INPLASY PROTOCOL

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The authors declare no conflict of interest.

Serum vitamin D levels and type 2 diabetic erectile dysfunction: a protocol for systematic review and meta-analysis

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Review question / Objective: **This systematic review aims to integrate and assess the impact of vitamin D on the body and to contribute a comprehensive summary of serum vitamin D levels alterations in patients with type 2 diabetic erectile dysfunction (T2DED). This study also will synthesize the correlation between the serum vitamin D level and T2DED. Additionally, how the serum vitamin D levels alter in patients with T2DED will be performed in this study.**
Condition being studied: **Erectile dysfunction (ED) is a common male sexual dysfunction. According to recent studies, approximately 37% of men over 70 years old and 11% of men over 30 years old suffer from ED. It not only impairs male sexual confidence but also severely impacts the quality of life and relationships of patients and their spouses. ED is a multifactorial medical disorder that has been linked to numerous aetiologies. Roles for nonendocrine (neurogenic, vasculogenic and iatrogenic) and endocrine pathways have been proposed.T2DM as metabolic syndrome has been found its strong association with ED. A lot of studies suggest that the factors of T2DM induce ED may be endothelial dysfunction, hypogonadism, and other potential moderators. Recently, serum vitamin D levels play a role in the process of T2DM induce ED according to some studies. 25-hydroxyvitamin D (25(OH)D) increases nitric oxide production in endothelial cells. Endothelial function is considered an important factor in initiating and maintaining penile erection, so 25(OH)D deficiency results in erectile dysfunction. We still need more large-sample and multicenter trials, although the present studies have confirmed the correlation between ED and vitamin D levels in type 2 diabetic patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 April 2020 and was last updated on 24 April 2020 (registration number INPLASY202040164).

INTRODUCTION

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METHODS

Search strategy: We will do electronic searches from English databases (PubMed, EMBASE, Web of Science, Cochrane Library) and Chinese databases (China Biology Medicine Database, Wanfang database, China National Knowledge Infrastructure (CNKI), VIP database) from their inception until June 2020 to recognize related studies. The following search strategy will run in PubMed and tailored to the other database when necessary: (Erectile Dysfunction OR Impoten* OR Erectile disturbance OR Erectile disorder OR Sexual Dysfunction OR Asynodia Erection failure OR Penile Erection) AND (vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR paricalcitol OR doxercalciferol OR calcitriol OR 25-Hydroxyvitamin D) AND (diabetes OR diabetes mellitus OR T2DM OR hyperglycemia OR hyperglycaemia OR glucose OR HbA1c OR glycated hemoglobin OR insulin resistance OR insulin sensitivity OR HOMA OR glucose homeostasis OR insulin secretion OR insulin OR beta-cell function OR glycemic control OR glucose tolerance OR glucose metabolism). Besides, the WHO International Clinical Trials Registry Platform will be searched for potential results. Secondly, the reference lists of all the included studies, relevant papers, and previous systematic reviews will be also hand-searched for the identification of additional studies.

Participant or population: Erectile dysfunction (ED) is a common male sexual dysfunction. According to recent studies, approximately 37% of men over 70 years old and 11% of men over 30 years old suffer from ED. It not only impairs male sexual confidence but also severely impacts the quality of life and relationships of patients and their spouses. ED is a multifactorial medical disorder that has been linked to numerous aetiologies. Roles for nonendocrine (neurogenic, vasculogenic and iatrogenic) and endocrine pathways have been proposed.T2DM as metabolic syndrome has been found its strong association with ED. A lot of studies suggest that the factors of T2DM induce ED may be endothelial dysfunction, hypogonadism, and other potential moderators. Recently, serum vitamin D levels play a role in the process of T2DM induce ED according to some studies. 25-hydroxyvitamin D (25(OH)D) increases nitric oxide production in endothelial cells. Endothelial function is considered an important factor in initiating and maintaining penile erection, so 25(OH)D deficiency results in erectile dysfunction. We still need more large-sample and multicenter trials, although the present studies have confirmed the correlation between ED and vitamin D levels in type 2 diabetic patients.

Intervention: Patients with T2DED should meet the diagnosis of both T2DM and ED. T2DM should be diagnosed through comprehensive history collection, physical examination and related blood glucose tests in accordance with the diagnostic guidelines of the ADA. Meanwhile, it is necessary to meet the clinical diagnosis of ED in patients with T2DM. The diagnosis can be diagnosed through comprehensive history collection, physical examination and even specific examination according to the diagnostic guidelines of the European Association of Urology, the American Urological Association, or other authoritative organisations. The cutoff points of vitamin D deficiency and insufficiency are still a topic of discussion, we will follow Endocrine Society clinical guidelines and previously recommended cutoff points in diagnosing vitamin D deficiency when serum 25(OH)D was <20 ng/mL and vitamin D insufficiency when 25(OH)D was between 20 and 29.9 ng/mL .25 (OH) D is the main circulating vitamin D metabolite and a reliable indicator of vitamin D levels. The overall vitamin D level can be determined by detecting 25 (OH) D. Patients with type 1 diabetes, prostate cancer, a history of prostatectomy and other diseases that can cause erectile dysfunction who have received or are currently receiving vitamin D replacement therapy were excluded from the study.

Comparator: The controls should be the healthy people who aged ≥18 years without T2DED.

Study designs to be included: The study will mainly include cross-sectional, case–control and both prospective and retrospective cohort studies.

Eligibility criteria: Type of studies cross-sectional, case-control and both prospective and retrospective cohort-studies will be included if: They investigate the association between serum Vitamin D levels and diabetic erectile dysfunction. The data reported in the study include serum Vitamin D levels, International Index of Erectile Function (IIEF) and glycated hemoglobin (GHb). They focus on the patient with diabetic erectile dysfunction.

Information sources: Electronic databases will include English databases (PubMed, MEDLINE, EMBASE, Web of Science, Cochrane Library) and Chinese databases (China National Knowledge Infrastructure, China Biology Medicine Database, Wanfang Database, VIP Database). Besides, the reference lists of review articles will be searched for any possible titles matching the inclusion criteria. We will also scan the database of Chengdu University of Traditional Chinese Medicine Library and our hospital's experts in endocrinology and ophthalmology will be consulted. Dissertations of degrees will be included. The WHO International Clinical Trials Registry Platform and Google Scholar will be searched for potential results. Besides, the ClinicalTrials.govregistry will be searched for any unpublished trials.

Main outcome(s): The main results of this study are investigating the concentration of vitamin D levels in subjects with and without Diabetic Erectile Dysfunction and target at the 5-item version of the international index of erectile function (IIEF-5) score in subjects with (20 ng/ml).

Additional outcome(s): The additional outcomes of this evaluation maily foucus on the association between diabetic erectile dysfunction and other biochemical tests, including plasma glucose levels, HbA1c, free testosterone, blood lipid profile (Triglycerides, total serum cholesterol, H-DL, L-DL levels) and so on. These clinical datas will be recorded and used to explain variability between studies if necessary.

Quality assessment / Risk of bias analysis: Two reviewers (Qiu and Li) will independently use different scales to assess the risk of bias based on the type of studies: cross-sectional studies will be assessed by the Agency for Healthcare Research and Quality (AHRQ) recommended criteria. The criteria include eleven items, answered by “yes”, “no”,

"unclear"; case-control and cohort studies will use the Newcastle-Ottawa Scale (NOS) which assess the quality of studies with eight questions in three broad categories: (1) patient selection; (2) comparability of study groups; (3) assessment of the outcome. The evaluation will use the semi-quantitative principle of the star system and the highest score is nine stars. Stars of 0-4 mean low-quality and 5-9 mean high-quality. Any disagreements will be solved by discussion or with arbitrament by the third reviewers Yao.

Strategy of data synthesis: Our primary outcome will mainly investigate the concentration of vitamin D levels in subjects with and without Diabetic Erectile Dysfunction. The secondary outcome will target at the 5-item version of the international index of erectile function (IIEF-5) score in subjects with (20 ng/ml). We will take standardised mean difference (SMD) to measure the difference of vitamin D levels or IIEF-5 scores and their corresponding 95% confidence intervals (95% CIs). We will assess heterogeneity with the $\chi 2$ goodness of fit and I2 statistics. Concerning I2, we will reference Cochrane recommendations. If the value of $p < 0.1$ or $I2 < 40\%$ that heterogeneity will be considered significant under the condition and the random-effects model is about to be employed. Otherwise, the fixed model will be conducted. In the case of the presence of heterogeneity, we will perform sensitivity analyses and retrogression when possible. Publication bias will be determined by a funnel plot and we will try to interpret funnel plot asymmetry by Egger's linear regression test if funnel plots are asymmetric.

Subgroup analysis: If there is a sufficient number of studies, we will investigate potential sources of heterogeneity by performing subgroup analyses: 1) According to type of testing: radioimmunoassay or immunoassay or some else. 2) The sample size of included studies. 3) Some biomarkers which connected with this disease: plasma glucose levels, HbA1c, free testosterone, blood lipid profile (Triglycerides, total serum cholesterol, H-DL, L-DL levels) and so on. 4) The sociodemographic characteristics of participants: age, BMI, history of DM, current smoking and alcohol status.

Sensibility analysis: If possible, a sensitivity analysis will be performed to test the reliability and stability of the review result, and to detect the source of heterogeneity. This can be done by excluding trials with a high risk of bias or eliminating each study individually. Then the analysis will be repeated after the exclusion of low methodological quality studies.

Language: English.

Country(ies) involved: China.

Keywords: Vitamin D, type 2 diabetes mellitus (T2DM), erectile dysfunction (ED), protocol.

Contributions of each author:
Author 1 - Fuhao, Li drafted the manuscript, screened the potential studies, and extract data.
Author 2 - Xianliang, Qiu drafted the manuscript, assessed the risk of bias and finished data synthesis.
Author 3 - Hangyu, Yao developed the search strategy, read, provided feedback and approved the final manuscript