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REVIEW ARTICLE

Effects of real-time continuous glucose monitoring in type 1 diabetes: a meta-analysis of randomized controlled trials

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Abstract

Aims Self-monitoring of blood glucose (SMBG) represented a major breakthrough in the treatment of type 1 diabetes. The aim of the present meta-analysis is to assess the effect of continues glucose monitoring (CGM) and flash glucose monitoring (FGM), on glycemic control in type 1 diabetes.

Materials and methods The present analysis includes randomized clinical trials comparing CGM or FGM with SMBG, with a duration of at least 12 weeks, identified in Medline or clinicaltrials.gov. The principal endpoint was HbA1c at the end of the trial. A secondary endpoint was severe hypoglycemia. Mean and 95% confidence intervals for HbA1c and Mantel–Haenzel odds ratio [MH-OR] for severe hypoglycemia were calculated, using random effect models. A sensitivity analysis was performed using fixed effect models. In addition, the following secondary endpoints were explored, using the same methods: time in range, health-related quality of life, and treatment satisfaction. Separate analyses were performed for trials comparing CGM with SMBG, and those comparing CGM + CSII and SMBG + MDI and CGM-regulated insulin infusion system (CRIS) and CSII + SMBG.

Results CGM was associated with a significantly lower HbA1c at endpoint in comparison with SMBG (− 0.24 [− 0.34, − 0.13]%); CGM was associated with a significantly lower risk of severe hypoglycemia than SMBG. Treatment satisfaction and quality of life were not measured, or not reported, in the majority of studies. FGM showed a significant reduction in the incidence of mild hypoglycemia and an increased treatment satisfaction, but no significant results are shown in HbA1c. CGM + CSII in comparison with SMBG + MDI was associated with a significant reduction in HbA1c. Only two trials with a duration of at least 12 weeks compared a CRIS with SMBG + CSII; HbA1c between the two treatment arms was not statistically significant (difference in means: − 0.23 [− 0.91; 0.46]%; $p = 0.52$).

Conclusion GCM compared to SMBG has showed a reduction in HbA1c and severe hypoglycemia in patient with type 1 diabetes. The comparison between CGM + CSII and SMBG + MDI showed a large reduction in HbA1c; it is conceivable that the effects of CSII + CGM on glycemic control additives. The only comparison available between FGM and SMBG was conducted in patients in good control.

Keywords Continuous glucose monitoring · Flash glucose monitoring · Type 1 diabetes

Introduction

Self-monitoring of blood glucose (SMBG) represented a major breakthrough in the treatment of type 1 diabetes, allowing a more accurate glycemic control with insulin therapy. Frequent self-monitoring was one of the key components of intensified diabetes therapy in the Diabetes Control and Complication Trial, which warranted a relevant reduction in long-term complications of diabetes [1]. The availability of a simple and relatively inexpensive method for measuring blood glucose several times a day allowed adjustments of insulin doses, inducing patients and clinicians to

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aim at glucose targets closer to normal [2]. The introduction of transcutaneous systems for the continuous monitoring of interstitial glucose allowed one further step toward the improvement in glucose control, providing the possibility of a much more frequent measure of glucose, also during night time [2]. Real-time sensors with transmission devices can also provide alarms for hypoglycemia, hyperglycemia, and rapid variations in glucose, increasing further the accuracy of corrections. In fact, previous meta-analyses suggest that real-time continuous glucose monitoring (CGM) is associated with an improvement in glycemic control in type 1 diabetes [3–5]. More recently, the technology related to continuous monitoring of interstitial glucose evolved in two distinct direction. On one side, simpler and less expensive devices without automatic data transmission and the related alarms were developed for wider use; this is the so-called "flash glucose monitoring" (FGM) [6]. In the opposite direction, some CGM systems were linked to devices for continuous subcutaneous insulin infusion (CSII), to create integrated systems in which insulin infusion is regulated by sensor results [7]. Current research is focused on the development of integrated systems in which the insulin infusion rate is regulated by a CGM sensor, to create a sort of artificial pancreas [8]. The wider use of CGM devices prompted also the introduction of new potential parameters for the assessment of glucose control, such as glycemic variability (often expressed as coefficient of variation or mean amplitude of glucose excursions), and time in range [9].

The assessment of the efficacy and safety of a new procedure should be primarily based on randomized clinical trials. Several interventional studies comparing CGM with SMBG have been performed over the years and summarized in meta-analyses [3–5, 10, 11], which suggested some clinical advantage for CGM. Such results need to be updated because of the technical evolution of monitoring systems and the continuously increasing number of trials.

Materials and methods

Search strategy and selection criteria

This meta-analysis is a part of a wider meta-analysis of randomized clinical trials on CSII, glucose sensors, and sensor-augmented therapy in either type 1 or type 2 diabetes (registered on PROSPERO, http://www.crd.york.ac.uk/PROSPERO, at CRD42016042323). The present analysis sought to include randomized studies comparing real-time CGM or FGM with SMBG, and CGM + CSII with SMBG + multiple insulin injections in type 1 diabetes, with a duration of at least 12 weeks. A Medline and EMBASE search (limits: Human studies; any date up to July 31, 2019) was performed, using the following search string: CSII or "continuous subcutaneous insulin infusion" or CGM or "continuous glucose monitoring" or FGM or "flash glucose monitoring" or "sensor-augmented pump"; trials on type 2 diabetes were then excluded. Moreover, an additional manual search of the references of included trials and former meta-analyses was carried out to identify other newly published and unpublished studies. Completed but yet unpublished studies were searched in the www.clinicaltrials.gov register. Authors of included studies were not contacted for additional information. This meta-analysis is reported following the criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]; the checklist is reported as Table 1 of Supplementary Material.

Data extraction

Summary estimates of the variables of interest were extracted from the principal publication, when available; whenever needed, secondary publications and clinicaltrials.gov registry were used for retrieval of missing information, in the hierarchical order reported above. Data extraction was performed independently by two of the authors (L.P and C.C.) and conflicts resolved by a third investigator (E.M.).

The risk of bias was described and assessed in seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The results of these domains were graded as 'low' risk of bias, 'high' risk of bias, or 'unclear' risk of bias.

Data analysis

The principal endpoint was HbA1c at the end of the trial. A secondary endpoint was severe hypoglycemia (i.e., that requiring hospitalization and/or help from third parties). Mean and 95% confidence intervals for HbA1c, and Mantel–Haenzel odds ratio [MH-OR] for severe hypoglycemia were calculated, using random effect models. A sensitivity analysis was performed using fixed effect models. In addition, the following secondary endpoints were explored, using the same methods: time in range, health-related quality of life, and treatment satisfaction.

Separate analyses were performed for trials comparing CGM with self-monitoring of blood glucose (SMBG) and those comparing CGM + CSII with SMBG + MDI and CGM-regulated insulin infusion system (CRIS) with CSII + SMBG.

In addition, separate analysis for subgroups of trials were performed for: duration of study, age and different devices.

Statistical heterogeneity was assessed by I^2 test, whereas Funnel plots were used to detect publication bias.

All analyses were performed using Review Manager (RevMan), Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Grading of Recommendations Assessment, Development an Evaluation (GRADE) methodology [13] was used to assess the quality of the body of retrieved evidence using GRADEpro GDT software (GRADEpro Guideline Development Tool; McMaster University, 2015. Available from gradepro.org).

Results

The trial flow summary is reported in Fig. 1 of Supplementary Materials. Manual search of references yielded no further studies which had not already been identified on Medline or clinicaltrials.gov. Trials comparing SMBG with either CGM (monitoring with alarms) or FGM (monitoring without alarms) were 21 [14–34] and [35], respectively. Three trials [36–38] compared CGM combined with CSII and SMBG associated with multiple daily injections (MDI). Furthermore, two trials [39, 40] assessed the effect, in comparison with SMBG associated to CSII, of an integrated system of CSII and CGM, with CGM glucose values regulating insulin infusion rate in the case of hypoglycemia (i.e., the so-called "low glucose suspend" [LGS] function). All the trials were published, except for one, the results of which were partly disclosed on the www.clinicaltrials.gov website [40]. The main characteristics of retrieved trials are summarized in Table 1 of Supplementary Materials.

The quality of studies, which were all open label, was generally good, although for a few trials the risk of attrition bias could not be excluded because of an elevated dropout rate; in addition, for some studies randomization and allocation procedures were not reported in sufficient detail to verify the reliability of methods Fig. 2 of Supplementary Materials.

CGM versus SMBG

The majority of available studies compared CGM with SMBG. The total number of enrolled patients was 1110 and 1142… in CGM and comparator groups, respectively, with a mean baseline HbA1c of 77 ± 5… mmol/mol. The visual analysis of Funnel plot, Egger's test, and Kendall's tau on HbA1c did not suggest any relevant publication bias (Fig. 3 of Supplementary Material). Heterogeneity across trials was relevant (I^2 54%). Using a random effects model, CGM was associated with a significantly lower HbA1c at endpoint in comparison with SMBG (−0.24 [−0.34, −0.13]%; Fig. 1, panel a). Five trials [17, 25, 28, 30, 33] did not report information on severe hypoglycemia, whereas four studies [14, 21, 24, 29] reported that no cases had occurred. In the remaining trials with at least one reported case, CGM was associated with a significantly lower risk of severe hypoglycemia than SMBG (Fig. 1, panel b). The overall number of reported cases of ketoacidosis was low (10 and 19 in the CGM and SMBG arms, respectively, with between-group difference not reaching full statistical significance (Fig. 1, panel c). Sensitivity analyses with fixed effects models provided the similar results (data not shown). Data on time in range of glucose were available for only four studies [18, 24, 30, 33]. A trend toward an increase in time in range was observed for CGM in comparison with SMBG, but the difference did not reach full statistical significance (difference in means: 3.1 [0.0–6.2]%; $p = 0.05$), and it is questionable to calculate a time in range from SMBG data.

Treatment satisfaction and quality of life were not measured, or not reported, in the majority of studies (Tables 1, 2, 3). The multiplicity of tests used, and heterogeneity in reporting, prevented a formal meta-analysis. In studies in which these parameters were reported, the results were generally inconclusive, failing to show significant differences between groups.

When trials enrolling patients either with CSII, MDI, or both, were analyzed separately, no clear effect of concurrent use of CSII could be detected on endpoint HbA1c or risk of severe hypoglycemia (Fig. 4 of Supplementary Materials Panel A and Panel B). The results on HbA1c and severe hypoglycemia in trials enrolling only children/adolescents, only adults, or both, did not show clear differences across groups (Fig. 5 of Suppl. Materials Panel A and Panel B). Individual studies used different devices for CGM: Seven trials were performed with Medtronic Enlite [15, 17, 19, 24–26, 31], four with Abbott Navigator [14, 23, 27, 30], and four with Dexcom G4 [16, 18, 22]; Medtronic Guardian [29] and Dexcom G7 [28] were used in one trial each, whereas one trial was performed with a multiplicity of devices [20]. The results on HbA1c and severe hypoglycemia in trials with different devices are summarized in Table 3 of supplementary material. Significant improvements of HbA1c were reported with Medtronic Enlite, Abbott Navigator, and Medtronic Guardian; the difference across group was not statistically significant. A further subgroup analysis was performed subdividing trials for trial duration (Table 4 of Supplementary materials): A significant reduction in HbA1c was observed in trials with a duration ≥ 52 [27, 32–34] and 26–51 [14–16, 18–23, 26, 28, 29] weeks, but not in those with a duration < 26 weeks [17, 24, 25, 30, 31]; across-group differences, however, were not statistically significant.

FGM versus SMBG

Among retrieved trials which fulfilled inclusion criteria, only one [35] compared FGM with SMBG. The study,

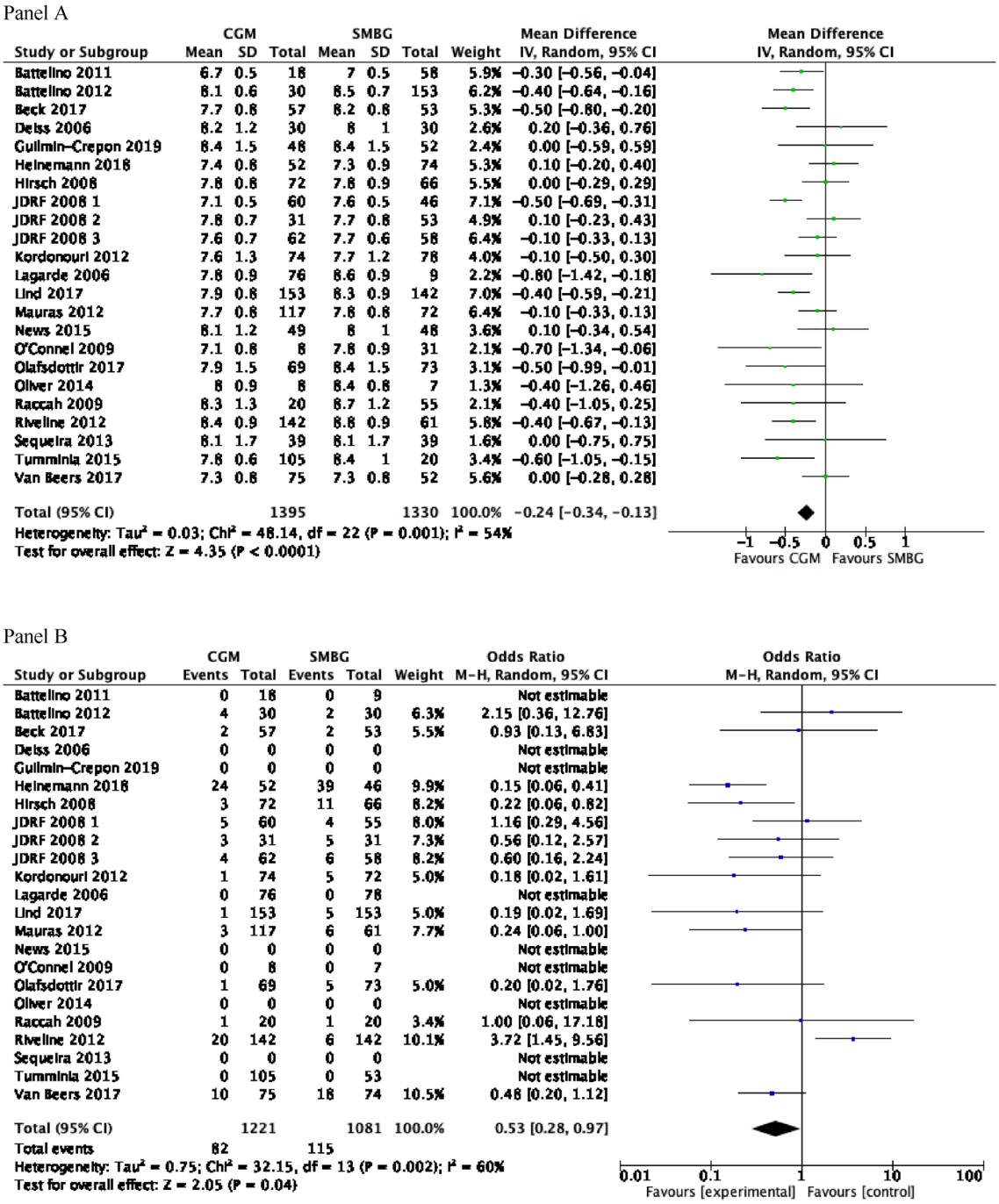

Fig. 1 Forest plot for HbA1c (**a**), hypoglycemia (**b**) and ketoacidosis (**c**) between CGM and SMBG

performed in patients with type 1 diabetes and good metabolic control, showed a significant reduction in the incidence of mild hypoglycemia with FGM, associated with increased treatment satisfaction; on the other hand, endpoint HbA1c and time in range were not significantly different between groups.

CGM + CSII versus SMBG + MDI

Three trials compared the combination of CGM and CSII with a traditional approach (multiple injection and conventional self-monitoring of capillary blood glucose) [36–38]. In these trials, CGM + CSII was associated with a significant reduction in HbA1c (difference in means: − 0.70 [− 1.25;

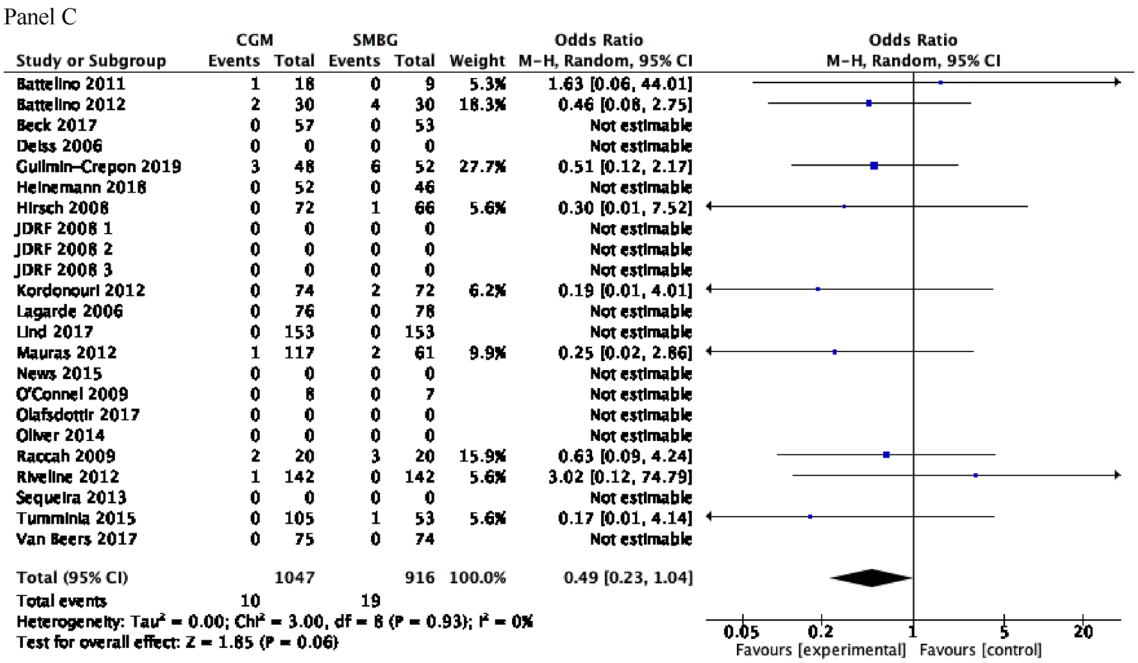

Fig. 1 (continued)

−0.16]; $p=0.01$), with no significant difference between groups for rates of severe hypoglycemia and ketoacidosis (Fig. 6 of Supplementary Materials Panel A, Panel B, and Panel C).

CGM-regulated insulin infusion system (CRIS) versus SMBG + CSII

Only two trials with a duration of at least 12 weeks compared a CRIS with SMBG + CSII [39, 40]. Both trials investigated a CRIS with low glucose suspend. Combining the two trials, the difference in endpoint HbA1c between the two treatment arms was not statistically significant (CRIS vs SMBG + CSII: −0.23 [−0.91; 0.46]; $p=0.52$). One of the two trials [39] reported six episodes of severe hypoglycemia, both in the SMBG + CSII arm, whereas the other [40] did not report any episode. No trials fulfilling inclusion criteria were available for comparisons of closed loop systems (i.e., upregulating insulin infusion rate in case of high glucose, beside downregulating CSII in case of hypoglycemia) with SMBG + CSII.

Discussion

The present meta-analysis shows that the use of continuous glucose monitoring improves glycemic control in patients with type 1 diabetes. This confirms the results of previous systematic reviews performed on a smaller number of studies [5]. Although the effect of CGM on HbA1c may seem relatively small, it should be noted that it is associated with a reduction in the incidence of severe hypoglycemia, which had previously remained undetected [5], possibly because of the relatively small size of available samples. Conversely, data on ketoacidosis are insufficient to draw any conclusion, because of the low incidence of this condition.

In recent years, the increasing availability of devices for continuous glucose measurement has produced a growing interest for the assessment of indices of glucose variability. Some of those indices have been proposed as measures of glycemic control, and possible therapeutic targets, as an adjunct or an alternative to HbA1c [9]. However, even though CGM allows for an easy determination of indices of glucose variability, those parameters are often unreported in randomized studies, particularly in older trials. Data on time in range of glucose were available for only four studies [18, 24, 30, 33], showing a trend toward an improvement with CGM, which did not reach statistical significance. The observation that CGM produces a reduction in both HbA1c and incidence of severe hypoglycemia suggests that it could have a beneficial effect on glucose excursions, i.e., on glucose variability; however, further trials are needed to settle this issue.

The use of CGM could theoretically be associated with an improvement in health-related quality of life and treatment satisfaction: The possibility of knowing blood glucose without the need for digito puncture can be perceived by patients as a relevant advantage. In addition, the possibility

Table 1 Comparison between SMBG and CGM/FGM on Quality of Life (QoL) and hypoglycemia in type 1 DM

Study	QoL	Fear hypoglicemia
CGM		
Battelino 2011	NR	NR
Battelino 2012	NR	NR
Beck 2017	NR	NR
Deiss 2006	NR	NR
Guilminn-Crepon 2019	PEDES QL: SMBG versus CGM NS	NR
JDRF 1 2008	NR	NR
JDRF 2 2008	NR	NR
JDRF 3 2008	NR	NR
Heineman 2018	EQ5D: SMBG versus CGM NS	HFD: SMBG versus CGM NS
Hirsch 2008	NR	NR
Kordonouri 2012	NR	NR
Lagarge 2006	NR	NR
Lind 2017	DTSQ: CGM better than SMBG WHO-5: SMBG versus CGM NS	HFD: SMBG versus CGM NS
Mauras 2012	PAID 20: SMBG versus CGM NS	HFD: SMBG versus CGM NS
New 2015	PAID 20: SMBG versus CGM NS	NR
O' Connel 2009	NR	NR
Olafsdottir 2017	DTSQ: SMBG versus CGM NS	NR
Olivier 2014	DTSQ: CGM better than SMBG	NR
Raccah 2009	NR	NR
Riveline 2012	SF36: CGM better than SMBG	NR
Sequeira 2013	PAID 5: SMBG versus CGM NS	NR
Tumminia 2013	NR	NR
Van Beers 2017	PAID 5: SMBG versus CGM NS WHO-5: SMBG versus CGM NS	HFD: SMBG versus CGM NS
FGM		
Bolinder 2016	DDS: SMBG versus CGM NS DTS: FGM better than SMBG	HFS: SMBG versus FGM NS

NR not reported, *NS* not significant

Table 2 Comparison between SMBG + MDI and CSII + CGM/FGM on quality of life (QoL) and hypoglycemia in type 1 DM

Study	QoL	Fear hypoglicemia
Bergenstal 2010	NR	NR
Hermanides 2011	NR	NR
Peyrot 2009	NR	NR

Table 3 Comparison between CRIS and SMBG + CSII on Quality of Life (QoL) and hypoglycemia in type 1 DM

Study	QoL	Fear hypoglicemia
Ly 2013	NR	NR
NCT 02423993	NR	NR

of verifying glucose levels at shorter time intervals, and the availability of alarms for hypo- and hyperglycemia, could improve the subjective feeling of control over diabetes. Furthermore, CGM systems allow the measurement of glucose in conditions in which traditional monitoring of capillary blood glucose would have been scarcely feasible. On the other hand, there are also some mechanisms through which CGM could impair, rather than improve, quality of life. The continuous feedback of CGM system could make some patients more aware of their heath condition, increasing the psychological burden of diabetes. Those who are unable to manage properly the results of continuous monitoring can feel lost in front of an overflow of glycemic data. Finally, alarms for glucose levels out of a defined range, although useful for avoiding nocturnal hyperglycemia and hypoglycemia, may disturb the quality of sleep. Unfortunately, treatment satisfaction and quality of life are not measured, or not reported, in the majority of studies on CGM; to date, the results on this point are inconclusive.

The first CGM systems were originally designed to be used in association with CSII. In fact, older studies assessed the effects of CGM in patients already using insulin pumps. More recently, a number of trials has been performed in subjects on multiple insulin injections. In the present meta-analysis, the beneficial effects of CGM seem to be greater in patients already on CSII, although the difference between trial subgroups is not statistically significant. It can be speculated that patients who are already using a CSII have developed greater skills for the management of technology, allowing them to fully exploit the advantages of CGM. On the other hand, the use of CGM appears to produce some reduction in HbA1c also in patients on MDI, although the difference from SMBG in this subgroup of trials does not reach statistical significance; on the other hand, the use of CGM in patients on MDI determines a significant reduction in the risk of severe hypoglycemia. Notably, the GRADE score classifies evidence of beneficial effects of CGM on HbA1c and hypoglycemia as "moderate" or "high" for both patients on CSII and MDI (Fig. 7 of Supplementary Materials).

The management of type 1 diabetes poses some specific problems in pediatric populations that are more exposed to the risk of both severe hypoglycemia and ketoacidosis; in addition, children have reduced abilities of self-adjusting insulin doses on the basis of current glucose, whereas adolescents pose peculiar issues of adaptation to the needs of diabetes therapy [41]. Despite these important clinical differences, CGM seems to produce similar effects on HbA1c and hypoglycemia both in pediatric and adult populations, as confirmed by the GRADE rating on the quality of evidence for both populations with respect to HbA1c and hypoglycemia (Fig. 8 of Supplementary Materials).

A few trials compared the combination of CGM and CSII with SMBG associated with MDI. In these trials, the experimental technologies determined a relatively wide reduction in HbA1c, whereas data on hypoglycemia and ketoacidosis were too scarce to draw any reliable conclusion. Since CSII is capable of producing a small improvement in HbA1c in type 1 diabetes [42], it is conceivable that the beneficial effects of CSII and CGM on glycemic control are additive; however, trials comparing the combination of CSII and CGM with either CSII + SMBG and/or MDI + CGM are needed to confirm this hypothesis.

The term "Sensor-Augmented Pump" (SAP) is used with several different meanings. For this reason, we opted for a new term (CGM-regulated insulin infusion system; CRIS), indicating integrated systems in which data from CGM automatically regulate insulin infusion rates with CSII. Currently available systems which can be classified as CRIS according to these criteria include: 640G Medtronic system and t:slim X2 Tandem with Basal IQ technology and MiniMed 670 G. Automated insulin management features of the MiniMed 640G and t:slim X2 Tandem with Basal IQ technology sensor-augmented pump system include suspension of insulin infusion in response to predicted low sensor glucose (SG) values ("suspend before low"), suspension in response to existing low SG values ("suspend on low"), and automatic restarting of basal insulin delivery upon SG recovery [43, 44]. Otherwise, in MiniMed 670G, when it is in Auto Mode function, basal insulin delivery is fully automated, and the algorithm enables variable insulin delivery doses every 5 min to a target of 120 mg/dL [45]. Only two trials with a duration of at least 12 weeks compared a CRIS with SMBG + CSII [13, 39]. CRISis yet at the beginning but it is promising. Although the future is, for its own nature, unpredictable, it seems very likely that closed loop systems, with automated insulin delivery regulated by glucose sensors, will have a large development, possibly replacing more traditional approaches to insulin replacement therapy in type 1 diabetes.

The so-called flash glucose monitoring (FGM) system is a device developed for continuous monitoring of interstitial glucose, which provides readings on demand. In other terms, FGM is similar to a CGM without alarms for hyper- or hypoglycemia. Only one trial on FGM fulfilled the inclusion criteria defined for the present systematic review [35]. In fact, despite a wide use of the device and a large number of observational retrospective studies [46], no major program for an accurate assessment of the actual effects of FGM through randomized controlled trials has been developed so far. Observational studies suggest possible benefits in terms of reduction in hypoglycemia and improvement in glucose control, but the results could be biased by uncontrolled confounders. The only available randomized trial was performed to assess a possible advantage of FGM over SMBG on risk of hypoglycemia, enrolling patients with acceptable glycemic control. The principal endpoint, i.e., time spent in hypoglycemia, was easily reached. This shows that the increased frequency of glucose monitoring is sufficient to reduce hypoglycemic risk, even in the absence of alarms, confirming data retrieved from observational studies [47]. In addition, in this trial FGM was associated with a greater treatment satisfaction than SMBG; the possibility of frequent monitoring with a simple noninvasive procedure, without the potentially annoying effect of alarms, could be very attractive for many patients. Not surprisingly, FGM did not produce any reduction in HbA1c in patients already fairly controlled at enrollment. Due to the study design and inclusion criteria, the only available study on FGM does not allow to draw any conclusion on the possibility of improving HbA1c in unsatisfactorily controlled patients with type 1 diabetes. Notably, FGM did not reduce HbA1c in patients with type 2 diabetes on basal-bolus insulin therapy, despite higher baseline HbA1c values [48], whereas CGM improved glycemic control in patients with similar characteristics [49]. The possibility that alarms for hypo- and hyperglycemia

contribute to the effects of CGM on HbA1c cannot therefore be ruled out. Two small randomized studies comparing FGM and CGM in patients with type 1 diabetes, which did not fall within the inclusion criteria of the present meta-analysis, showed that FGM could be less effective in the prevention of hypoglycemia in individuals with hypoglycemia unawareness, despite a similar accuracy [50, 51].

There are some limitations in our study: Despite the relatively large number of trials, overall samples are limited, because of the small size of most studies; as a consequence, the sample sizes are insufficient to draw reliable conclusions on some comparisons. In addition, some relevant outcomes, such as quality of life and glucose variability, are not reported in the majority of trials. Furthermore, the duration of trials is relatively short, allowing an estimate of the effects of CGM in the short, but not in the long term.

Some of the observed results (i.e., effects on HbA1c and severe hypoglycemia) show a relevant heterogeneity, which has several possible explanations. Separate analyses of subgroups of trials (pediatric vs adult, MDI vs CSII, different devices, short- vs longer-term trials) failed to identify determinants of this heterogeneity. This means that the effects of CGM on glucose control and hypoglycemic risk could be different from the observed mean in specific subgroups of patients that we are currently unable to define. Although subgroup analyses based on age at enrollment did not reveal any significant effect of age as moderator of the results, it is possible that characteristics of patients enrolled differed across trials for some other feature. In addition, differences in educational management across different investigator might contribute to heterogeneity of results. A further source of heterogeneity is the type of device used, with possible differences in accuracy. Finally, the quality of trials is not homogeneous, particularly for older studies.

In addition, it should be noted that randomized trials are performed in a highly controlled setting and on selected patients, possibly differing from those of routine clinical practice. Observational studies have shown remarkable benefits with FGM in type 1 diabetes [46], which were not documented in clinical trials. On the other hand, a large multicenter cohort study showed a deterioration of HbA1c in a pediatric population of sub-optimally controlled patients with type 1 diabetes despite a wide introduction of CGM [52]. Although this latter result could have been determined by organizational, clinical or socio-demographic factors different from the use of glucose monitoring, data from observational studies suggest that the effects observed in randomized clinical trials cannot be immediately extrapolated to all clinical settings.

A comprehensive assessment of the impact of a new technology should include a cost-effectiveness evaluation, which is beyond the aims of the present meta-analysis. Glucose sensors could be perceived by healthcare payers as an additional cost; on the other hand, they reduce some direct and indirect health costs (e.g., those for hypoglycemia). The formal assessment of cost-effectiveness with data derived from clinical trials suggests a positive result for CGM systems [53].

In comparison with other therapeutic interventions (i.e., drugs), available evidence on the effects of CGM is relatively scarce. This is not surprising, since the lower efficacy of patent protection, the relatively smaller requirements of regulatory agencies, and the remarkable swiftness of innovation, make large-scale, long-term randomized trials economically unfeasible. In fact, the dilated times of randomized clinical trials do not seem to keep at pace with a very fast innovation. As a consequence, clinical practice is often more empirical than evidence-based. Despite this phenomenon, an accurate search of available evidence remains essential for making appropriate clinical decisions. In this respect, the use of CGM appears to provide beneficial effects in type 1 diabetes patients with insufficient glucose control and in those with hypoglycemia unawareness and/or frequent hypoglycemia.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval This article does not contain any studies with human or animal performed by any authors.

Informed consent Informed consent is not required.

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