Comparing effects of continuous glucose monitoring systems (CGMs) and self monitoring of blood glucose (SMBG) among adults with type 2 diabetes mellitus: A systematic review protocol

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Abstract

Background: Continuous glucose monitors (CGMs) have been used to manage diabetes with reasonable glucose control among patients with type 2 diabetes (T2D) in recent decades. CGM systems measure interstitial fluid glucose levels to provide information about glucose levels, which identifies fluctuation that would not have been identified with conventional self-monitoring. Self-monitoring of blood glucose (SMBG) is a classical tool to achieve glycaemic control. However, the effectiveness of glucose control, costs, and quality of life are needed to evaluate and compare CGM and SMBG among adults with T2D.

Methods: The review will compare the various forms of CGM systems (i.e flash-CGM, real-time-CGM, retrospective-CGM) versus SMBG/usual intervention regarding diabetes management among adults with T2D. The following databases will be searched: Cochrane Library, Science Direct, PubMed, EMBASE, CINAHL, PsycINFO, Scopus and grey literature for the identification of studies. The studies involving adults (aged ≥ 18 years old) will be included. We will include and summarise randomised clinical trials (RCTs) with respect to authors, publication type, year, status, and type of devices. Studies published in English between February 2010 and March 2020 will be included as the field of CGMs among T2D patients has emerged over the last decade. Primary outcomes that will be measured will be; HbA1c, body weight, time spent with hypoglycaemia or hyperglycaemia, blood pressure, quality of life. Secondary outcome measured will be morbidity, all-cause mortality, user satisfaction, and barriers. Study selection, data extraction, and risk of bias assessment will be conducted independently by at least two authors. A third author will determine and resolve discrepancies. Moreover, the quality of the evidence of the review will be assessed according to the Grading of Recommendations Assessment, Development and Evaluation Tool (GRADE).

Discussion: The systematic review will synthesise evidence on the comparison between using CGMs and SMBG. The results will support researchers and health care professionals to determine the most effective methods/technologies in the overall diabetes management. Moreover, this review will provide more detailed information about the barriers of using CGMs to improve implementation.

Systematic review registration: PROSPERO CRD42020149212
Background
Type 2 diabetes (T2D) is the most prevalent form of diabetes mellitus, characterized by β-cell dysfunction and insulin resistance. T2D is also a common global health problem and leads to severe damage and complications to the heart, kidneys, nerves, blood vessels, and eyes over time [1]. By 2040, the number of diabetic patients (aged 20-79) worldwide is expected to increase to 642 million [2]. The effect of diabetes extend beyond the individual to affect their families and societies such as reducing employment and thus increasing the economic burden [2].

Sustaining reasonable blood glucose control is important to manage T2D and avoid the short-and long-term diabetic complications including hypoglycaemia and vascular complications [3, 4]. However, blood glucose levels can undergo large fluctuations after meals, secondary to daily activities and after sleep, consequently creating control difficulties [5]. The monitoring tools needed to achieve reasonable glycaemic control continue to evolve, including more convenient self-monitoring blood glucose meters (SMBG), continuous glucose monitoring (CGM), and a better understanding of the strengths and limitations of glucose measurement. SMBG and CGM are the two most important tools for blood glucose monitoring among patients with T2D. SMBG is a traditional method for glucose measurement [4], which requires manual finger-prick blood test and checking the blood glucose levels with a glucometer. SMBG is inconvenient to afford a complete set of full profile of blood glucose fluctuation. By contrast, the CGM can deliver a complete blood glucose profile and the later have the capability to connect to insulin pumps and function as an alarm too. The CGM can provide a more comprehensive report of blood glucose levels of individuals than SMBG alone. Overall, CGM was generally accepted by patients with T2D and was suggested to play an essential role in diabetes management.

Clinical application of CGM started in the year 2000 and was generally indicated as a significant improvement in diabetes management [6]. Over the last decade, CGM has been demonstrated to be clinically valuable due to its accuracy, convenience, and improvement of software [7]. CGM use can promote glycemic and weight control, to help reduce risk of hypoglycemia and hyperglycemia, and improve relevant lifestyle behaviour [6, 7] [8]. It has become a useful tool for real-time monitoring of
blood glucose in clinical and public diabetes management settings, and for assessing the impact of treatment and lifestyle on daily changes in blood glucose levels [7, 9]. CGM devices are intravascular devices, which can be minimally invasive, or even non-invasive. Two types of CGM systems can be defined in clinical practice: retrospective systems and real-time systems. A reduced requirement for frequent calibration has accompanied the improvement in accuracy of CGM sensors. For example, flash CGM could be considered a unique subset of CGM which forms the blood glucose values only when the user scans the sensor by passing a cell phone or a reader near the sensor instead of updating a show of blood glucose continuously at five minutes intervals [6]. However, several potential common patient-reported barriers of CGM use including sensor insertion with pain or problems of high costs, accidental removal of the device or the adhesive strip, CGM impacts with sports and daily activities, and skin reactions of sensor adhesion [10, 11].

A review published in 2009 analyzed the CGM data by statistical tools and then strongly encouraged researchers and clinicians to adopt the rich information contained in CGM data to guide their research and to offer feedback and suggestion to diabetic patients by reports on CGM [12]. A meta-analysis of four RCTs of the systematic review indicated that real-time CGM has better control in reducing HbA1c levels compared with SMBG among patients with T2D [4], even those RCTs in this review had inadequate sample size for achieving the legacy impacts. Besides, many of the included studies were short-term with a small number of participants. A systematic review indicated that real-time CGM (RT-CGM) and professional CGM compared with usual care are effective in improving HbA1c control but could not form the conclusions on the effectiveness of flash CGM due to insufficient evidence [13]. A recent meta-analysis published in 2019 found that CGM can reduce HbA1c levels and time spent with hypoglycaemia among T2D. However, it has only searched three databases; it may not include all relevant studies. Besides, it did not compare different types of CGM devices [14].

There is uncertainty between different CGM interventions/systems (i.e. flash CGM, RT-CGM, retrospective CGM) and outcomes such as; hypoglycemia, weight change, quality of life, and user satisfaction. A systematic review is also lacking about comparing those aspects between CGM systems and SMBG. Therefore, this systematic review of RCTs aims to evaluate the effects of CGM vs
SMBG on blood glucose levels, body weight, blood pressure, hypoglycemia, quality of life, and user satisfaction among adults with T2D.

Methods
This protocol follows the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [15] (Additional file 1). This protocol will guide the review and any deviations while conducting the review will be reported including the reasons for the changes made in the method section of the final published manuscript. The review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) CRD42020149212.

Eligibility Criteria
The inclusion criteria of the review are: a) study design as having randomised controlled trials only; b) studies conducted in adults (aged ≥ 18 years old) diagnosed with T2D; c) have defined both use of real-time or non-real-time CGM as the intervention group and SMBG or routine glucose monitoring as the control group; and d) studies published in English. Studies published between February 2010 and March 2020 will be included as the field of CGMs among T2D has emerged over the last decade. Abstracts will be eligible for inclusion if sufficient information is provided to judge the quality and potential for bias of these trials. Non-RCT studies, non-type 2 diabetes, follow-up duration less than 6 weeks, and duplicate studies will be excluded.

Studies involving adults among T2D (aged ≥ 18 years old) have adopted CGMs as interventions will be included in this review. Inclusion criteria: a) Adults diagnosed with T2D (diagnostic criteria including the American Diabetes Association or World Health Organization or national guidelines); b) T2D of at least eight weeks duration; and 3) reporting HbA1c as one of the outcome measure.

Exclusion criteria: a) Adolescents (under 18 years of age) and elderly people (over 70); b) Gestational diabetes mellitus; and c). Other types of diabetes (such as idiopathic diabetes or type 1 diabetes).

Information Sources and Search Strategy
The following databases will be searched: Cochrane Library, Science Direct, PubMed, EMBASE, CINAHL, PsycINFO, Scopus and grey literature for the identification of studies. The studies involving adults (aged ≥ 18 years old) will be included. We will include and summarize randomized clinical trials
with respect to authors, publication type, year, status, and type of devices. Primary outcomes will be HbA1c, body weight, time spent with hypoglycaemia or hyperglycaemia, blood pressure, quality of life. Secondary outcome measures will be morbidity, all-cause mortality, user satisfaction, and barriers. Besides, the inclusion of grey literature (i.e. non-published, internal or non-reviewed articles, repositories, blogs) in the systematic review may help to overcome the publication bias that may arise due to the selective availability of data [16], thereby this review will include grey literature after reviewing the title and abstract accordingly.

Additionally, the reference list of identified systematic reviews and RCTs will also be updated to identify if references or bibliographies include relevant studies that might be included for the review (cross-referencing). Furthermore, indexed keywords in the Medical Subject Headings will be used to guarantee unified search terms. A comprehensive PubMed retrieval strategy (Additional file 2) will be developed in consultation with a medical librarian experienced in systematic database searching. Other databases will be searched and corresponding search strategies and logic grid will be adopted (Additional file 3).

**Study Selection**

Citation management system (Endnote X9) will be adopted to manage records exported from all the databases. First, all the studies will be screened by their titles using the Endnote X9. Then, the shortlisted studies will then be screened by their abstracts. Finally, the full-text of nominated studies will be screened according to the eligibility criteria. Study selection, data extraction, and risk of bias assessment will be conducted independently by at least two reviewers (MZ and YL). A pre-defined screening form will be designed and pilot testing will be conducted as per the eligibility criteria to ensure reliability of screening articles among the two reviewers (MZ and YL). Both reviewers will describe outcome measures after reviewing the studies to confirm the relevance of RCTs. A third author (WL) will determine and resolve discrepancies to make the final decision about whether the study meets the eligibility criteria for being included in the review in a consensus meeting. The process of study screening and selection will be reported via PRISMA flow diagram [17] (Additional file 4).
Data extraction and management

A data extraction form (Additional file 5) will be designed and edited by the review team after consultation. We will extract data by predesigned forms about characteristics of the studies to be included in the current study (including author, publication year, country, sample size, types of CGM devices, duration of diabetes, patient’s baseline, clinic history, basic treatment, and intervention/treatment duration). Continuous variables will illustrate as mean values, standard deviations, standard errors, or 95% CI, whereas binary variables will be expressed as frequencies and percentages (%). Studies comparing one SMBG group with two or more intervention groups will be treated as two or more studies sharing an SMBG group. Two reviewers (MZ and YL) will independently evaluate the quality of each study that meet the inclusion criteria of the systematic review. Another researcher (WL) will provide judgement when two authors have different reviews if necessary. We will evaluate duplicate publications, assess all available data simultaneously, maximizing the extraction of data for a bias assessment precisely. Authors will be contacted by emails to acquire missing or relevant material of their papers if necessary.

Quality Assessment of Included Studies

Cochrane’s risk of bias tool will be used for evaluating the quality of RCTs [18]. The following seven constructs will be evaluated as low, moderate, and high risk of bias or unclear risk of bias: random sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome assessors, incomplete data, selective reporting, and other potential risks (Additional file 6). Moreover, the quality of the evidence of the review will be assessed according to the Grading of Recommendations Assessment, Development and Evaluation Tool (GRADE) [19]. Two reviewers (MZ and YL) will independently evaluate the quality of each study. Any disagreement at this stage will be discussed and resolved by consultation and consensus within the review team if necessary. The summary of the quality of all included studies will be presented in a table.

Data synthesis and statistical analysis

This systematic review will synthesise a quantitative analysis known as meta-analysis. It seems that units may express the continuous variables differently in each included study; analysis will be
performed using standardised mean difference (SMD) and 95% CIs. Binary variables will be analysed by risk ratio (RR) and 95% CIs. When only the standard error of p-value is reported, standard deviation (SD) will be considered according to the method recommended by Altman and Bland (1996). Moreover, if no description for SD is reported, we will calculate from 95% CIs, t-test values, or p-values. The sensitivity analysis will be used to test the robustness of the choices made, such as changing the cut-off for high - or low-quality included studies. Besides, the heterogeneity (by Cochrane chi-square $\chi^2$ and the $I^2$ statistics) will be described via reporting differences in the study design and the characteristics of the study population [20]. A random-effect model will be used for analysis if appropriate; $I^2$ will be used for evaluating statistical heterogeneity ($I^2 \geq 50\%$ is considered as heterogeneous), since it is the percentage of total variation provided between the studies ($I^2$ values of 75%, 50% and 25% represent high, moderate and low heterogeneity, respectively) [21]. If sufficient RCTs are available and variability among those studies is low i.e. they are homogenous, a meta-analysis will be conducted as per the following subgroups if appropriate: a) real-time CGM vs SMBG; b) resorative CGM vs SMBG; c) real-time CGM vs routine care, and d) resorative CGM vs routine care. According to these categories, measures of associations such as relative risks, and odds ratios will be synthesized and reported. Beside this, when the number of included studies for this review is more than ten studies, a funnel plot will be plotted for evaluating publication bias. We will also use the Eggers’ regression test to statistically evaluate the asymmetry of the funnel plot.

Moreover, subgroup analysis via baseline HbA1c levels (< 6.5%, 6.6-7.9%, 8.0-11.0% and >11.0%) will be performed to assess the impact of baseline HbA1c on the effectiveness of CGM. Additionally, if heterogeneity is identified, a meta-regression analysis will be conducted on whether baseline information such as HbA1c, gender, age, and frequency and types of CGM sensor use has affected the impact of CGM on HbA1c levels.

Discussion
The main aim of this review is to compare the effectiveness between different types of GCM systems and SMBG or routine care. A systematic review is lacking to analyse the effectiveness of not only glucose control but also costs associated with it, and the quality of life. It will also analyse the
subgroups by comparing the differences between various types of CGM devices to help in the improvement of developing these devices. The review will have some advantages. The predefined approach is according to the Cochrane Handbook for Systematic Reviews of Interventions and considers the risk of bias and GRADE assessment [22] [23]. Intervention and control groups will be evaluated jointly and separately, so this systematic review will be able to determine why CGMs work as an intervention and under what circumstances. Therefore, risks of systematic error, random error, and design error of the review will be avoided [24]. A potential limitation of this review might be the inclusion of RCTs only and that too in the English language and the grey literature without peer-review. The results of this review will be publicly available and will be disseminated via academic presentations (both locally and internationally) and peer-reviewed publications. The review is anticipated to classify research gaps in the existing literature and provide evidence for further studies regarding CGM intervention and effective implementation.

Additional Files
Additional file 1: Table S1. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and checklist
Additional file 2: Table S2. Preliminary search strategy for PubMed
Additional file 3: Table S3. Logic grid
Additional file 4: Table S4. PRISMA-2009 flow diagram
Additional file 5: Table S5. Data extraction form
Additional file 6: Table S6. Classification of randomised trails at low and at high risk of biases

Abbreviations
T2D: type 2 diabetes; SMBG: self-monitoring blood glucose meters; CGM: continuous glucose monitoring; RT-CGM: real-time continuous glucose monitoring; RCTs: randomized controlled trials; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; PROSPERO: International Prospective Register of Systematic Reviews; GRADE: Grading of Recommendations Assessment, Development and Evaluation Tool; SMD: standardised mean difference; RR: risk ratio; SD: standard deviation.

Declarations
**Ethics approval and consent to participate**

The proposed systematic review will be based on previously published studies and will not include any human participants, the ethics approval and consent to participate is not applicable.

**Consent for publication**

All participants agreed that we use the collected data for academic publications.

**Availability of data and materials**

All data analyzed during this study are included in this manuscript and additional files.

**Competing Interests**

All authors of the study stated that there were no conflicts of interest.

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**Authors’ contributions**

MZ conceived and designed the study. MZ drafted the manuscript and is the guarantor of the systematic review. MZ, YL, WL designed the tables for included studies and evaluated the quality of included studies in the systematic review. MZ, YL, AK, QH, WZ developed search strategy and conducted data extraction and synthesis. PH, SY extensively revised the manuscript. All authors reviewed and approved the final manuscript as submitted and agreed to be responsible for all aspects of the work.

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Supplementary Files

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- Table S3. Logic grid.docx
- Table S4. PRISMA-2009 Flow Diagram.doc
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