings. One study of 26 RCTs in T2D demonstrated a significant HbA1c improvement with CGM versus self-monitoring mean difference 0.19%; [95% CI 0.04, 0.34]).[12] The advantage was even greater with isCGM (mean difference 0.31%; [95% CI 0.17, 0.46]) and results were similar for populations using or not using insulin. A second meta-analysis explored six RCTs that focused on non-insulin-using individuals and found an HbA1c reduction advantage of 0.31% (95%CI 0.21, 0.42), TIR gain of 8.6% (95%CI 4.54, 12.71) and improved treatment satisfaction.[13]

Historically, the value of glucose self-monitoring for non-insulin-users with T2D has been challenging to demonstrate convincingly. As more expensive and complex systems such as continuous glucose monitoring gain popularity in all populations with diabetes, understanding their value in non-insulin-users becomes even more germane. The accumulating evidence of research over the past decade indicates that both rtCGM and isCGM are both more effective at glycemic control than conventional self-monitoring alone, even among individuals not using insulin therapy.

How is CGM use in non-insulin users contributing to the improved glycemic control seen in these studies? Such individuals, after all, aren't adjusting their therapy many times a day, as insulin users do. The studies also indicated no overall change in the mean dose, or number or type of non-insulin therapies used. Interestingly, as seen in the GEM study, even intermittent CGM use may have glycemic control benefit, when supported with sufficient diabetes self-management education.[5] Of note, isCGM studies (including IMMEDIATE) did not find a relationship between number of scans per day and the resulting glycemic benefit. Among insulin users, scanning frequency is usually associated with outcome, most likely because the more frequent awareness of glucose level leads to real-time dosing changes. However, in the case of non-insulin-users a different mechanism may be in play. Episodic scanning may contribute to a glycemic benefit through the pathway of larger behaviour change, such as subtle changes to medication adherence not detectable through, for example, the ARMS-D scale in IMMEDIATE, or through improved dietary and lifestyle choices.

Finally, we might consider the degree of the potential benefit of increased TIR and reduced HbA1c to non-insulin-users. IMMEDIATE achieved a nearly 10% gain in TIR (and an additional HbA1c reduction of 0.3%) versus self-monitoring. In general, a gain of 5% in mean TIR has been considered clinically meaningful. Further, as with most interventions in diabetes, those with poor glycemic control derived even greater benefit.

Summary

An accumulating body of evidence, culminating in the recent IMMEDIATE randomized, controlled trial, has confirmed the value of continuous glucose monitoring technology for individuals with T2D who are not using insulin if they have been unable to achieve control with prior measures. Future research into these approaches for non-insulin-users will provide additional insights into mechanism and help build the body of data on optimal application for inclusion in future updates of clinical practice guidelines.

Correspondence:

Dr Ronnie Aronson
Email: Ronnie.Aronson@LMC.ca

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