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Diabetes-related symptoms, acute complications and management of diabetes mellitus in palliative care: a protocol for a systematic review.

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Diabetes-related symptoms, acute complications and management of diabetes mellitus in palliative care: a protocol for a systematic review.

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ABSTRACT

Introduction: Worldwide, an estimated 40 million people are in need of palliative care each year, but only 14% receive it. The incidence of diabetes mellitus (DM) in patients receiving palliative care is higher than in general population. This association is intended to grow as a result of the rising burden on DM worldwide, ageing populations and the improved overall survival time in last decades in several diseases. Recommendations for DM management in the context of palliative care are mainly based on expert opinions. There is a lack of suitable evidence base and randomized clinical trials in palliative care are scarce. The aim of our systematic review is to access the best management of DM in order to reduce important DM-related symptoms and acute complications in patients receiving palliative care.

Methods and analysis: The authors will study the state of the art on DM treatment and management, surveying the different approaches employed in palliative care adult patients. Sources of data will be Ovid MEDLINE, Embase, PubMed, Web of Sciences, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Scopus, CINAHL, and grey literature. Details regarding diet, oral and injectable antidiabetic drugs, insulin regimens and blood glucose monitoring strategies will be evaluated. Primary outcomes will be the presence of symptoms (polyuria, polydipsia, and polyphagia) and acute complications (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis) of DM. Secondary outcomes will be hospital admission and deaths due to DM-related complications, health-related quality of life, and glycemic control.

Ethics and dissemination: The systematic review methodology does not require ethical approval due to the nature of the study design. The results of the systematic review will be published in a peer-reviewed journal and publically available. It will also be disseminated electronically and in print.

PROSPERO registration number: CRD42018115772

Strengths and limitations of this study:

- The present protocol is an outline of the systematic review specificities that will guide the authors while conducting the systematic review on the diabetes-related symptoms, acute complications and management of diabetes mellitus in palliative care.
- The results of this systematic review will be strength of evidence of the different approaches used to manage diabetes mellitus in palliative care, identified from clinicians as need in the daily-care of patients with diabetes mellitus receiving palliative care.
- This systematic review will include studies of any study design because, as far as we know, this is the first systematic review on the diabetes-related symptoms and complications in palliative care and we do not want to miss any information.

INTRODUCTION

The World Health Organization (WHO) defines palliative care as an approach that improves the quality of life (QOL) of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual [1]. It can be provided at any age and is not limited to the end of life, being appropriate at any stage (stable, unstable, deteriorating or terminal) in a serious illness (cancer and/or other disease). The palliative care should be applicable early in the course of illness and can be provided along with curative treatment or other therapies that are intended to prolong life, such as chemotherapy or radiation therapy. Worldwide, an estimated 40 million people are in need of palliative care each year, but only 14% receive it. The majority of adults in need of palliative care have serious diseases such as cardiovascular diseases (38.5%), cancer (34%) and chronic respiratory diseases (10.3%) [2].

Diabetes mellitus (DM) affects more than 400 million people, corresponding to 8.5% of adults worldwide [2]. The incidence of DM in patients receiving palliative careis higher than in general population due to several factors: age, diabetogenic drugs such as corticosteroids, metabolic changes due to chronic disease, etc. This association is intended to grow as a result of the rising burden on DM worldwide, ageing populations and the improved overall survival time in the last decades in several diseases [3]. The diagnosis of DM has already been made in the majority of patients who are referred to palliative care services. However, in patients receiving palliative care, DM can be secondary to drugs such as corticosteroids. Furthermore, DM is, by itself, an increased cause of palliative enrollment in some countries with advanced health system integration [4,5]. Evidence-based practice guidelines for the management of DM were developed by several scientific associations[6–9]. Nutrition, pharmacologic therapy, self-monitoring blood glucose and HbA1c targets should be individualized for each patient. Goals should be individualized based on

duration of DM, age or life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. Although it is usually suggested less restrictive glycemic targets for DM management in the context of palliative care, recommendations are mainly based on expert opinions. Indeed, there is a lack of suitable evidence base and randomized clinical trials in palliative care are scarce. To our best knowledge, the most resourceful nutritional approach, oral and injectable (non-insulin) agents, types of insulin or insulin regimens, are still unknown.

Palliative medicine provides relief from pain and other distressing symptoms at any stage of the disease. Important hyperglycemic-related symptoms, such as polyuria, polydipsia and polyphagia, and DM-related acute complications, namely hypoglycemia, hyperglycemic hyperosmolar state and diabetic ketoacidosis, are of main concern and should be avoided. They can contribute to worsening patients' general condition and QOL, particularly acute complications, which commonly lead to hospital admission and additional consequences. Comfort, patient preferences, evaluation of oral intake, and preservation of QOL are of particular importance.

Objectives

This systematic review was developed after a multidisciplinary discussion between the authors of shared doubts and concerns regarding DM management in palliative care. The aim of our systematic review is to access the best management of DM in order to reduce important DM-related symptoms (polyuria, polydipsia, and polyphagia) and acute complications (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis) in patients receiving palliative care. The results of this systematic review could be important to improved patients' care and be a stimulus for additional studies regarding DM management in palliative care.

METHODS AND ANALYSIS

The present protocol followed the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) that was defined in 2015 [10], subsequent to the PRISMA

Statement. The protocol is registered online on the International prospective register of systematic reviews, PROSPERO.

Eligibility criteria

The population, intervention, comparator and outcomes as described by the PRISMA Statement [11] are reported below.

Type of population

We will include studies of diabetic adult (≥ 18 years old) patients on palliative care. We will exclude studies with pediatric population, absence of DM, and with patients who are not in palliative care.

Type of intervention

We will include studies reporting the intervention: management of DM. Details regarding diet, oral and injectable (non-insulin) antidiabetic drugs, insulin regimens and blood glucose monitoring strategies will be evaluated. Different approaches according to etiology of DM, duration of DM, stage of palliative disease (stable, unstable, deteriorating, terminal) will also be assessed.

Type of comparator

The comparator item will be the different treatments and/or approaches used to manage DM in patients receiving palliative care.

Type of outcome

Primary outcomes will be the presence of symptoms (polyuria, polydipsia, and polyphagia) and acute complications (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis) of DM. If data exists, we will also report the secondary outcomes: hospital admission due to DM-related complications, deaths due to DM-related complications, health-related QOL (objective measures), and glycemic control measured by HbA1c or average glycemia.

Type of studies

We will include studies of any design regarding DM treatment and management in adult patients on palliative care. We will include only studies with the minimum of 10 participants. We will exclude

editorials, comments, case reports, and other reviews and studies before 1990 (year of the first formal definition of palliative care by World Health Organization).

Information sources

We will search the following electronic bibliographic databases: Ovid MEDLINE, Embase, PubMed Central, Web of Sciences, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Search strategy

The search will be conducted in December 2018. Core health bibliographic databases will be searched from January 1990 to December 2018.

The search strategy will include only terms relating to or describing the intervention. The search strategy will be defined for Ovid MEDLINE and then will be adapted for use with other bibliographic databases. No filters or limitations were applied to the search strategy to ensure retrieval of pre-indexed materials. Only studies in English, Spanish and Portuguese will be included. The authors will also search for grey literature, including unpublished conference proceedings or abstracts from relevant specialty conferences. Reference lists of previous reviews and of included studies will also be screened looking for potential eligible studies. The full search strategy for each database is available in the supplementary material.

Study records

Data management

We will apply the inclusion and exclusion criteria outlined above to the potential eligible studies retrieved using our search strategy. For studies selection we will use Covidence – Better Systematic Review Management [12]. All the records identified in the search strategy will be downloaded as Research Information Systems (RIS) files, and uploaded to EndNote (as a security copy) and to Covidence.

Selection process

Covidence will automatically identify and exclude the duplicates. After obtaining the final potentially eligible articles to include in this systematic review, titles and abstracts will be screened by two independent reviewers. The conflicts will be solved by a third author not involved in voting the specific study. Potentially eligible studies will be uploaded into Covidence for full-text screening. Similarly, this process will be done by two independent reviewers. The same procedure will be applied and any disagreement between them will be resolved by a third reviewer.

Data collection process

Relevant data will be extracted into a predefined data extraction sheet. This data extraction sheet will be designed for the purpose of this study and will be piloted per the authors responsible for the data extraction with a minimum of 5 studies.

Seven authors will extract data from the potential eligible studies. Each study will be double-reviewed: one author will extract the data and a second author will independently check the data extraction forms for accuracy and detail. Discrepancies between the authors will be solved by another author and discussed until reaching consensus. Data extraction will also be done using the software Covidence. Authors of eligible studies will be contacted by email to provide missing or additional data.

Data items

The data extraction sheet will contain information regarding study setting, study population, participant's characteristics, study methodology, life-threatening illness related data (etiology of disease, stage of palliative care), details of DM (type and duration of DM, usual treatment namely class of oral or injectable [non-insulin] antidiabetic drugs, type of insulin, insulin regimen), type of DM management used in the palliative care (diet, oral antidiabetic drugs, type of insulin, insulin regimen, blood glucose monitoring strategies) and information for assessment of the risk of bias. The frequency of DM-related symptoms (polyuria, polydipsia, and polyphagia) and DM-related acute complications (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis) will be extracted and evaluated according to different DM approaches. Hospital

admission and deaths due to DM-related complications, QOL, HbA1c and average glycemia will also be extracted when available.

Outcomes and prioritization

All the variables will be extracted as string variables. As mentioned on the type of outcomes, we will extract all the data available regardless if it is a main or additional outcome. We will not apply prioritization schemes as meta-analysis will not be performed.

Risk of bias in individual studies

Two independent reviewers will assess the risk of bias and quality evidence of the eligible studies. Disagreements between the review authors over the risk of bias will be resolved by a third author and discussed until reaching consensus. We will use the Study Quality Assessment Tools of the *National Institutes of Health* [13]. Any discrepancies or unusual patterns will be checked with the study investigator.

Data synthesis

The results will be summarized in tables containing the population, type of treatment and/or approach for DM, and the outcomes. The comparison between these variables will be further described. We will write a descriptive synthesis of the findings from the included studies, structured from the patient's characteristics, type of diabetes management, data from the disease referred to palliative care, and acute complications and symptoms of DM. If data exists, we will provide summaries of intervention effects for each study.

Analysis of subgroups or subsets

If there is enough data, we will perform sub-group analysis by age groups, sex, etiology of the disease requiring palliative care, stage of palliative care, type of DM, different settings (acute or primary care sector, professional or family care), and study design.

Patient and public involvement

Patients and public were not involved in this study.

Ethics and dissemination: The systematic review methodology does not require ethical approval due to the nature of the study design. The results of the systematic review will be published in a peer-reviewed journal and publically available. It will also be disseminated electronically and in print.

Authors' contributions: RBS is the primary author for the study and approved the final manuscript. RBS and MSP conceived, designed the study and drafted the protocol. MSP is the corresponding author. MSP and LÖ performed the full search strategy for each database. LÖ provided feedback on study protocol design and critically revised earlier versions of the manuscript. BA, VSA, RB, VG, MJMR and DC critically revised earlier drafts of the manuscript for intellectual content. All the authors read and approved the final manuscript.

Funding statement: This study did not require any funding.

Competing interests: None.

Data sharing: No additional data available.

Patient consent: Not required per the study design.

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Diabetes-related symptoms, acute complications and management of diabetes mellitus in palliative care: a systematic review.

Search strategy for **PubMed**:

(((((((((diabetes mellitus[MeSH Terms]) OR diabet*[Title/Abstract])) OR T1DM[Title/Abstract]) OR T2DM[Title/Abstract]) OR NIDDM[Title/Abstract]) OR IDDM[Title/Abstract]) OR hyperglycemia[MeSH Major Topic]) OR hyperglycemia*[Title/Abstract]) AND (((((((((palliative care[MeSH Major Topic]) OR terminal care[MeSH Major Topic]) OR palliative[Title/Abstract]) OR "terminal care"[Title/Abstract]) OR “supportive care”[Title/Abstract]) OR “Terminal patient” [Title/Abstract]) OR “terminal patients” [Title/Abstract]) OR “End of Life Care”[Title/Abstract]) OR “Terminal Phase”[Title/Abstract])

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	2, 3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	11
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	5, 6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	6
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	7
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	8
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	9
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	9
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	10
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	NA
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	NA

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Palliative care
Keywords:	DIABETES & ENDOCRINOLOGY, PALLIATIVE CARE, Adult palliative care < PALLIATIVE CARE, General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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ABSTRACT

Introduction: Worldwide, an estimated 40 million people are in need of palliative care each year, but only 14% receive it. The incidence of diabetes mellitus (DM) in patients receiving palliative care is higher than in the general population. This association is intended to grow as result of the rising burden on DM worldwide, ageing populations and the improved overall survival time of several diseases over the last few decades. Recommendations for DM management in the context of palliative care are mainly based on expert opinion. There is a lack of suitable evidence base and randomized clinical trials in palliative care are scarce. The aim of our systematic review is to assess the best DM management practices in order to reduce important DM-related symptoms and acute complications in patients receiving palliative care.

Methods and analysis: The authors will study the DM treatment and management literature, surveying the different approaches employed in palliative care adult patients. Data sources will include Ovid MEDLINE, Embase, PubMed, Web of Sciences, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Scopus, CINAHL, and grey literature. Details regarding diet, oral and injectable glucose-lowering medicines, insulin regimens and blood glucose monitoring strategies will be evaluated. Primary outcomes will be the presence of symptoms (polyuria, polydipsia, and polyphagia) and acute complications of DM (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis). Secondary outcomes will be hospital admissions and deaths due to DM-related complications, health-related quality of life, and glycemic control.

Ethics and dissemination: The systematic review methodology does not require ethics approval due to the nature of the study design. The results of the systematic review will be published in a peer-reviewed journal and will be publically available.

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Strengths and limitations of this study:

- The present protocol is an outline of the systematic review specificities that will guide the authors while conducting the systematic review on the diabetes-related symptoms, acute complications and management of diabetes mellitus in palliative care.
- The search strategy will be limited to studies other than in English, Portuguese or Spanish language and before 1990.
- One of diabetes mellitus related outcomes will be the HbA1c, this is an average measure of blood glucose and many factors can affect its accuracy, but we will consider this during risk of bias and quality of evidence assessment.
- The inclusion of grey literature will make this study wider in terms of included information.
- This systematic review will include studies of any design because, as far as we know, this is the first systematic review on the diabetes-related symptoms and complications in palliative care.

INTRODUCTION

The World Health Organization (WHO) defines palliative care as an approach that improves the quality of life (QOL) of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual [1]. Palliative care can be provided to a person of any age and it is not limited to patients at the end of life, is appropriate at any stage (stable, unstable, deteriorating or terminal) of serious illnesses (cancer and/or another disease) [2]. Palliative care should be applicable early in the course of illness and it can be provided alongside curative treatment or other therapies that are intended to prolong life, such as chemotherapy or radiation therapy. Worldwide, an estimated 40 million people are in need of palliative care each year, but only 14% receive it [3]. The majority of adults in need of palliative care have serious diseases such as cardiovascular diseases (38.5%), cancer (34%) and chronic respiratory diseases (10.3%) [3].

Diabetes mellitus (DM) affects more than 400 million people, corresponding to 8.5% of adults worldwide [3]. The incidence of DM in patients receiving palliative care is higher than in the general population due to several factors, such as age, use of diabetogenic drugs such as corticosteroids and metabolic changes due to chronic disease. This association is intended to grow as a result of the rising burden of DM worldwide, ageing populations and the improved overall survival time of several diseases over the last few decades [4,5]. The diagnosis of DM has already been made in the majority of patients who are referred to palliative care services [6]. However, in patients receiving palliative care, DM can be secondary to drugs such as corticosteroids [7]. Furthermore, DM is, by itself, an increased cause of palliative enrollment in some countries with advanced health system integration [8,9]. Evidence-based practice guidelines for the management of DM have been developed by several scientific associations [10–13] which highlight that nutrition, pharmacologic therapy, self-monitoring blood glucose and

HbA1c targets should be individualized for each patient. Additionally, goals should be individualized based on the duration of DM, age or life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. Although less restrictive glycemic targets for DM management in the context of palliative care are usually suggested, recommendations are mainly based on expert opinion [10]. Indeed, there is a lack of relevant evidence particularly from randomized clinical trials that guides DM management in the context of palliative care. To the best of our knowledge, the most resourceful nutritional approach, oral and injectable (non-insulin) agents, types of insulin or insulin regimens, are still unknown to manage DM in the palliative context.

Palliative medicine manages the whole person, providing not only relief from pain and other distressing symptoms at any stage of the disease, but also treating concomitant chronic diseases. Comfort, patient preferences and preservation of QOL are of particular importance. As such, treatment of hyperglycemia-related symptoms and DM-related acute complications, that can contribute to worsening patients' general condition and QOL and lead to hospital admission, is paramount. Therefore, interdisciplinary team care and early referral to relevant clinicians are essential.

Objectives

This systematic review was developed after a multidisciplinary discussion between the authors of shared doubts and concerns regarding DM management in the context of palliative care. The aim of our systematic review is to access the best management of DM in order to reduce important DM-related symptoms (polyuria, polydipsia, and polyphagia) and acute complications (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis) in patients receiving palliative care. The results of this systematic review may guide practices to improve patient care and be a stimulus for additional studies regarding DM management in palliative care.

METHODS AND ANALYSIS

The present protocol followed the preferred reporting items for systematic reviews and meta-analysis protocols (PRISMA-P) that was defined in 2015 [14], subsequent to the PRISMA Statement. The protocol is registered online on the International prospective register of systematic reviews, PROSPERO: CRD42018115772.

Eligibility criteria

The population, intervention, comparator and outcomes as described by the PRISMA Statement [15] are reported below.

Type of population

We will include studies of diabetic adult (≥ 18 years old) patients receiving palliative care. We will exclude studies with the pediatric population, those who do not have DM, and the patients who are not in palliative care.

Type of intervention

We will include primary studies reporting the intervention: management of DM. Details regarding diet, oral and injectable (non-insulin) glucose-lowering drugs, insulin regimens and blood glucose monitoring strategies will be evaluated. Different approaches according to the etiology of DM, duration of DM, stage of palliative disease (stable, unstable, deteriorating, terminal) will also be assessed.

Type of comparator

The comparator item will be the different treatments and/or approaches used to manage DM in patients receiving palliative care.

Type of outcome

Primary outcomes will be the presence of symptoms (polyuria, polydipsia, and polyphagia) and acute complications of DM (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis). If data exists, we will also report the secondary outcomes: hospital admissions due to DM-related complications, deaths due to DM-related complications, health-related QOL

(objective measures), advanced care planning, documented advance care plans and glycemic control measured by HbA1c or average glycemia.

Type of studies

We will include studies of any design regarding DM treatment and management in adult patients receiving palliative care. We will include only studies with a minimum of 10 participants. We will exclude editorials, comments, case reports, and other reviews and studies before 1990 (year of the first formal definition of palliative care by the World Health Organization).

Information sources

We will search the following electronic bibliographic databases: Ovid MEDLINE, Embase, PubMed Central, Web of Sciences, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL). Grey literature will be searched at the Grey Literature Report and Open Grey databases. The inclusion and exclusion criteria applied will be the same used for medical bibliographic databases.

Search strategy

The search will be conducted as soon as this protocol is published. Core health bibliographic databases will be searched from January 1990 to the current time.

The search strategy will include only terms relating to or describing the intervention. The search strategy will be defined for Ovid MEDLINE and then will be adapted for use with other bibliographic databases. No filters or limitations will be applied to the search strategy to ensure retrieval of pre-indexed materials. Only studies in English, Spanish and Portuguese will be included. Grey literature will include unpublished conference proceedings or abstracts from relevant speciality conferences. Reference lists of previous reviews and of included studies will also be screened looking for potentially eligible studies. The full search strategy for each database is available in the supplementary material.

Study records

Data management

We will apply the inclusion and exclusion criteria outlined above to the potentially eligible studies retrieved using our search strategy. For studies selection, we will use Covidence – Better Systematic Review Management [16]. All the records identified in the search strategy will be downloaded as Research Information Systems (RIS) files and uploaded to EndNote (as a security copy) and to Covidence.

Selection process

Covidence will automatically identify and exclude the duplicates. After obtaining the final potentially eligible articles to include in this systematic review, titles and abstracts will be screened by two independent reviewers. The two independent reviewers will screen all titles and abstracts considering the inclusion and exclusion criteria outlined. Based on that they will vote the potentially eligible study to be included or excluded. Each study will be voted by the two authors and conflicts will be solved by a third author not involved in screening the papers. Potentially eligible studies will be uploaded into Covidence for full-text screening. Similarly, this process will be done by two independent reviewers. The same procedure will be applied and any disagreement between them will be resolved by a third reviewer.

Data collection process

Relevant data will be extracted into a predefined data extraction sheet. This data extraction sheet will be designed for the purpose of this study and will be piloted per the authors responsible for the data extraction with a minimum of 5 studies.

Seven authors will extract data from potentially eligible studies. Each study will be double-reviewed: one author will extract the data and a second author will independently check the data extraction forms for accuracy and detail. Discrepancies between the authors will be solved by another author and discussed until reaching consensus. Data extraction will also be done using

the software Covidence. Authors of eligible studies will be contacted by email to provide missing or additional data.

Data items

The data extraction sheet will contain information regarding study setting, study population, participant's characteristics, study methodology, life-threatening illness related data (etiology of disease, stage of palliative care), details of DM (type and duration of DM, usual treatment namely class of oral or injectable (non-insulin) glucose-lowering drugs, type of insulin, insulin regimen), type of DM management used in the palliative care (diet, oral glucose-lowering medicines, type of insulin, insulin regimen, blood glucose monitoring strategies) and information for assessment of the risk of bias. The frequency of DM-related symptoms (polyuria, polydipsia, and polyphagia) and DM-related acute complications (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis) will be extracted and evaluated according to different DM approaches. Hospital admission and deaths due to DM-related complications, QOL, advanced care planning, documented advance care plans, HbA1c and average glycemia will also be extracted when available.

Outcomes and prioritization

All the variables will be extracted as string variables. As mentioned on the type of outcomes, we will extract all the data available regardless if it is a main or additional outcome. We will not apply prioritization schemes as meta-analysis will not be performed.

Risk of bias in individual studies

Two independent reviewers will assess the risk of bias and quality evidence of the eligible studies using the Study Quality Assessment Tools of the *National Institutes of Health* [17]. Disagreements between the review authors over the risk of bias will be resolved by a third author and discussed until reaching consensus. Any discrepancies or unusual patterns will be checked with the study investigator, although we will not exclude studies based on their quality report, we will just describe it

Data synthesis

The results will be summarized in tables containing the year, country, population, type of treatment and/or approach for DM, and the outcomes. The comparison between these variables will be further described. We will write a descriptive synthesis of the findings from the included studies, structured from the patient's characteristics, type of diabetes management, data from the disease referred to palliative care, and acute complications and symptoms of DM. If data exists, we will provide summaries of intervention effects for each study.

Analysis of subgroups or subsets

If there is enough data, we will perform sub-group analysis by age groups, sex, etiology of the disease requiring palliative care, stage of palliative care, type of DM, different settings (acute or primary care sector, professional or family care), and study design.

Patient and public involvement

Patients and the public were not involved in this study.

Ethics and dissemination: The systematic review methodology does not require ethics approval due to the nature of the study design. The results of the systematic review will be published in a peer-reviewed journal and will be publically available. It will also be disseminated electronically and in printed versions.

Authors' contributions: RBS is the primary author for the study and approved the final manuscript. RBS and MSP conceived, designed the study and drafted the protocol. MSP is the corresponding author. MSP and LÖ performed the full search strategy for each database. LÖ provided feedback on study protocol design and critically revised earlier versions of the manuscript. BA, VSA, RB, VG, MJMR and DC critically revised earlier drafts of the manuscript for intellectual content. All the authors read and approved the final manuscript.

Funding statement: This study did not require any funding.

Competing interests: None.

Data sharing: No additional data available.

Patient consent: Not required per the study design.

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Diabetes-related symptoms, acute complications and management of diabetes mellitus in palliative care: a systematic review.

Search strategy for **PubMed**:

((((((((((diabetes mellitus[MeSH Terms]) OR diabet*[Title/Abstract])) OR T1DM[Title/Abstract]) OR T2DM[Title/Abstract]) OR NIDDM[Title/Abstract]) OR IDDM[Title/Abstract]) OR “glucose lowering medicine*”[Title/Abstract]) OR hyperglycemia[MeSH Major Topic]) OR hyperglycemia*[Title/Abstract]) AND ((((((((palliative care[MeSH Major Topic]) OR terminal care[MeSH Major Topic]) OR palliative[Title/Abstract]) OR "terminal care"[Title/Abstract]) OR “supportive care”[Title/Abstract]) OR “Terminal patient” [Title/Abstract]) OR “terminal patients” [Title/Abstract]) OR “End of Life Care”[Title/Abstract]) OR “Terminal Phase”[Title/Abstract])

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	2, 3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	11
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	5, 6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	6
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	7
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	8
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	9
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	9
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	10
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☒	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	NA
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	NA

BMJ Open

Diabetes-related symptoms, acute complications and management of diabetes mellitus of patients who are receiving palliative care: a protocol for a systematic review.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028604.R2
Article Type:	Protocol
Date Submitted by the Author:	01-May-2019
Complete List of Authors:	Bettencourt-Silva, Rita; Centro Hospitalar Universitário São João, Department of Endocrinology, Diabetes and Metabolism; Faculty of Medicine, Instituto de Investigação e Inovação em Saúde, University of Porto Aguiar, Beatriz; Unidade de Saúde de Ilha de São Miguel, Unidade de Saúde de Rabo de Peixe Sá-Araújo, Vânia; Instituto Português de Oncologia do Porto Francisco Gentil, Department of Palliative Care Barreira, Rosa; Unidade de Saúde Familiar Maresia, Unidade Local de Saúde de Matosinhos Guedes, Vânia; Unidade de Saúde Familiar São João do Porto, Agrupamento de Centros de Saúde (ACES) do Porto Ocidental Marques Ribeiro, Maria João; Centro Hospitalar Universitário São João, Department of Medical Oncology Carvalho, Davide ; Centro Hospitalar Universitário de São João, Department of Endocrinology, Diabetes and Metabolism; Faculty of Medicine, Instituto de Investigação e Inovação em Saúde, University of Porto Östlundh, Linda; United Arab Emirates University College of Medicine and Health Sciences, National Medical Library Paulo, Marília Silva; United Arab Emirates University College of Medicine and Health Sciences, Institute of Public Health; Universidade Nova de Lisboa Instituto de Higiene e Medicina Tropical,
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Palliative care
Keywords:	DIABETES & ENDOCRINOLOGY, PALLIATIVE CARE, Adult palliative care < PALLIATIVE CARE, General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Diabetes-related symptoms, acute complications and management of diabetes mellitus of patients who are receiving palliative care: a protocol for a systematic review.

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ABSTRACT

Introduction: Worldwide, an estimated 40 million people are in need of palliative care each year, but only 14% receive it. The incidence of diabetes mellitus (DM) in patients receiving palliative care is higher than in the general population. This association is intended to grow as result of the rising burden of DM worldwide, ageing populations and the improved overall survival time of several diseases over the last few decades. Recommendations for DM management in the context of palliative care are mainly based on expert opinion as there is a lack of suitable evidence base and randomized clinical trials in palliative care are scarce. The aim of our systematic review is to identify the best DM management practices in order to reduce important DM-related symptoms and acute complications in patients receiving palliative care.

Methods and analysis: The authors will study the DM treatment and management literature, surveying the different approaches employed to treat adult palliative patients. Core health bibliographic databases will be searched from January 1990 to May 2019. Data sources will include Ovid MEDLINE, Embase, PubMed, Web of Sciences, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Scopus, CINAHL, and grey literature. Details regarding diet, oral and injectable glucose-lowering medicines, insulin regimens and blood glucose monitoring strategies will be evaluated. We defined the primary outcomes to compare between DM management approaches as the presence of symptoms (polyuria, polydipsia, and polyphagia) and acute complications of DM (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis), and secondary outcomes as hospital admissions and deaths due to DM-related complications, health-related quality of life, and glycemic control.

Ethics and dissemination: The systematic review methodology does not require ethics approval due to the nature of the study design. The results of the will be published in a peer-reviewed journal and will be publically available.

PROSPERO registration number: CRD42018115772

Strengths and limitations of this study:

- The present protocol is an outline of the systematic review specificities that will guide the authors while conducting the systematic review on the diabetes-related symptoms, acute complications and management of diabetes mellitus in palliative care.
- Limitations of this review include the exclusion of papers reported in languages other than English, Portuguese or Spanish and those published prior to 1990.
- The inclusion of grey literature will broaden this study in terms of included information.
- This systematic review will include primary studies of any design because, as far as we know, this is the first systematic review on the diabetes-related symptoms and complications in palliative care.

INTRODUCTION

The World Health Organization (WHO) defines palliative care as an approach that improves the quality of life (QOL) of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual [1]. Palliative care can be provided to a person of any age and it is not limited to patients who are actively dying, is appropriate at any stage (stable, unstable, deteriorating or terminal) of serious illnesses (cancer and/or another disease) [2]. Palliative care is best introduced early in the course of illness and it can be provided alongside curative treatment or other therapies that are intended to prolong life, such as chemotherapy or radiation therapy. Worldwide, an estimated 40 million people are in need of palliative care each year, but only 14% receive it [3]. The majority of adults in need of palliative care have serious diseases such as cardiovascular diseases (38.5%), cancer (34%) and chronic respiratory diseases (10.3%) [3].

Diabetes mellitus (DM) affects more than 400 million people, corresponding to 8.5% of adults worldwide [3]. The incidence of DM in patients receiving palliative care is higher than in the general population due to several factors, such as age, use of diabetogenic drugs such as corticosteroids and metabolic changes due to chronic disease. This association is intended to grow as a result of the rising burden of DM worldwide, ageing populations and the improved overall survival time of several diseases over the last few decades [4]. The diagnosis of DM has already been made in the majority of patients who are referred to palliative care services. Furthermore, DM is, by itself, an increased cause of palliative enrollment in some countries with advanced health system integration as it can be considered as a life-threatening illness [5–7]. Evidence-based practice guidelines for the management of DM have been developed by several scientific associations [8–12] which highlight that nutrition, pharmacologic therapy, self-monitoring blood glucose and HbA1c targets should be individualized for each patient. Additionally, goals

should be individualized based on the duration of DM, age or life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations [13]. Although less restrictive glycemic targets for DM management in the context of palliative care are usually suggested, recommendations are mainly based on expert opinion. Indeed, there is a lack of relevant evidence particularly from randomized clinical trials that guides DM management in the context of palliative care. Even the opinions of Diabetologists and Oncologists were different dealing with diabetes care in people with cancer [14]. To the best of our knowledge, the most resourceful nutritional approach, oral and injectable (non-insulin) agents, types of insulin or insulin regimens, are still unknown to manage DM in the palliative context. Therefore, the DM management in these patients remains a challenge.

Palliative medicine manages the whole person, providing not only the relief from pain, depression and other distressing symptoms at any stage of the disease but also treats joint chronic diseases. As such, the appropriate treatment of hyperglycemia-related symptoms and DM-related acute complications that can contribute to worsening patients' general condition and QOL, particularly acute complications, which commonly lead to hospital admissions and additional consequences. Comfort, patient preferences, evaluation of oral intake, and preservation of QOL are of particular importance in palliative medicine and interdisciplinary team care and early referral to relevant clinicians are essential.

Objectives

This systematic review was developed after a multidisciplinary discussion between the authors of shared doubts and concerns regarding DM management in the context of palliative care. The aim of our systematic review is to identify the best management of DM in order to reduce important DM-related symptoms (polyuria, polydipsia, and polyphagia) and acute complications (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis) in patients

receiving palliative care. The results of this systematic review may guide practices to improve patient care and be a stimulus for additional studies regarding DM management in palliative care.

METHODS AND ANALYSIS

The present protocol followed the preferred reporting items for systematic reviews and meta-analysis protocols (PRISMA-P) that was defined in 2015 [15], subsequent to the PRISMA Statement. The protocol is registered online on the international prospective register of systematic reviews, PROSPERO: CRD42018115772.

Eligibility criteria

The population, intervention, comparator and outcomes as described by the PRISMA Statement [16] are reported below.

Type of population

We will include studies of diabetic adult (≥ 18 years old) patients receiving palliative care. We will exclude studies of pediatric population, those who do not have DM, and the patients who are not in palliative care.

Type of intervention

We will include primary studies reporting the intervention: management of DM. Details regarding diet, oral and injectable (non-insulin) glucose-lowering drugs, insulin regimens and blood glucose monitoring strategies will be evaluated. Different approaches according to the etiology of DM, duration of DM, stage of palliative disease (stable, unstable, deteriorating, terminal) will also be assessed.

Type of comparator

The comparator item will be the different treatments and/or approaches used to manage DM in patients receiving palliative care.

Type of outcome

We have defined primary outcomes as specific measures of the presence of symptoms (polyuria, polydipsia, and polyphagia) and acute complications of DM (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis) in order to make a feasible comparison of the different types of DM management approaches. If data exists, we will also report the secondary outcomes: hospital admissions due to DM-related complications, deaths due to DM-related complications, health-related QOL (objective measures), advanced care planning, documented advance care plans and glycemic control measured by HbA1c or average glycemia.

Type of studies

We will include studies of any design regarding DM treatment and management in adult patients receiving palliative care. We will include only studies with a minimum of 10 participants. We will exclude editorials, comments, case reports, and other reviews and studies before 1990 (year of the first formal definition of palliative care by the World Health Organization).

Information sources

We will search the following electronic bibliographic databases: Ovid MEDLINE, Embase, PubMed Central, Web of Sciences, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL). Grey literature will be searched using the Grey Literature Report and Open Grey databases.

Search strategy

The search will be conducted as soon as this protocol is published. Core health bibliographic databases will be searched from January 1990 to May 2019.

The search strategy will include terms defined in accordance to population, intervention, comparator and outcomes as described above. The search strategy will be defined for Pubmed and then will be adapted for use with other bibliographic databases. No filters or limitations will be applied to the search strategy to ensure retrieval of pre-indexed materials. Only studies in English, Spanish and Portuguese will be included. Grey literature will include unpublished conference

proceedings or abstracts from relevant speciality conferences. Reference lists of previous reviews and of included studies will also be screened looking for potentially eligible studies. The full search strategy for each database is available in the supplementary material.

Study records

Data management

We will apply the inclusion and exclusion criteria outlined above to the potentially eligible studies retrieved using our search strategy. For studies selection, we will use Covidence – Better Systematic Review Management [17]. All the records identified in the search strategy will be downloaded as Research Information Systems (RIS) files and uploaded to EndNote (as a security copy) and to Covidence.

Selection process

Covidence will automatically identify and exclude the duplicates. After obtaining the final potentially eligible articles to include in this systematic review, titles and abstracts will be screened by two independent reviewers considering the inclusion and exclusion criteria outlined. Based on these criteria, the independent reviewers will accept or reject studies. Each study will be voted by the two authors. Conflicts will be solved by a third author not involved in screening the papers. Potentially eligible studies will be uploaded into Covidence for full-text screening. Similarly, this process will be done by two independent reviewers. The same procedure will be applied and any disagreement between them will be resolved by a third reviewer.

Data collection process

Relevant data will be extracted into a predefined data extraction sheet. This data extraction sheet will be designed for the purpose of this study and will be piloted per the authors responsible for the data extraction with a minimum of 5 studies.

Seven authors will extract data from potentially eligible studies. Each study will be double-reviewed: one author will extract the data and a second author will independently check the data extraction forms for accuracy and detail. Discrepancies between the authors will be solved by

another author and discussed until reaching consensus. Data extraction will also be done using the software Covidence. Authors of eligible studies will be contacted by email to provide missing or additional data.

Data items

The data extraction sheet will contain information regarding study setting, study population, participant's characteristics, study methodology, life-threatening illness related data (etiology of disease, stage of palliative care), details of DM (type and duration of DM, usual treatment namely class of oral or injectable (non-insulin) glucose-lowering drugs, type of insulin, insulin regimen), type of DM management used in the palliative care (blood glucose monitoring strategies, diet, oral glucose-lowering medicines, type of insulin and insulin regimen such as sliding scale insulin or scheduled insulin therapy with only basal insulin treatment or basal bolus insulin regimen) [18] and information for assessment of the risk of bias. The frequency of DM-related symptoms (polyuria, polydipsia, and polyphagia) and DM-related acute complications (hypoglycemia, hyperglycemic hyperosmolar state, and diabetic ketoacidosis) will be extracted and evaluated according to different DM approaches, such as insulin treatment alone or combined with other glucose lowering-drugs. Hospital admission and deaths due to DM-related complications, QOL, HbA1c and average glycemia will also be extracted where available.

Outcomes and prioritization

All the variables will be extracted as string variables. As mentioned in the type of outcomes section, we will extract all the data available regardless if it is a main or additional outcome. We will not apply prioritization schemes as meta-analysis will not be performed.

Risk of bias in individual studies

Two independent reviewers will assess the risk of bias and quality evidence of the eligible studies using the Study Quality Assessment Tools of the *National Institutes of Health* [19]. Disagreements between the review authors over the risk of bias will be resolved by a third author and discussed until reaching consensus. Any discrepancies or unusual patterns will be checked with the study

investigator, although we will not exclude studies based on their quality report, we will describe the quality of the included studies.

Data synthesis

The results will be summarized in tables containing the year, country, population, type of treatment and/or approach for DM, and the outcomes. The comparison between these variables will be further described. We will write a descriptive synthesis of the findings from the included studies, structured from the patients' characteristics, type of diabetes management, details of the disease for which the patient was referred to palliative care, and acute complications and symptoms of DM. If data exists, we will provide summaries of intervention effects for each study.

Analysis of subgroups or subsets

If there is enough data, we will perform sub-group analysis by age groups, sex, etiology of the disease requiring palliative care, stage of palliative care, type of DM, different settings (acute or primary care sector, professional or family care), and study design.

Patient and public involvement

Patients and the public will not be involved in this study.

Ethics and dissemination: The systematic review methodology does not require ethics approval due to the nature of the study design. The results of the systematic review will be published in a peer-reviewed journal and will be publically available. It will also be disseminated electronically and in printed versions.

Authors' contributions: RBS is the primary author for the study. RBS and MSP conceived, designed the study and drafted the protocol. MSP is the corresponding author. MSP and LÖ performed the full search strategy for each database. LÖ provided feedback on study protocol design and critically revised earlier versions of the manuscript. BA, VSA, RB, VG, MJMR and DC critically revised earlier drafts of the manuscript for intellectual content. All the authors read and approved the final manuscript.

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Competing interests: None.

Data sharing: No additional data available.

Patient consent: Not required per the study design.

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Diabetes-related symptoms, acute complications and management of diabetes mellitus in palliative care: a systematic review.

Search strategy for **PubMed**:

((((((((((diabetes mellitus[MeSH Terms]) OR diabet*[Title/Abstract])) OR T1DM[Title/Abstract]) OR T2DM[Title/Abstract]) OR NIDDM[Title/Abstract]) OR IDDM[Title/Abstract]) OR “glucose lowering medicine*”[Title/Abstract]) OR hyperglycemia[MeSH Major Topic]) OR hyperglycemia*[Title/Abstract]) AND (((((((((palliative care[MeSH Major Topic]) OR terminal care[MeSH Major Topic]) OR palliative[Title/Abstract]) OR "terminal care"[Title/Abstract]) OR “supportive care”[Title/Abstract]) OR “Terminal patient” [Title/Abstract]) OR “terminal patients” [Title/Abstract]) OR “End of Life Care”[Title/Abstract]) OR “Terminal Phase”[Title/Abstract])