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Effect of bile acid sequestrants on glycaemic control: Protocol for a systematic review with meta-analysis of randomised controlled trials

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Keywords: bile acid sequestrants, glycaemic control, HbA1c, type 2 diabetes, meta-analysis

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ABSTRACT

Introduction: In addition to the lipid-lowering effect of bile acid sequestrants (BASs) they also lower blood glucose, and therefore, could be beneficial in the treatment of patients with type 2 diabetes mellitus (T2DM). Three oral BASs are approved by the US Food and Drug Administration (FDA) for treatment of hypercholesterolaemia: colestipol, cholestyramine and colesevelam. The BAS colestide/colestilan is used in Japan. Colesevelam was recently approved by the FDA for treatment of T2DM. We plan to provide a systematic review with meta-analysis of the glucose-lowering effect of BASs with the aim to evaluate their potential as glucose-lowering agents in patients with T2DM.

Methods and analysis: In accordance with the Preferred reporting items for systematic reviews and meta-analyses statement a systematic review with meta-analysis of randomised clinical trials of BASs (vs. placebo, oral antidiabetes drugs or insulin), reporting measures of glycaemic control in adult patients with T2DM will be performed. Change in glycated haemoglobin (HbA_1c) constitutes the primary endpoint and secondary endpoints include changes in fasting plasma glucose, low density lipoprotein cholesterol, high density lipoprotein cholesterol, total cholesterol, triglycerides, body weight and body mass index and adverse events. Electronic searches will be performed in The Cochrane Library, MEDLINE and EMBASE, along with manual searches in reference lists of relevant papers. The analyses will be performed based on individual patient data and summarised data. The primary meta-analysis will be performed using random effects models due to expected inter-trial heterogeneity. Dichotomous data will be analysed using risk difference and continuous data using weighted mean differences, both with 95% confidence intervals.

Ethics and dissemination: The study will evaluate the potential of BASs as glucose-lowering agents and possibly contribute to the clinical management of patients with T2DM. Results of the study will be disseminated by peer-review publication and conference presentation.

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INTRODUCTION

Description of the condition

Type 2 diabetes mellitus (T2DM) is a severe metabolic disease characterised by relative insulin deficiency, including defective insulin secretion, insulin resistance, inappropriate glucagon secretion and impaired incretin effect resulting in fasting and postprandial hyperglycaemia [1,2]. T2DM is associated with overweight and dyslipidaemia and increases long-term risk of micro and macrovascular disease [3].

Description of the intervention

In recent years it has become clear that bile acids are not only simple fat solubilisers, but also signalling molecules that play an important role in lipid, glucose and energy metabolism [4–6]. In line with this, clinical studies have shown that bile acid sequestrants (BASs) in addition to their well-established lipid-lowering effects [7–9] can lower blood glucose, and therefore, potentially, could be beneficial in the treatment of patients with T2DM [10–12]. BASs, also known as resins, are large, non-absorbable, polymer molecules that bind negatively charged bile salts in the intestine. This diverts bile acids from the enterohepatic cycle and increases their faecal excretion [13]. The end result is increased bile acid (and cholesterol) synthesis with upregulation of the LDL receptors. Four oral BASs are available for treatment of low density lipoprotein (LDL)-hypercholesterolaemia: colestipol, cholestyramine, colestilan/colestimide (in Japan) and colesevelam. In 2008 colesevelam was approved by the US Food and Drug Administration (FDA) - based on three large pivotal studies [10–12] - for treatment of hyperglycaemia in T2DM.

How the intervention might work

The mechanism(s) by which BASs exert their glucose-lowering action is incompletely understood. Data from *in vitro* and *in vivo* animal and human studies have suggested different mechanisms including enhanced glucose-stimulated release of the incretin hormone glucagon-like peptide-1 (GLP-1) [14–18], and activation of the nuclear Farnesoid X receptor (FXR), which is implicated in lipid and glucose metabolism [6,19]. It has been speculated that increased GLP-1 secretion induced by BASs may dependent on increased concentration of bile acids in the lumen of the gut and subsequent bile acid-mediated activation of the 7-transmembrane receptor TGR5 present in GLP-1 secreting enteroendocrine L cells [20,21] - thereby explaining their glucose-lowering effect [22]. GLP-1 glucose-lowering actions are mediated by glucose-stimulated insulin secretion, inhibition of glucagon secretion, and a suppressive effect on appetite and food intake [23]. Also, although studies are conflicting [24,25], it is believed that the disturbed glucose homeostasis in diabetes is associated with changes in bile acid pool size and composition [6,13,26].

Why it is important to do this review?

T2DM affects more than 300 million people worldwide according to the World Health Organization (WHO) [27]. High levels of glycated haemoglobin (HbA_1c) is an established predictor of cardiovascular disease in patients with T2DM [28–30]. However, recent large clinical trials have shown that intensive treatment (resulting in HbA1c of ≤6.0%) in longstanding T2DM might be harmful [31–33], and, thus, individualised glycaemic control is pivotal in reducing morbidity and mortality of T2DM [34,35]. Hyperlipidaemia is an important part of the pathophysiology of T2DM, and treatment with lipid-lowering drugs

reduces cardiovascular mortality in T2DM [3]. However, despite numerous glucose and lipid-lowering agents being used in the management of patients with T2DM, there is still an unmet need for effective, individualised and safe treatment, as only a small fraction of the patients reach the treatment goals [36,37]. To our knowledge a systematic review with meta-analysis on the glucose-lowering effect of BASs is lacking, but at the same time is needed to evaluate the potential of BASs as glucose-lowering agents in patients with T2DM.

OBJECTIVES

The primary objective of the present protocol is to evaluate the impact of BASs on glycaemic control (HbA_1c) and secondary objectives include effects on fasting plasma glucose, body weight (and body mass index (BMI)) and lipids and adverse events associated with the use of BASs in patients with T2DM.

METHODS

The review will be performed according to the recommendations specified in the Cochrane Handbook for Intervention Reviews [38]. The reporting of the review will follow the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [39]. The analyses will be performed based on analyses of individual patient data from published randomised trials and summarised data presented in published trials or supplied by authors of included trials.

Criteria for considering studies for this review

Types of studies

The review will include randomised controlled trials, irrespective of blinding, publication status, or language. The first period of any cross over trials will be included. Unpublished trials will be included if the methodology and data are accessible in written form.

Types of participants

Adult patients (at least 18 years of age) of both genders with T2DM will be included. Inclusion criteria should be reported in the included trials. Ideally, the diagnostic criteria for T2DM should be based on the criteria of the WHO, the American Diabetes Association (ADA) and/or the European Association for the Study of Diabetes (EASD) [37,40], but if necessary, trials will be included with the definition of T2DM used by the authors of the trial in question.

Types of interventions

The intervention comparisons will include BASs (cholestyramine, colestilan/colestimide, colestipol, or colesevelam) versus placebo, oral antidiabetic drugs or insulin. Co-interventions with other anti-diabetic agents will be accepted if administered to the intervention and control group.

Types of outcome measures

The following outcome measures will be assessed based on analyses of individual patient data from included trials or from published reports:

Primary outcome measure

- HbA_1c

Secondary outcome measures

- Fasting plasma glucose
- LDL cholesterol, high density lipoprotein (HDL) cholesterol, total cholesterol and triglycerides
- Body weight and BMI
- Adverse events (defined based on the international guidelines for good clinical practice as any untoward medical occurrence)

Search methods for identification of studies

Electronic searches

The electronic searches will be performed in The Cochrane Library, MEDLINE and EMBASE, using the following strategy:

- *Cochrane Library* ("bile acid sequestrants" OR "sequestrants") AND "type 2 diabetes"
- *Medline* 1. exp type 2 diabetes, bile acid sequestrants/; 2. sequestrants.mp [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
- *Embase* 1. exp bile acid sequestrants/; 2. sequestrants.mp [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

Searching other resources

Manual searches including scanning of reference lists in relevant papers, specialist journals, and conference proceedings will be performed. Additional trials will be sought through the WHO Trial Register [41], ClinicalTrials.gov [42] and through correspondence with experts.

Data collection and analysis

Three authors (MH, DPS and KHM) will independently extract data and resolve disagreements through discussion before analysis. In case of unresolved matters, a third party (TV, LLG and/or FKK) will be involved. When necessary data are not included in the published trial reports, authors of included trials will be contacted for additional information. Also, principal investigators of the included randomised trials will be contacted to obtain validated data based on individual patients.

Selection of studies

Trials identified through the electronic and manual searches will be listed and included trials selected using the criteria described above. Excluded trials will be listed with the reason for exclusion. All authors will participate in the selection of trials for inclusion.

Data extraction and management

Standardised extraction forms will be used. The following data will be extracted from included trials:

- Patient characteristics: inclusion criteria, proportion of patients with T2DM, mean age, proportion of men, BMI, baseline HbA_1c, baseline fasting plasma glucose, baseline total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and antidiabetic background treatment

- Intervention characteristics: type, dose, and duration of interventions applied
- Trial characteristics: number of clinical sites, country of origin and funding

Assessment of risk of bias in included studies

- Randomisation (selection bias): Based on empirical evidence, the randomisation methods will be extracted as the primary measure of bias control [43]. Methodological quality in the randomisation methods will be based on the allocation sequence generation (classed as adequate if based on computer-generated random numbers, a table of random numbers, or similar) and allocation concealment (classed as adequate if randomisation was performed through a central independent unit, identically appearing coded drug containers, serially numbered opaque sealed envelopes or similar) and incomplete outcome data (whether all patients were accounted for)
- Blinding (performance and detection bias): We will extract data on whether single or double blinding was performed, the method of blinding (e.g. use of placebo) and the persons who were blinded with regard to the interventions assessed (i.e. patients, health care providers or other persons involved in the trial)
- Incomplete outcome data (attrition bias): The extent to which all patients lost to follow-up are accounted for will be evaluated as a measure of attrition bias
- Outcome reporting (reporting bias): The extent to which clinically relevant outcome measures are reported and differences between trial protocols and subsequent reports will be evaluated as a marker of reporting bias
- Other biases: Sample size calculations and whether the planned sample size was achieved will be evaluated

Measures of treatment effect

Dichotomous data will be analysed using risk differences (RD) and continuous data using weighted mean differences, both with 95% confidence intervals (CI). For dichotomous data, the number needed to treat will be calculated based on the RD as 1/RD.

Unit of analysis issues

For cross-over trials, data from the first treatment period will be used. For trials in which more than one control group was assessed, the primary analysis will combine data from each control group. Subgroup analyses on control groups will also be performed. Each patient will be counted only once in the analysis.

Dealing with missing data

Intention to treat analyses including all patients randomised will be performed. For patients with missing outcome data, carry forward of the last observed response will be used. Individual patient data will be sought from the original source or from the published trial reports where individual patient data are unavailable.

Assessment of heterogeneity

The inter-trial heterogeneity will be expressed as I-square values.

Assessment of reporting biases

We will extract whether clinically relevant outcomes are reported and compare trial protocols with subsequent publications when available.

Data Analysis

Analyses will be performed in RevMan [44] and Stata version 11 (Stata Corp, TX, USA). The primary meta-analyses will be performed using random effects models due to an expected inter-trial heterogeneity.

Sequential analysis

Sequential analyses will be performed to evaluate the robustness of the results after correction for potential errors associated with cumulative testing. The analyses will be performed using the results of the primary meta-analysis, model-based heterogeneity and an alpha value of 5% and a power of 80%.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be performed to analyse the influence of patient, intervention and trial characteristics and inter-trial heterogeneity. The subgroup analyses will compare the different types of BASs. The test for subgroup differences will be calculated and the results presented as *P* and I-square values.

Sensitivity analysis

Fixed effect meta-analyses will be performed to evaluate the influence of small trials. Additional sensitivity analyses with exclusion of trials with unclear randomisation will also be performed.

ETHICS AND DISSEMINATION

The study will evaluate the impact of BASs on glycaemic control (HbA_1c) and also assess effects on fasting plasma glucose, body weight and lipids and adverse events associated with the use of BASs in patients with T2DM, and hence possibly contribute to the clinical management of patients with T2DM. Morten Hansen will draft a paper describing the systematic review and the study will be disseminated by peer-review publication and conference presentation.

HISTORY

Protocol first published: XX.XX.XXXX

CONTRIBUTION OF AUTHORS

"MH, TV, LLG and FKK participated in the conception and design of this protocol including search strategy development. MH, DPS and KHM participated in search strategy development and performed pilot searches. LLG provided statistical advice for the design. All authors drafted and critically reviewed the manuscript and approved the final version."
Cheers,

FUNDING

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interpretation of data. Writing of the report and the decision to submit the results for publication is strictly made by the authors.

DECLARATION OF INTEREST

The authors declare no conflict of interests.

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The review will include randomised controlled trials, irrespective of blinding, publication status, or language. The first period of any cross over trials will be included. Unpublished trials will be included if the methodology and data are accessible in written form.

Types of participants

Adult patients (at least 18 years of age) of both genders with T2DM will be included. Inclusion criteria should be reported in the included trials. Ideally, the diagnostic criteria for T2DM should be based on the criteria of the WHO, the American Diabetes Association (ADA) and/or the European Association for the Study of Diabetes (EASD) [37,40], but if necessary, trials will be included with the definition of T2DM used by the authors of the trial in question.

Types of interventions

The intervention comparisons will include BASs (cholestyramine, colestilan/colestimide, colestipol, or colesevelam) versus placebo, oral antidiabetic drugs or insulin. Co-interventions with other anti-diabetic agents will be accepted if administered to the intervention and control group.

Types of outcome measures

The following outcome measures will be assessed based on analyses of individual patient data from included trials or from published reports:

Primary outcome measure

- HbA_1c

Secondary outcome measures

- Fasting plasma glucose
- LDL cholesterol, high density lipoprotein (HDL) cholesterol, total cholesterol and triglycerides
- Body weight and BMI
- Adverse events (defined based on the international guidelines for good clinical practice as any untoward medical occurrence)

Search methods for identification of studies

Electronic searches

The electronic searches will be performed in The Cochrane Library, MEDLINE and EMBASE, using the following strategy:

- *Cochrane Library* ("bile acid sequestrants" OR "sequestrants") AND "type 2 diabetes"
- *Medline* 1. exp type 2 diabetes, bile acid sequestrants/; 2. sequestrants.mp [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
- *Embase* 1. exp bile acid sequestrants/; 2. sequestrants.mp [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

Searching other resources

Manual searches including scanning of reference lists in relevant papers, specialist journals, and conference proceedings will be performed. Additional trials will be sought through the WHO Trial Register [41], ClinicalTrials.gov [42] and through correspondence with experts.

Data collection and analysis

Three authors (MH, DPS and KHM) will independently extract data and resolve disagreements through discussion before analysis. In case of unresolved matters, a third party (TV, LLG and/or FKK) will be involved. When necessary data are not included in the published trial reports, authors of included trials will be contacted for additional information. Also, principal investigators of the included randomised trials will be contacted to obtain validated data based on individual patients.

Selection of studies

Trials identified through the electronic and manual searches will be listed and included trials selected using the criteria described above. Excluded trials will be listed with the reason for exclusion. All authors will participate in the selection of trials for inclusion.

Data extraction and management

Standardised extraction forms will be used. The following data will be extracted from included trials:

- Patient characteristics: inclusion criteria, proportion of patients with T2DM, mean age, proportion of men, BMI, baseline HbA_1c, baseline fasting plasma glucose, baseline total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and antidiabetic background treatment

- Intervention characteristics: type, dose, and duration of interventions applied
- Trial characteristics: number of clinical sites, country of origin and funding

Assessment of risk of bias in included studies

- Randomisation (selection bias): Based on empirical evidence, the randomisation methods will be extracted as the primary measure of bias control [43]. Methodological quality in the randomisation methods will be based on the allocation sequence generation (classed as adequate if based on computer-generated random numbers, a table of random numbers, or similar) and allocation concealment (classed as adequate if randomisation was performed through a central independent unit, identically appearing coded drug containers, serially numbered opaque sealed envelopes or similar) and incomplete outcome data (whether all patients were accounted for)
- Blinding (performance and detection bias): We will extract data on whether single or double blinding was performed, the method of blinding (e.g. use of placebo) and the persons who were blinded with regard to the interventions assessed (i.e. patients, health care providers or other persons involved in the trial)
- Incomplete outcome data (attrition bias): The extent to which all patients lost to follow-up are accounted for will be evaluated as a measure of attrition bias
- Outcome reporting (reporting bias): The extent to which clinically relevant outcome measures are reported and differences between trial protocols and subsequent reports will be evaluated as a marker of reporting bias
- Other biases: Sample size calculations and whether the planned sample size was achieved will be evaluated

Measures of treatment effect

Dichotomous data will be analysed using risk differences (RD) and continuous data using weighted mean differences, both with 95% confidence intervals (CI). For dichotomous data, the number needed to treat will be calculated based on the RD as 1/RD.

Unit of analysis issues

For cross-over trials, data from the first treatment period will be used. For trials in which more than one control group was assessed, the primary analysis will combine data from each control group. Subgroup analyses on control groups will also be performed. Each patient will be counted only once in the analysis.

Dealing with missing data

Intention to treat analyses including all patients randomised will be performed. For patients with missing outcome data, carry forward of the last observed response will be used. Individual patient data will be sought from the original source or from the published trial reports where individual patient data are unavailable.

Assessment of heterogeneity

The inter-trial heterogeneity will be expressed as I-square values.

Assessment of reporting biases

We will extract whether clinically relevant outcomes are reported and compare trial protocols with subsequent publications when available.

Data Analysis

Analyses will be performed in RevMan [44] and Stata version 11 (Stata Corp, TX, USA). The primary meta-analyses will be performed using random effects models due to an expected inter-trial heterogeneity.

Sequential analysis

Sequential analyses will be performed to evaluate the robustness of the results after correction for potential errors associated with cumulative testing. The analyses will be performed using the results of the primary meta-analysis, model-based heterogeneity and an alpha value of 5% and a power of 80%.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be performed to analyse the influence of patient, intervention and trial characteristics and inter-trial heterogeneity. The subgroup analyses will compare the different types of BASs. The test for subgroup differences will be calculated and the results presented as *P* and I-square values.

Sensitivity analysis

Fixed effect meta-analyses will be performed to evaluate the influence of small trials. Additional sensitivity analyses with exclusion of trials with unclear randomisation will also be performed.

ETHICS AND DISSEMINATION

The study will evaluate the impact of BASs on glycaemic control (HbA_1c) and also assess effects on fasting plasma glucose, body weight and lipids and adverse events associated with the use of BASs in patients with T2DM, and hence possibly contribute to the clinical management of patients with T2DM. Morten Hansen will draft a paper describing the systematic review and the study will be disseminated by peer-review publication and conference presentation.

HISTORY

Protocol first published: XX.XX.XXXX

CONTRIBUTION OF AUTHORS

Morten Hansen has prepared this protocol in collaboration with David P. Sonne, Kristian H. Mikkelsen, Tina Vilsbøll, Lise Lotte Gluud and Filip K. Knop, and all authors have participated in search strategy development.

FUNDING

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publication is strictly made by the authors.

DECLARATION OF INTEREST

The authors declare no conflict of interests.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	-
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	-
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	-
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	-
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	-
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	-
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	7

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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