INPLASY PROTOCOL

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Support: **CONACYT.**

Review Stage at time of this submission: **Formal screening of search results.**

Conflicts of interest:
None declared.

Diabetes mellitus alters intracellular calcium homeostasis in vascular endothelial cells: a systematic review

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Review question / Objective: **What are the effects of diabetes mellitus on the calcium homeostasis in vascular endothelial cells? -To describe the effects of diabetes on the mechanisms that regulate intracellular calcium; -To describe other molecules/mechanisms that alters intracellular Ca2+ homeostasis.**
Condition being studied: **Diabetes mellitus is a pathology with a high incidence in the population, characterized by an increase in blood glucose. People with diabetes are 2-4 times more likely to suffer from a cardiovascular complication, such as total or partial loss of sight, myocardial infarction, kidney failure, among others. Cardiovascular complications have been reported to derive from dysfunction of endothelial cells, which have important functions in blood vessels. In order to understand the etiology of this poor function of endothelial cells, it is necessary to study the molecular mechanisms involved in these functions, to identify the effects of diabetes and thus, develop new research that will mitigate the effects of this pathology.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 May 2022 and was last updated on 16 May 2022 (registration number INPLASY202250104).

INTRODUCTION

Review question / Objective: **What are the effects of diabetes mellitus on the calcium homeostasis in vascular endothelial cells? -To describe the effects of diabetes on the mechanisms that regulate intracellular calcium -To describe other molecules/ mechanisms that alters intracellular Ca2+ homeostasis.**

Rationale: **Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body**

cannot effectively use the insulin it does produce. In the world, 537 million adults (20-79 years) live with diabetes. This number is predicted to increase to 643 million by 2030 and 783 million by 2045. Diabetes was responsible for 6.7 million deaths in 2021. Cardiovascular disease represents the leading cause of death and morbidity among people with diabetes, especially in those with type 2 diabetes mellitus. Adults with diabetes have a 2-4-fold increased cardiovascular risk compared to adults without diabetes. It has been reported that endothelial dysfunction is the event that precedes the appearance and development of pathologies in the cardiovascular system. Endothelial dysfunction is the systemic pathological condition in which there is an imbalance in the production of vasoconstrictor and vasorelaxant substances; this alteration is characterized by a decrease in the bioavailability of nitric oxide, a critical factor in the regulation of vascular tone and hemostasis. The functions of the endothelium, including the production of vasoactive substances, are regulated by the intracellular concentration of calcium. Several studies evaluate the effect of different types of diabetes on the calcium signal in endothelial cells. However, due to the expansion of knowledge and because the mechanisms involved are partially clear, in this article we will systematically review, describe, and compile all available information on the effect of diabetes mellitus on calcium signaling in endothelial cells.

Condition being studied: Diabetes mellitus is a pathology with a high incidence in the population, characterized by an increase in blood glucose. People with diabetes are 2-4 times more likely to suffer from a cardiovascular complication, such as total or partial loss of sight, myocardial infarction, kidney failure, among others. Cardiovascular complications have been reported to derive from dysfunction of endothelial cells, which have important functions in blood vessels. In order to understand the etiology of this poor function of endothelial cells, it is necessary to study the molecular mechanisms involved in these functions, to identify the effects of diabetes and thus, develop new research that will mitigate the effects of this pathology.

METHODS

Search strategy: The databases used for this systematic review are: Web of Science, PubMed and Scopus. We only searched original articles, in english language, excluding reviews and meeting abstracts, from 1980 to the present. We use specific search algorithms for each database, since the use of MeSH and Boolean terms is different for each one. The algorithm used for Web of Science is the following:
((("calcium signaling" [MeSH Terms] OR "Calcium homeostasis" OR "Ca2+ homeostasis" OR "Calcium signaling" OR "Ca2+ signaling" OR "Calcium handling" OR "Ca2+ handling" OR "Intracellular calcium" OR "Intracellular Ca2+" OR "Calcium signalling" OR "Ca2+ signalling" OR "Calcium imaging" OR "Ca2+ imaging" OR "Calcium influx" OR "Ca2+ influx" OR "Calcium entry" OR "Ca2+ entry" OR SERCA OR PMCA OR NCX OR MCU) AND ("Diabetes Mellitus" [MeSH Terms] OR diabet*) AND ("endothelium" [MeSH Terms] OR endothel*)) NOT ("review" [Publication Type] OR "review literature as topic" [MeSH Terms] OR "review" [All Fields]).

Participant or population: Endothelial cells (isolated and cultured/cell lines).

Intervention: ·Cell lines/cultives that are exposed in a High glucose medium 25-35mM, in 1, 3, 7 or 14 days ·STZ induced diabetes: mice or rats develop diabetes with a single dose or multiple dose of STZ depending of the weight and size of the specimen. ·Cells isolated and cultured from diabetic patients·Exposure to drugs/agonists that affects or restores calcium homeostasis in diabetes models.

Comparator: ·Age, weight or strain matched animals ·Normal glucose concentrations in medium (5mM) ·Normal glucose concentration in control patients.

Study designs to be included: Original basic research studies.

Eligibility criteria: English language, basic research studies

Information sources: Electronic databases: Web of Science, PubMed and Scopus Study authors will be contacted via Research Gate or e-mail to further information required.

Main outcome(s): -Identify which molecular mechanisms are affected by diabetes -Report which mechanisms are the most affected by diabetes -Intracellular calcium measurements, using fluorescent techniques -Protein expression, using western blot, immunostaining, RT-PCR, flow cytometry.

Additional outcome(s): -Other molecules that alter intracellular calcium signaling.

Data management: The data extraction will be concentrated in a Microsoft Excel Table, that includes the most relevant information about the article as the authors and journal information, the most relevant results and the material and methods employed. All the researchers will be doing the data extraction independently, and have a color code to avoid confusion. If there are any doubts about the inclusion of studies, researches will have a weekly meeting to discuss them. If further information about articles is required, the author will be contacted via e-mail or Research Gate.

Quality assessment / Risk of bias analysis: We will be using the Quality assessment instrument adapted by Hadley et al., 2018, as there are not instruments for basic research. To assess risk of bias, we will be using the OHAT Risk of Bias Rating Tool for Human and Animal Studies.

Strategy of data synthesis: The results will be written in a manuscript by the researchers. The data obtained in this study will be presented via diagrams and tables, as well as a brief essay explaining the results.

Subgroup analysis: Mechanisms that allow Ca2+ entry from extracellular space; Mechanisms that remove Ca2+ from cytosol; Mechanisms that stores Ca2+.

Sensitivity analysis: Not applicable.

Language: English.

Country(ies) involved: México, Italy.

Keywords: diabetes mellitus; endothelial cells; intracellular calcium homeostasis.

Dissemination plans: The objective of this study is its publication in an indexed journal, for the dissemination of the results.

Contributions of each author:

Author 1 - Paulina del Carmen Sosa Munguía - Study design, developed research algorithms. Afterwards, will be doing the data extraction, the data synthesis and the manuscript draft; also the quality and risk of bias assessments.
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