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Protocol for systematic review and meta-analysis of sex hormones and diabetes risk in ageing men and women of African ancestry

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ABSTRACT

Aim To present the protocol of a systematic review and meta-analysis of the available evidence examining the association between sex hormones and type 2 diabetes risk in ageing men and women of African descent.

Methods We shall conduct a comprehensive search of published studies that examined the association between sex hormones and type 2 diabetes risk in men and women aged ≥40 years from 01/01/1980 to 31/03/2018 with no language restriction. Databases to be searched include: PubMed, Scopus, Cochrane Library, Cumulative Index to Nursing and Allied Health, ISI Web of Science, Clinical Trial registries, Google Scholar and institutional websites such as the WHO, American Diabetes Association, International Diabetes Federation, World Diabetes Foundation, European Association for the Study of Diabetes, African Journal Online and ProQuest databases. This protocol is developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines. Independent screening for eligible studies using defined criteria and data extraction, will be completed in duplicate. Discrepancies will be resolved by consensus or consultation with a third researcher. Risk of bias of included studies will be assessed by the appropriate Cochrane risk of bias tool. The overall association estimates will be pooled using appropriate meta-analytic techniques. Heterogeneity will be assessed using Cochrane Q statistic and the inconsistency index (I^2). The random effects model will be used to calculate a pooled estimate.

Ethics and dissemination No ethics clearance is required as no primary data will be collected. The systematic review and meta-analysis are part of a PhD project at WITS University (Johannesburg, South Africa) and results will be presented at conferences and published in a peer-review journal. The results will guide future population specific interventions.

PROSPERO registration number CRD42017074581.

Strengths and limitations of this study

- This review will provide an overview of the existing knowledge gap on the association between sex hormones and the risk for type 2 diabetes in ageing men and women of African origin.
- The review will provide a synthesis of the available studies and therefore, may have implications for research and management guidelines of type 2 diabetes mellitus.
- This review will be used to establish whether more studies are needed and interventions warranted.
- Differences in diagnostic methods of diabetes in the studies may be a limitation.

INTRODUCTION

Diabetes is a growing global public health problem affecting approximately 425 million adults (8.8%) in 2017, with almost 80% of these living in low-income and middle-income countries.[1] It is estimated that between 2015 and 2040 the global number of people with type 2 diabetes mellitus (T2DM) will increase by 50%, with the largest increase in Africa estimated at 140%. In addition, approximately 62% of people in Africa are unaware that they have this condition. Accordingly, the burden of T2DM in Africa is exacerbated by late diagnosis after preventable complications of the disease have occurred.[1] Africa has a poorly funded and understaffed health system exhausted by malaria, HIV and tuberculosis, however it is estimated that by 2045–2050, Africa will witness an 11-year increase in life expectancy, with a population ≥60 years of age increasing from 5% to 9%.[2]

The incidence and prevalence of type 2 diabetes increases with age.[3] Ageing is associated with a decline in gonadal sex steroids in men and women, as well as a decrease in insulin sensitivity due to the progressive loss of proliferative and regenerative capacity of beta cells.[3 4] Notably, there are sex-specific influences of endogenous sex hormones on glycaemic status and diabetes risk.[5]

Ageing in men is associated with declining testosterone levels which start to decrease late

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in the fourth decade of life and reduce at a constant rate thereafter.[6 7] Studies have demonstrated an association between low levels of testosterone and the development of insulin resistance and T2DM in men,[8 9] which may also be associated with an increasing centralisation of body fat that occurs with ageing.[10 11]

Testosterone has the opposite effect in women where high testosterone levels increase the risk of T2DM.[7] Earlier menopause is associated with an increased risk of T2DM, cardiovascular disease and stroke.[12 13] Premenopausal women have higher insulin sensitivity than their age-matched male counterparts, however, following menopause, this is no longer the case.[14] In both men and women, lower sex hormone binding globulin (SHBG) is associated with an increased risk of T2DM.[5]

Notably, studies on the putative link between endogenous sex hormones and T2DM are sparse with respect to ethnic differences, specifically for subjects of African ancestry, and no meta-analyses exist. It is therefore important to collate studies on the association between sex hormones and type 2 diabetes risk in African men and women. This will assist in developing effective interventions to prevent or delay the onset of T2DM in populations of African ancestry, and generate hypotheses to understand the effects of ageing and decline in sex hormones on T2DM in African populations.

OBJECTIVES

The aim of this study is to present a protocol paper for a systematic review and meta-analysis of data to answer the following research question.

Review question

What is the association between oestradiol, follicle stimulating hormone (FSH), and luteinising hormone (LH) in women, free and total testosterone in men, and SHBG in women and men, and type 2 diabetes risk, in ageing men and women of African descent, as reported in studies between January 1980 and March 2018?

METHODS

Patient and public involvement statement

Patients were not involved in the development of this protocol.

Study design

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 guidelines,[15] informed the development of this protocol, online supplementary material entitled research checklist.

Search strategy for relevant studies

1. The following electronic databases of peer-reviewed journals will be systematically searched with no language restriction and limited to studies of humans only by use of the filter NOT ('animals' NOT 'humans'): PubMed, Scopus, Cochrane Library, Cumulative Index to Nursing and Allied Health and ISI Web of Science (Science Citation Index).
2. Google Scholar search engine will be used to scan through grey literature of relevant unpublished data and relevant websites such as WHO, International Diabetes Federation (IDF), World Diabetes Foundation (WDF), American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), African Journal Online, African Index Medicus and workshop and conference proceedings on sex hormones and type 2 diabetes risk. ProQuest databases will also be searched for grey literature.
3. Trial registries such as clinicaltrials.org will be consulted to track publications that may not have been indexed in the databases.
4. Relevant publications will be retrieved manually where electronic means are not applicable.

For studies in PubMed, Medical Subject Headings terms will be used. Individual African country names, regional names (sub-Saharan Africa, Africa South of the Sahara, North or Northern African, East or Eastern Africa, South or Southern Africa, Central Africa, West or Western African, Middle Africa), continents (Africa, Europe, America, Asia) and African Americans, African migrants will be used to identify studies that are indexed under regional names. Search terms to be used will include keywords referring to 'sex hormones', 'diabetes risk' and 'African ancestry'. Appropriate search terms and their free text words will be combined as needed by each database. The summary of the main search terms is found in box 1.

Electronic searches will be complimented by a manual search of reference lists of identified articles, as well as tracing their citation via Web of Science for additional publications. Only studies with participants aged ≥40 years will be retained. Existing literature noted marked variation in sex hormones in late third and early forth decade of life.[7 16–20] Relevant investigators will be contacted for unpublished studies where relevant.

Study selection

Inclusion criteria

- Type of studies: the systematic review will include cross-sectional, case-control, cohort and randomised control trials with no language restriction.
- Population: study participants include only humans aged ≥40 years of African ancestry.
- Exposure: all studies on oestradiol, FSH, and LH in women, and free and/or total testosterone in men, and SHBG in both men and women.
- Outcomes: the prevalence/incidence of T2DM or pre-diabetes (impaired glucose tolerance (IGT), impaired fasting glucose (IFG)), or insulin sensitivity/resistance. The definition and diagnosis of pre-diabetes (IGT, IFG), and T2DM will be according to WHO criteria of 1980,[21] 1985,[22] 1999[23] and 2006 according to WHO/IDF[24] for studies in these periods, respectively.

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Box 1 Search terms

Search Terms 1:#1
"Androgens*" OR "Oestrogen" OR "Oestradiol" OR "Testosterone" OR "Luteinising Hormone" OR "Luteinizing Hormone" OR "LH" OR "Follicle Stimulating Hormone" OR "FSH" OR "Sex Hormone Binding Globulin" OR "SHBG" OR "Sex Hormones*".

Search Terms 2:#2
"Diabetes*" OR "pre-diabetes*" OR "Insulin Resistance" OR "Insulin Sensitivity" OR "Vasomotor Syndrome" OR "Obesity" OR "Overweight" OR "Cardiovascular Disease" OR "CVD" OR "Metformin" OR "Glucophage" OR "Thiazolidinediones" OR "Biguanides" OR "Sulphonylureas" OR "Meglitinide" OR "Glinide" OR "α-Glucosidase Inhibitors" OR "Alpha Glucosidase Inhibitors" OR "Dipeptidyl Peptidase-4" OR "DPP-4" OR "Sodium-Glucose Co-Transporter 2" OR "SGLT2" OR "Dapagliflozin" OR "Pioglitazone" OR "Rosiglitazone" OR "Troglitazone" OR "Oral Hypoglycemic Agents" OR "OHA" OR "Impaired Glucose Tolerance" OR "IGT" OR "Impaired Fasting Glucose" OR "IFG" OR "Oral Glucose Tolerance Test" OR "OGTT" OR "Fasting glucose" OR "2-hour glucose" OR "Random blood glucose" OR "Glycosylated Haemoglobin" OR "HbA1c*" OR "Glycated Haemoglobin" OR "Glycated HemoglobinHaemoglobin" OR "HemoglobinHaemoglobin A1c" OR "A1c*" OR "Haemoglobin A1c*" OR "Hyperglycaemia*".

Search Terms 3:#3
"Africa*" OR "Algeria" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cameroun" OR "Cape Verde" OR "Central African Republic" "République Centre Afrique" OR "RCA" OR "CAR" OR "Chad" OR "Tchad" OR "Comoros Islands" OR "Comoros" OR "Congo" OR "Democratic Republic of Congo" OR "DRC" OR "République Démocratique du Congo" OR "RDC" OR "Djibouti" OR "Egypt" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea Bissau" OR "Ivory Coast" OR "Cote d'Ivoire" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Libya" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mayotte" OR "Morocco" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Principe" OR "Sao Tome" OR "Sao Tome and Principe" OR "Sao Tome & Principe" OR "Rwanda" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "Somali Land" OR "South Africa*" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Tunisia" OR "Uganda" OR "Western Sahara*" OR "Zambia" OR "Zimbabwe" OR "Central Africa*" OR "West Africa*" OR "Western Africa*" OR "East Africa*" OR "Eastern Africa*" OR "North Africa*" OR "Northern Africa*" OR "Southern Africa*" OR "sub Saharan Africa*" OR "sub-Saharan Africa*" OR "Africa South of Sahara*" OR "African descent" OR "African ancestry" OR "Africans" OR "African Europeans*" OR "African/Europeans*" OR "America*" OR "African Asians*" OR "African/Asians*" OR "African Americans*" OR "African/Americans*" OR "African migrants" OR "Southern African Development Community" OR "SADC" OR "African Caribbeans*" OR "African/Caribbeans".

Search Terms 4: #1 AND #2 AND #3.

Screening and data extraction

Citations will be imported into the EndNote 7 citation management software and duplicates will be removed. Eligibility of the studies will be ascertained by two independent researchers who will screen the titles and abstracts. Retained articles will be assessed by the two researchers for inclusion in the review. In case of disagreement about the eligibility, a third investigator will be consulted. Articles will be archived in a data extraction spreadsheet pilot-tested on a similar study (population, exposure and outcome) to evaluate its appropriateness. The spreadsheet will consist of a screening checklist made up of study details (author, year of study, year of publication, type of publication, country in which study was carried out), study characteristics (study design, mean age and age range of participants, number of men and women, and sample size). The measures of sex hormones (oestradiol, FSH, LH, free and total testosterone, SHBG), measure of glucose/insulin homeostasis or dysregulation (T2DM, pre-diabetes, insulin resistance/sensitivity) and measure of the association between sex hormones and type 2 diabetes risk (odds ratios, relative risk or hazard ratios), with their related variability (SD, SEs and CIs), will also be included. Study limitations and confounders will be noted and other additional relevant information requested from corresponding authors if required.

Data synthesis and analysis

Data will be summarised by region or continent (Sub-Saharan Africa, or Africa, America, Europe) and by gender. If sufficient studies or enough data are obtained, we shall conduct meta-analysis and meta-regression analysis for similar covariates in studies identified using the R statistical software (The R Foundation for statistical computing Vienna, Austria. 2015; http://www.R-project.org/) or STATA/IC V.15.0 (StataCorp). Random effects models with inverse variance weighing will be fitted and 95% CIs determined in pooled estimates.[25] Statistical heterogeneity in the association between sex hormones and T2DM risk between different studies will be investigated using Cochrane's Q statistic and the inconsistency index (I^2),[26] with I^2 of 0% indicating no heterogeneity and 50% indicating moderate heterogeneity.[27] If studies cannot be combined for meta-analysis a narrative synthesis will be implemented following accepted guidelines.[28] We envisage doing subgroup analysis by gender, menopausal stage (premenopausal, perimenopausal and postmenopausal) for women and by geographical region (Africa, America and Europe), in order to assess differences between the studies and potential impact of the confounders. Funnel plots will be employed to assess publications bias and if deemed relevant further statistical based tests such as Egger's test[29] and Begg's test,[30] may be implemented. In addition, trim and fill methods will be implemented to test the robustness of the findings.[31]

Risk of bias assessment for retained studies

This systematic review falls under the category of aetiology and risk reviews. It follows the population, exposure and outcome question development strategy.

The search for studies will be completed in duplicate by two independent researchers. Critical appraisal of risk of bias and quality will be assessed by two researchers. Discrepancies will be resolved by consensus or consultation with a third researcher. A validated quality appraisal

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tool will be used for internal and external validity and risk of bias according to Strengthening the Reporting of Observational Studies in Epidemiology.[32] Depending on the studies retained different tools will be used for their appraisal. For observational studies, the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines will be used.[33] If randomised control trials are retained the Cochrane tool for assessing risk of bias for randomised controlled trials will be used. Each end-point and risk factor will be assessed individually to generate an overall score. For quality assessment of non-randomised experimental studies we will use the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool developed by the Cochrane Bias Methods Group and the Cochrane Non-Randomised Studies Methods Group. This tool assesses the methodological quality to determine how it addressed bias arising from design, conduct and analysis.[34] The quality and strength of evidence will be assessed and reported using the Grading of Recommendations Assessment, Development and Evaluation system which addresses other evidence not taken into consideration by existing models such as assessment of methodological shortcomings within the component studies, consistency of results across diverse studies, precision of effect estimates, risk of publication bias and how effective the treatments were in experimental studies.[35]

Presentation of results and reporting

The PRISMA guidelines,[15] will be used and the checklist will accompany the publication. Quantitative data will be summarised and presented in tables and as forest plots where necessary. Association of sex hormones and type 2 diabetes risk studies separately for men and women will be presented by continents (Africa, Europe, America, Asia), by menopausal stage (pre, peri and post) for women and for men of same age.

Potential amendments

We do not envisage any amendments to the present protocol. But should an amendment be necessary, it will be notified, registered and reported.

CONCLUSION

This systematic review will address the existing knowledge gap on the association between sex hormones and the risk for type 2 diabetes mellitus in men and women of African origin aged≥40 years. A synthesis of the available studies will identify the quality of data. This review will be used to inform future interventions and establish whether more research is warranted.

DISSEMINATION

The results of the systematic review and meta-analysis will be published in peer-review journals and will form part of a PhD thesis at the University of the Witwatersrand, Johannesburg, South Africa. The findings will also be presented at conferences and shared with relevant health authorities.

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Contributors NCK conceived the review approach, drafted and revised the manuscript. MM, TO, TC, JHG, LKM and APK gave general guidance on the drafting of the protocol. NCK and MM performed the literature searches and data extraction. TC and TO carried out critical appraisal. NCK and APK carried out data analyses. All authors read and approved the final version of the manuscript. Guarantors of the protocol are LKM and APK.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval is not necessary. The systematic review and meta-analysis will use data from published and unpublished studies and poses no risk to participants' or their privacy.

Provenance and peer review Not commissioned; externally peer reviewed.

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