INPLASY PROTOCOL

To cite: MacGirlley et al. Impacts of Vitamin D on inflammation and lipid profile in adult patients with diabetes mellitus . A protocol for systematic review. Inplasy protocol 202260022. doi: 10.37766/inplasy2022.6.0022

Received: 06 June 2022

Published: 06 June 2022

Corresponding author:
Kabelo Mokgalaboni

mokgak@unisa.ac.za

Author Affiliation:
University of South Africa.

Support: **Not applicable.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Impacts of Vitamin D on inflammation and lipid profile in adult patients with diabetes mellitus. A protocol for systematic review

MacGirlley, R[1]; Mokgalaboni, K[2].

Review question / Objective: **To evaluate the effect of vitamin D on markers of inflammation and lipid profile amongst adults diabetic patients.**
Rationale **The effect of vitamin D supplementation on diabetes-related complications is controversial since most randomized controlled trials (RCTs) conducted utilised small sample size or have used different doses of vitamin D. Thus we aimed to conduct this systematic review and meta-analysis to evaluate the impacts of vitamin D supplementation in T2DM, and help to further clarify its beneficial action on lipid profile and inflammation in diabetic patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 June 2022 and was last updated on 06 June 2022 (registration number INPLASY202260022).

INTRODUCTION

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Rationale: **The effect of vitamin D supplementation on diabetes-related complications is controversial since most randomized controlled trials (RCTs) conducted utilised small sample size or have used different doses of vitamin D. Thus we aimed to conduct this systematic review and meta-analysis to evaluate the impacts of vitamin D supplementation in T2DM, and help to further clarify its beneficial action on lipid profile and inflammation in diabetic patients.**

Condition being studied: **Type 2 diabetes mellitus (T2DM) is a metabolic disorder**

affecting approximately 462 million individuals' globally. It is characterized by chronic hyperglycemia, persistent insulin resistance and dysfunctional insulin secretion by the pancreatic β-cells. A number of genes relating to insulin resistance and impaired insulin secretion as well as environmental factors such as age, obesity, physical inactivity and stress contributes to the onset of T2DM. Furthermore, previous studies have demonstrated that low-grade inflammation contributes to the development and pathophysiology of T2DM. Inflammation in the islets of Langerhans specifically affecting the β-cells is common in both type I and type II diabetes mellitus, this effect of local inflammation alters the balance between the function and cell mass of the β-cell. Various experimental studies of T2DM have shown that macrophages play a crucial inflammatory role in the islets of Langerhans. Moreover, the Inflammasome/IL-1β signaling pathway is triggered in the islets resulting in the dysfunction of the β-cells. In β-cells, oxidative stress may induce reactive oxygen species (ROS) and proinflammatory cytokines causing the disruption of blood flow and thereby causing dysfunction. Further evidence suggests that T2DM is characterized by impaired inflammatory biomarkers including increased serum concentrations of IL-6, IL-18 and C-reactive protein (CRP). Tumor necrosis factor alpha (TNF-α) is an important link between islet inflammation, diabetes and insulin resistance.6 Due to the excess of TNF-α produced by macrophages in adipose tissue it may induce inflammation in peripheral tissues resulting in insulin resistance and β-cell death.

METHODS

Search strategy: The search will be conducted using EMBASE, Google Scholar, Web of Science, PUBMED and Science Direct. The following key word, Mesh terms and their synonyms will be applied in all databases, "Vitamin D", "inflammation", "Diabetes mellitus".

Participant or population: Adult patients with type 2 diabetes mellitus.

Intervention: Vitamin D supplementations of any dose.

Comparator: Placebo/healthy patient without treatment.

Study designs to be included: Only randomised controlled trials.

Eligibility criteria: The selection of inclusion and exclusion criteria will be defined in accordance with our PICO guideline. This planned systemeatic review and meta-analysis will include studies focusing on adult patients with T2DM.There will be no language limitations and all studies published since inception until June 2022 will be considered. The reviews, books, letters and animal studies experimenting on diabetes will be excluded. Furthermore, cross sectional, cohort studies, case-control studies and case reports will all be excluded.

Information sources: The search will be conducted using EMBASE, Google Scholar, Web of Science, PUBMED and Science Direct databases.

Main outcome(s): Lipid profile defined by triglyceride, total cholesterol, HDL and LDL.

Additional outcome(s): Inflammation as defined by proinflammatory markers (TNF, IL-6 and CRP).

Data management: The information that will be sought for extraction will include the author and year of publication, country where study was conducted, sample size, gender, age, form of vitamin D, dosage, duration of treatment, lipid profile parameters, pro-inflammatory markers. Excell sheet will be used to extract all relevant data fromeach stuy. Data will be confirmed by contacting investigators if insufficient information has been provided on the published article.

Quality assessment / Risk of bias analysis: The risk of bias will be assessed using the methods recommended in the Cochrane risk of bias assessment tool (2), this assessment includes 6 domains namely, selection bias, attention bias, reporting bias, performance bias, attrition bias and other bias. Judgments will be used to determine whether the bias is high risk, low risk or unclear due to insufficient information or potential bias.

Strategy of data synthesis: Statistical analysis will be analysed using the Review Manager (RevMan) version 5.4 by the Cochrane Collaboration. From each studies two reviewer will independently extract data as a standard deviation (SD), mean and sample size in each group. Where mean and SD are not reported, estimation will be made using online calculator by Hozzo et al (4). The forest plots will be used to determine the pooled estimates and classify level of heterogeneity based on I2 and p-value (5). The estimated pool will be reported as either mean and standard deviation or standardized mean difference and 95% confidence interval (CI). Furthermore, a chi-square test ($\chi 2$) and I2 will be used to assess the level of heterogeneity among the included studies (6,7). To explore the sources of high heterogeneity, subgroup analysis conducted, and sensitivity analysis will be used to assess the stability of the re-analysed pool estimates. The value of $p < 0.05$ was considered statistically significant.

Subgroup analysis: Subgroup analysis will be performed if there is substantial heterogeneity amongst the studies to find the exact source.

Sensitivity analysis: Sensitivity analyses will be performed to determine the effect of individual trial on the overall outcome. We will also performed the meta-regression analysis to evaluate the correlation of post-treatment or percentage change of lipid profiles and inflammatory markers.

Language: There will be no language restriction to avoid missing important studies published in languages other than English.

Country(ies) involved: South Africa.

Keywords: Vitamin D, diabetic neuropathy, inflammation, hyperglycemia, type 2 diabetes mellitus.

Contributions of each author:

Author 1 - Rizqah MacGirlley - RM conceptualized, designed, drafted and this manuscript. RM approved final version of the manuscript.
Email: 10916970@mylife.unisa.ac.za
Author 2 - Kabelo Mokgalaboni - KM conceptualized, designed, drafted and this manuscript. KM supervised the writeup of this protocol. KM approved final version of this manuscript.
Email: mokgak@unisa.ac.za