Marked Improvement in A1C Levels After Initiation of Intermittently Scanned Continuous Glucose Monitoring Is Maintained Over 4 Years in Patients With Type 1 Diabetes

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OBJECTIVE | This study aimed to demonstrate the effectiveness of long-term use of intermittently scanned continuous glucose monitoring (isCGM) in adult patients with type 1 diabetes.

DESIGN AND METHODS | In this retrospective real-world study, 689 patients with type 1 diabetes who were >18 years of age and using isCGM were identified from the electronic patient records in North Karelia, Finland. A1C data were collected before and after the initiation of isCGM. The primary outcome was a change in the mean A1C over time after isCGM started.

RESULTS | The greatest reductions in the mean A1C levels were observed 6 months (−0.54% [−5.9 mmol/mol], \(P < 0.001\)) and 12 months (−0.42% [−4.6 mmol/mol], \(P < 0.001\)) after the initiation of isCGM. Reduction in A1C remained significant for 4 years, although the mean reduction in A1C was −0.18% (−2.05 mmol/mol) \((P = 0.009)\) at 48 months compared with baseline. In a subgroup analysis, patients with a baseline A1C >9% (75 mmol/mol) benefited the most from initiation of isCGM (reduction −0.97% [−10.6 mmol/mol], \(P < 0.001\), at 12 months and −0.92% [−10.1 mmol/mol], \(P < 0.001\), at 48 months). Neither sex nor age at the start of isCGM were correlated with A1C reduction.

CONCLUSION | Use of isCGM improves A1C levels significantly in adult patients with type 1 diabetes. Significant reduction in A1C persisted over 4 years of use, although the effect diminished over time.
Research Design and Methods

Setting and Patients

This study was conducted in the area of the Joint Municipal Authority for North Karelia Social and Health Services (Siun Sote), which provides social and health care services (both primary and specialized health care) for the inhabitants of the catchment area (n = 166,400). In the Siun Sote region, isCGM was introduced in 2016. From 2016 to 2020, Siun Sote–funded isCGM was limited to adult patients with type 1 diabetes who fulfilled special criteria. These criteria were in line with the national type 1 diabetes guidelines (Finnish Current Care Guidelines [12]) and included:

1) suboptimal A1C despite optimized treatment, with repeated hypoglycemic events;
2) planning to become or being pregnant;
3) fear of hypoglycemia;
4) fear of needles, leading to inability to perform SMBG;
5) end-stage renal disease and dialysis treatment;
6) inability to execute SMBG because of amputation or disability; and
7) difficulties in carrying out SMBG because of occupation.

If at least one of these criteria was fulfilled, isCGM could be initiated.

In the Siun Sote region, follow-up of adults with type 1 diabetes is organized in both primary health centers and a specialized diabetes clinic in the secondary care hospital. As a result, initiation of isCGM and follow-up of patients using it can be done either in the primary or specialized care setting.

Identification of patients with type 1 diabetes in the Siun Sote region was done using International Classification of Diseases, 10th revision, codes (E10.1–E10.9), and data were collected from the electronic health record (EHR) as described previously (13). A total of 1,764 patients with type 1 diabetes were identified; 805 who were domiciled in the Siun Sote region, alive at the end of 2020, and >18 years of age at the time of isCGM initiation were included. Patients who continuously used isCGM were identified from the EHR (Figure 1). The starting date of continuous use of isCGM was identified from the EHR, and if the use of isCGM had ended, the end date was also registered.

A1C data were also collected from the EHR. We included patients with at least one A1C measurement during the period from 6 months before to 1 month after isCGM initiation. The mean of these measurements was used as the baseline A1C. Because of the nature of the retrospective register study, A1C measurements after the start of isCGM were divided into 6-month time periods, and if there were multiple measurements within a 6-month period, the mean of the values was used. Patients with baseline A1C and at least one A1C measurement within one or more of the specified time intervals during follow-up were included in the analysis.

Additionally, the method of insulin delivery was obtained from EHRs.

In addition to EHR data, severe hypoglycemic events requiring ambulance visits were retrieved from the records of the ambulance service. Self-reported hypoglycemia was not registered and thus was excluded from the analysis.

Patients starting isCGM had a 1- to 2-hour introduction from a nurse who specialized in diabetes care. The patients received standard clinical care during the time of isCGM use (including a visit to a nurse within 6 months of starting isCGM and one or two visits to a diabetologist or a nurse per year thereafter). isCGM data were used to optimize treatment during visits, but no special interventions were introduced to the patients after starting isCGM. The specific isCGM system used in this study.

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FIGURE 1 Patient selection.
was the FreeStyle Libre 1, which was available during the whole study period. The FreeStyle Libre 2 was introduced in clinical practice in the Siun Sote region in the latter part of 2020. The earlier isCGM system used in the study did not have alarm functions and required patients action (scanning the sensor with a reader or smartphone) to get glucose information.

Biochemical Methods

All laboratory samples were analyzed in the same regional laboratory (the Eastern Finland Laboratory). A1C was measured using the turbidimetric inhibition immunoanalysis method throughout the 2016–2020 period. The normal A1C range was 4.0–6.0% (20–42 mmol/mol), and the average coefficient of variation was 3%. The A1C analysis was standardized to International Federation of Clinical Chemistry units.

Statistical Analyses

Patients were followed from the register from the initiation of isCGM until end of 2020. If isCGM use was discontinued, data were collected from the isCGM start date until the day of discontinuation. Statistics such as means, SDs, ranges, and proportions were used to describe the data. Linear mixed models were used to assess differences in mean A1C between time points, sexes, and ages and their interactions. A linear mixed model was used for the correlation structure of the data because of the repeated measurements. Poisson regression with generalized estimating equations was used to assess differences in hypoglycemic events per person-year before and after the start of isCGM. The SPSS statistical software for Windows, v. 27.0 (IBM, Armonk, NY), was used for statistical analyses. P values <0.05 were regarded as statistically significant, and 95% CIs were included in the statistics.

Results

Baseline characteristics are presented in Table 1. After exclusions, as shown in Figure 1, 689 patients were included in the analysis. Of these, 373 (54.1%) were men, and the age of the patients ranged from 18 to 83 years at the isCGM start date (Table 1). isCGM was discontinued for 15 patients (2.2%). The most common recorded reason for the discontinuation of isCGM was the start of another CGM system or an allergy to the isCGM sensor adhesive. At the time of initiation of isCGM, 625 patients (80.7%) used a multiple daily injection (MDI) insulin regimen, and 64 patients (9.3%) used continuous subcutaneous insulin infusion (CSII). After the initiation of isCGM, CSII was introduced for 25 patients who had been using MDI, and these patients continued to use isCGM after making this switch.

Changes in mean A1C between baseline and different time points were significant throughout the 4-year follow-up period (Figure 2). The greatest reductions in the mean A1C were observed at 6 months (−0.54% [−5.9 mmol/mol]) and 12 months (−0.42% [−4.6 mmol/mol]) after the start of isCGM. At 48 months, the reduction in mean A1C was −0.18% (−2.1 mmol/mol) from baseline (P = 0.009).

Figure 3 shows the mean change of the A1C from baseline in subgroups stratified by the baseline A1C. Patients with a baseline A1C >9% (75 mmol/mol) had the greatest reduction in A1C at all time points (−0.97% [−10.6 mmol/mol] at 12 months and −0.92% [−10.1 mmol/mol] at 48 months). Only 8.7% of patients had baseline A1C levels <7% (53 mmol/mol). These patients showed a significant increase in A1C at all time points (+0.2% [+2.2 mmol/mol] at 6 months, P = 0.010; +0.29% [+3.2 mmol/mol] at 12 months, P <0.001; and +0.54% [+5.9 mmol/mol] at 48 months, P <0.001). Patients whose baseline A1C was <7% (<53 mmol/mol) showed a declining trend in severe hypoglycemic events requiring professional support after the start of isCGM (0.11 vs. 0.05 hypoglycemic events per person-year before and after starting isCGM, respectively), although the difference was not significant (P = 0.719).

There was no significant difference between men and women in change in A1C after starting isCGM (P = 0.839). When divided into subgroups by age (<30, 30–50, and >50 years of age), all age-groups showed similar trends in change in A1C. Age at initiation of isCGM was not correlated with change in A1C level.

A1C levels were significantly higher in patients starting isCGM in 2016 than in the years 2017–2019 (9.5% [77.95 mmol/mol] in 2016 vs. 8.6% [70.37 mmol/mol] in 2017, P <0.001; 8.7% [71.42 mmol/mol] in 2018, P = 0.015; and

| TABLE 1 Patient Characteristics at Baseline |
|-------------------------------------------|
| Characteristic | Value |
|----------------|-------|
| Age, years     | 47.2 ± 16.25 |
| Age range, years | 18.1–83.4 |
| A1C, % (mmol/mol) | 8.7 ± 3.6 (71.7 ± 16.0) |
| A1C range, % (mmol/mol) | 5.2–15.3 (33.0–144.0) |
| A1C <7% (<53 mmol/mol) | 60 (8.7) |
| Sex            |       |
| Male           | 373 (54.1) |
| Female         | 316 (45.9) |
| Insulin therapy regimen* |       |
| CSII           | 64 (9.3) |
| MDI            | 625 (80.7) |

Data are mean ± SD, range, or n (%). *Before starting isCGM.
8.6% [69.96 mmol/mol] in 2019, P < 0.001). There was no significant difference between baseline A1C at the start of isCGM for the years 2016 and 2020 (P = 0.286).

Patients who used CSII before starting isCGM had lower baseline A1C levels than those using MDI. During follow-up, there was no significant difference in A1C between patients using an MDI or a CSII regimen and using isCGM.

**Discussion**

In this retrospective real-world study, we examined the effect of isCGM on glycemic control in adults with type 1 diabetes. This is one of the first long-term real-world studies demonstrating significant reductions in A1C for up to 4 years of isCGM in a real-world setting.

The reduction in the A1C levels in our study at 6 and 12 months (−0.54% [−5.9 mmol/mol] and −0.42% [−4.6 mmol/mol], respectively) after the start of isCGM is in line with previous real-world studies (9,14). Tyndall et al. (10) demonstrated a −0.37% (−4 mmol/mol) decrease in A1C in a prospective cohort of 900 patients. In that study, the median interval from baseline to final A1C measurement was 245 days, whereas, in our study, the median follow-up time was 2.5 years. In a retrospective analysis of 131 patients with type 1 diabetes, Rose et al. (15) showed a significant reduction in A1C levels (−0.75% [−8.2 mmol/mol]) after 3 months of isCGM, and the reduction was maintained for 12 months.

In a real-life study in Denmark, Hansen (16) presented clinically significant improvements in A1C after 2 years of isCGM use. In that study, the mean A1C reduction for the whole study group was −0.37% (−4 mmol/mol), which is in line with our findings, although their baseline A1C was lower than that in our study. In their study, patients had unrestricted access to isCGM, whereas in our study isCGM users were selected based on predefined criteria. When interpreting the results, it is important also to notice that the first patients starting isCGM had significantly higher baseline A1C values, and this could have affected change in A1C over the long term.

In a 3-year follow-up of the COMISAIR (Comparison of Sensor-Augmented Insulin Regimens) study, Soupal et al. (17) demonstrated the long-term sustainability of rtCGM. In that study, patients using rtCGM had significantly lower A1C levels throughout the 3-year study, and A1C levels achieved at 12 months were maintained. This finding is in contrast to our finding that the reduction in A1C starts to diminish over time. There can be multiple reasons for this finding that is not answered by our data, and we can only speculate about causes. In the COMISAIR study, the CGM systems used provided real-time glucose information without the need for
user action but also required calibration via SMBG, and both of these features differ from the isCGM system used on our study. Additionally, in the COMISAIR study, patients had scheduled clinic visits every 3 months throughout the follow-up period (17), whereas in our study, follow-up visits were scheduled once or twice per year. Although patients find isCGM easy to use (6) and isCGM has been found to ease diabetes distress (18), it is unclear how well patients managed to adhere to isCGM in the longer term. Despite the advantages of glucose-monitoring technologies, insulin therapy is complex and challenging for patients and also requires self-management skills related to insulin dosing.

As seen in other studies (8,9,14,17), the patients in our study with poor glucose control (baseline A1C >9% [75 mmol/mol]) benefited the most from initiation of isCGM (A1C reduction −0.97% [−10.6 mmol/mol] at 12 months). In a subgroup analysis, patients with poor glycemic control (A1C >9% [75 mmol/mol]) before starting isCGM maintained the achieved A1C level for a longer time period. Patients with moderate glucose control at baseline returned to the baseline level 2 years after starting isCGM, which is in contrast to findings of Hansen (16) that the effect of isCGM remained after 2 years of use.

In our study, patients with a baseline A1C <7% (<53 mmol/mol) had a significant deterioration in A1C after 6 months. A similar trend was seen in a study by Paris et al. (9) in which patients with optimal glycemic control (<7.5% [<58 mmol/mol]) showed a significant increase in A1C at 12 months. In the IMPACT (Randomized Controlled Study to Evaluate the Impact of Novel Glucose Sensing Technology on Hypoglycemia in Type 1 Diabetes) trial (7), patients with well-controlled type 1 diabetes showed a minor (+0.16% [+1.7 mmol/mol]), nonsignificant deterioration in A1C levels after starting isCGM. In an RCT setting, Bolinder et al. (7) and, in a real-world setting, Nana et al. (8) demonstrated that isCGM use led to a reduction in hypoglycemic events in patients with well-controlled type 1 diabetes without a significant change in glycemic control. In the HypoCompass (Comparison of Optimized MDI Versus Pumps With or Without Sensors in Severe Hypoglycemia) trial (19) and in a trial using the HypoAware intervention (20), the use of rtCGM resulted in a reduction of hypoglycemic episodes and no negative change in A1C levels.

Because of the selective criteria for starting isCGM, the possible reduction in the time spent in hypoglycemia may have influenced A1C levels in patients with strict glycemic control in our study population. Because of the retrospective nature of our analysis, we have no exact data about each patient's glucose trends or time in range, but the incidence of severe hypoglycemia (primary care and hospital visit or ambulance visit without transport) was lower after the initiation of isCGM, although this difference did not reach statistical significance. Because of limitations of

![FIGURE 3 Change in mean A1C over 4 years in different A1C subgroups.](image-url)
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different registers and changes in ambulance service register during follow-up, we were not able to get EHR-based hypoglycemia data. Rather, to get these data, we had to go through the patient files manually. Because of this data collection burden, data were collected only for the group with the lowest A1C.

We did not find any significant differences between women and men in change in glycemic control after isCGM was introduced, which is in line with findings of Tyndall et al. (10) and Lameijer et al. (14). When patients were stratified by age at the start of isCGM, no difference was observed between age-groups. This finding is in line with previous studies showing no association between age and likelihood of achieving lower A1C levels (8,10,14,15). In a randomized trial, Pratley et al. (21) demonstrated that patients >60 years of age benefited the most from rCGM.

In the current study, patients received brief education on the use of isCGM and otherwise received standard clinical care. The efficacy of structured education on the use of isCGM has been demonstrated by Hermanns et al. (22). In their study, the education program took place over 6 weeks and consisted of four 90-minute sessions. This kind of intervention may have helped patients in our study maintain their achieved A1C levels for a long period of time. Broos et al. (23) also found that diabetes knowledge and health literacy have an influence on A1C in patients starting isCGM.

It has been shown previously that CGM sensors must be worn at least 70% of the time to achieve A1C benefits and that improvement in glycemic control is greatest in patients who use the sensor most frequently (24). An optimal daily scan rate has been suggested, and the relationship between scanning frequency and A1C levels has been demonstrated (25), but data are lacking on sensor use in the long term. Unfortunately, in the current study, we were not able to answer this question because our data did not contain information about patients’ exact sensor usage.

Ours is the first study to report real-world outcomes of isCGM use for up to 4 years. The strength of this study is its large study population. It is also notable that in the Siun Sote region, eligible patients do not have to pay for isCGM themselves; thus, financial issues do not play a significant role in patient engagement with the use of isCGM. Naturally, there are also some limitations. Foremost, our study lacked a control population and was retrospective. The special eligibility criteria for starting isCGM resulted in a selective group of patients. In addition, because the data were obtained from an electronic database, some essential data (such as patients’ exact usage of sensors and number of daily scans) were not available.

Conclusion

This retrospective real-world study showed that the use of isCGM leads to better glycemic control in real-life settings, although the effect diminishes over a period of years. Continuous technical and psychological education may prevent this diminished effect, and more research is warranted. Patients with higher A1C levels when starting isCGM benefited the most from it. It is important to notice that patients experienced A1C reductions regardless of their age. Further studies are needed to explore the beneficial effects of isCGM on complication rates perhaps resulting from increased time in the target glycemic range.

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DUALITY OF INTEREST

J.Ma. is a founding partner of ESIOIR Oy and a board member of Sitana Oy. These companies were not involved in carrying out this research. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

J.Mu., P.R., J.Ma., and T.L. planned the study design. J.Mu. edited the data from the electronic database, and M.-L.L. researched data and contributed to the statistical methods and results. P.L. verified the analytical methods. J.Mu. wrote and edited various versions of the manuscript. All authors participated in the interpretation of the data, contributed to the discussion, and reviewed and commented on the manuscript. All authors read and approved the final version of the manuscript. J.Mu. 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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