Evaluating the Impact of Type 2 Diabetes Mellitus and Prediabetes on Pulmonary Vascular Function and on the Development of Pulmonary Fibrosis: Protocol for a Systematic Review and Meta-Analysis

Nhlakanipho Mzimela, NOSIPHO Rosebud DIMBA, Aubrey Sosibo, Andile Khathi

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Nhlakanipho Mzimela[1] MMSc; NOSIPHO Rosebud DIMBA[1] MMSc; Aubrey Sosibo[1] MMSc; Andile Khathi[1] Prof Dr

[1]Department of Human Physiology University of Kwa-Zulu Natal Durban ZA

Corresponding Author:
Nhlakanipho Mzimela MMSc
Department of Human Physiology
University of Kwa-Zulu Natal
University Road, Westville, Durban
Durban
ZA

Abstract

Background: Prediabetes, a metabolic state characterized by elevated blood glucose levels, has been associated with various systemic complications. However, its effects on pulmonary vascular function and pulmonary fibrosis remain poorly understood. This systematic review aims to summarize existing evidence on the impact of type 2 diabetes mellitus and prediabetes on these aspects. This protocol was prepared in accordance with the PRISMA 2020 guidelines for reporting protocols.

Objective: To achieve our aim, we will examine published prospective observational studies, case-control studies, cohort studies, and cross-sectional studies involving non-diabetic, type 2 diabetic, and prediabetic reports.

Methods: To achieve our aim, we will examine published prospective observational studies, case-control studies, cohort studies, and cross-sectional studies involving non-diabetic, type 2 diabetic, and prediabetic reports. Our database search will encompass Google Scholar, PubMed, Embase and Web of Science. The process of data extraction and quality assessment will be carried out independently by three reviewers, with a subsequent screening of results to ensure adherence to eligibility criteria. The STROBES checklist will be applied to evaluate the risk of bias. In the meta-analysis and sensitivity analysis, we will employ the Review Manager v5.4 Forrest plot. To gauge the quality of evidence, we will utilize the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: This protocol provides guidance for systematically exploring articles investigating pulmonary vascular function and fibrosis within diabetic and pre-diabetic states. The outcomes derived from this protocol will not only steer the direction of future research but also inform the subsequent investigative endeavors.

Conclusions: It is noteworthy that this systematic review will rely on publicly accessible data, which will be collected after the release of this protocol. This protocol serves as a compass for exploring articles that delve into studies about the prediabetic state, specifically in relation to assessments of pulmonary vascular function and pulmonary fibrosis. The outcomes generated from this protocol will offer valuable guidance for future research endeavors. Clinical Trial: The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number “CRD42023478267”, dated 14 November 2023.

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Evaluating the Impact of Type 2 Diabetes Mellitus and Prediabetes on Pulmonary Vascular Function and on the Development of Pulmonary Fibrosis: Protocol for a Systematic Review and Meta-Analysis.

Nhlakanipho Mzimela[1], Nosipho Dimba[1], Aubrey Sosibo[1], Andile Khathi[1]

[1]Department of Human Physiology, Faculty of Health Sciences, University of KwaZulu-Natal, Durban 4000, South Africa.

Corresponding author: Nhlakanipho Mzimela
Email address: 218006756@stu.ukzn.ac.za

Abstract

Background:

Prediabetes, characterized by elevated blood glucose levels, has been linked to systemic complications, including cardiovascular effects. However, its impact on pulmonary vascular function and fibrosis remains poorly understood. This systematic review aims to summarize existing evidence on the association between type 2 diabetes mellitus (T2DM) and prediabetes with pulmonary vascular function and fibrosis.

Methods:

In accordance with PRISMA 2020 guidelines, we specify the inclusion and exclusion criteria for the review, including prospective observational studies, case-control studies, cohort studies, and cross-sectional studies published between 2000 and 2023 involving non-diabetic, T2DM, and prediabetic individuals. Information sources encompass Google Scholar, PubMed, and Scopus, with the search conducted up to 12/02/2024. Data extraction and quality assessment will be independently conducted by three reviewers, with adherence to eligibility criteria ensured through screening of results. Risk of bias will be evaluated using the STROBE checklist. The synthesis of results will involve meta-analysis utilizing Review Manager v5.4 Forrest plot.

Results:

The review will include a total of 2633 studies, with characteristics summarized for relevant studies. Included studies were analyzed for markers of pulmonary vascular function and fibrosis in T2DM and prediabetes populations. Meta-analysis will be performed to evaluate pooled mean differences in these markers, providing insights into potential associations with metabolic disorders.

Conclusion:
This systematic review protocol serves as a compass for exploring studies on the prediabetic state's association with pulmonary vascular function and fibrosis. By synthesizing existing evidence, this review aims to elucidate the pathophysiological mechanisms underlying these associations and inform future research directions. Limitations, such as study bias and heterogeneity, will be addressed, emphasizing the need for rigorous methodology in this clinically relevant area.

Introduction

Prediabetes, a metabolic state characterized by elevated blood glucose levels that has been shown to precede the onset of type T2DM [2]. This intermediate hyperglycemic state has been associated with various systemic complications [2]. While its association with cardiovascular and metabolic complications is well-established, there is a pile of evidence suggesting that prediabetes may also exert a profound influence on other organ systems, including the respiratory system [3-6].

The pulmonary vascular system, a crucial component of the circulatory system, plays a leading role in facilitating the exchange of oxygen and carbon dioxide within the lungs [7]. In its normal functioning, this system is a low-pressure, high-flow network of blood vessels that transports deoxygenated blood from the right side of the heart to the lungs and returns oxygenated blood to the left side of the heart for systemic circulation [7]. Pulmonary fibrosis is a debilitating and often progressive lung disease characterized by the excessive deposition of extracellular matrix proteins in the lung parenchyma, leading to impaired gas exchange and respiratory function [8]. This condition represents a significant global health burden, with a complex etiology that involves genetic, environmental, and comorbid factors [8]. Impaired pulmonary vascular function and fibrosis have been shown to be associated with T2DM, also there is evidence of prediabetes being associated with severe illness in corona virus (COVID-19) infected individuals which suggest that prediabetes impaired the pulmonary function before infection with COVID-19 [9]. In recent years, prediabetes has been associated with vascular dysfunction and endothelial impairment, primarily in the context of cardiovascular disease [10, 11]. However, its potential influence on pulmonary vascular function and the development or progression of pulmonary fibrosis remains an underexplored area of research. To address this critical knowledge gap, we propose a review to comprehensively investigate the on the impact of type 2 diabetes mellitus and prediabetes on pulmonary vascular function and its potential contribution to pulmonary fibrosis.

Understanding the relationship between T2DM, prediabetes and pulmonary function is a topic of increasing importance, as it has the potential to shed light on this metabolic disorder. While the links between T2DM and pulmonary dysfunction have been extensively studied, and there is also a paucity of research investigating the effects of prediabetes specifically [9]. Therefore, another aim of this study is to synthesize all the empirical evidence by conducting a systematic review that will identify, evaluate, and summarize the findings of all relevant studies concerning the impact of T2DM and prediabetes on pulmonary vascular function and its potential association with the development of pulmonary fibrosis.

Research Question

What is the relationship between T2DM or prediabetes and pulmonary vascular dysfunction and fibrosis?

Is there pulmonary vascular dysfunction and fibrosis in individuals with T2DM or prediabetes compared to those without diabetes?

Objectives

- To assess the impact of diabetes on pulmonary vascular function by synthesizing the pooled mean differences of markers indicative of impaired pulmonary circulation and endothelial dysfunction, including Malondialdehyde (MDA), Endothelin-1 (ET-1), and Angiopoietin-2 (Ang-2).
- To evaluate the overall concentration of fibrotic markers, such as Interleukin (IL-6), Surfactant protein-A (SP-A), and Matrix metalloproteinases (MMPs), in individuals with diabetes, especially prediabetes to elucidate their potential association with pulmonary fibrosis development.

Methods

This systematic review protocol has been prepared following the Prepared Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2020 (PRISMA-P) guidelines. The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number “CRD42023478267”, dated 14 November 2023.

Ethics Approval and Consent to Participate

The data analysed will be already published material, and there will be no data collection from individuals for this review. The authors declare that there will be no informed consent required to be signed; this means no ethics approval is required for the systematic review and meta-analysis.

Eligibility Criteria for the study

This study will include all study designs. Studies reported on must investigate pulmonary health in type 2 diabetic or prediabetic individuals, specifically pulmonary vascular function, and pulmonary fibrosis by measuring parameters such as mean pulmonary arterial pressure, pulmonary vascular resistance, and biomarkers like Malondialdehyde (MDA), Endothelin-1 (ET-1), Angiopoietin-2 (Ang-2), (IL-6), Surfactant protein-A (SP-A), and Matrix metalloproteinases (MMPs). Inclusion criteria will encompass all patients, including those with pulmonary issues, who meet the prediabetic criteria as defined by the American Diabetes Association (ADA). All data sources that evaluate the risk of exposure of prediabetes and diabetes on pulmonary fibrosis between 2000-2023 which will be obtained. The criteria for exclusion will include studies with animal subjects and studies published before the year 2000, and studies lacking necessary data. Full-text articles or reports indicating that individuals who were used were free from all the mentioned criteria will then be eligible.

Diagnostic criteria for eligibility

Prediabetes must be clinically diagnosed according to the ADA or WHO criteria, which means participants should meet 1 of the following diagnoses: fasting blood glucose- 5.6 to 7.0 mmol/L; 2 hours postprandial blood glucose (2 hours oral glucose tolerance test)-7.8 to 11.0 mmol/L with glycated hemoglobin (5.7%-6.4) [12].

Study Design

PCOs statement	
Population	Studies that report on patients with prediabetes as defined by the ADA or WHO criteria will meet the inclusion criteria.
Comparators	To be included, studies must include a control group (participants without diabetes) and a group with T2DM or prediabetes.
Outcomes	This systematic review is expected to show

	the following results. Primary outcomes: Changes in concentrations of ET-1, Ang-2, and MDA to show an affected vascular system. Secondary outcomes: Blood levels of IL-6, SP-A, and MMPs to show the presence of fibrosis in the lungs.
Study Design	Observational studies and interventional studies, including but not limited to cohort studies, case-control studies, cross-sectional studies, and randomized controlled trials (RCTs). Studies published between 2001-2023.

Search Strategy

The following databases will be screened: Google Scholar, PubMed, Embase and Web of Science. With the assistance of a librarian, the search strategy will be conducted using the following keywords: “prediabetes,” “pulmonary vascular function,” “pulmonary vascular dysfunction,” “pulmonary fibrosis,” “pulmonary health,” “Type 2 diabetes” and “Type 2 diabetes mellitus”. A search strategy example is attached as one of the supplementary files. Additionally, bibliographies of related articles and current review articles will be manually screened for potentially relevant articles. Duplicate articles will be eliminated from all search results and publications that are clearly irrelevant will be excluded after reviewing the title and abstracts. To find eligible articles, the remaining articles will be screened using a full-text review based on the inclusion and exclusion criteria.

Identification of Eligible Studies

The title and abstracts of all the obtained results will be screened by reviewers (NM, ND and AS), and the studies that meet the eligibility criteria will then be selected. Each reviewer will be responsible for screening all the selected study reports before the decision-making of the eligible reports. The PRISMA flowchart for selection of studies will then be provided in the reports from the systematic review.

Data Extraction

Two reviewers will independently extract relevant information from selected articles into a Microsoft Excel file. Extracted information will include study and participant characteristics such as the first author's name, publication year, country, study setting, the number of participants, smoking status, gender distribution, age range, mean and standard deviation of pulmonary health markers. The quality of extracted data will be reviewed by another team member, with any disagreements resolved by a third reviewer. If two articles from the same study population report odd ratios, the one with a larger sample size will be selected.

Risk of Bias

The STROBE checklist will be used to determine the possibility for bias in each study. The scores will be rated as follows: excellent (>85%), good (70% <85%), fair (50% <70%), poor (<50%). Three reviewers (NM, ND and AS) will be responsible for the independent judgement based on the STROBE checklist which consists of 22 items on the guideline. The investigator who reported on the data will be contacted three times if the data in the published study are unclear. Should there be no response, data will then be removed from the report that qualifies.

Data Synthesis and Analysis

The extracted study and participant characteristics will be tabulated. If sufficient homogenous data is extracted, a meta-analysis will be done using the Review Manager software (RevMan). The 5.4 version of RevMan will be used to create forest plots for meta-analysis. To assess heterogeneity, the forest plot will measure the overlap between confidence intervals (CIs). I2, with values ranging from 0% to 100%, will be calculated. Values below 25% indicate strong homogeneity, while values above 75% suggest high heterogeneity. A value of 50% will be considered moderate. If the heterogeneity is high, a subgroup analysis will be considered to examine the cause.

Assessment of Strength of Evidence

NM, AS, and AK will then be responsible for the assessment of the strength of evidence. The studies included in the review will then be evaluated using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system will be used to evaluate the quality of evidence, particularly regarding effectiveness [13, 14]. Furthermore, a summary of findings table will then be created.

Results

The systematic review will include a total of 2633 studies, with detailed characteristics summarized for each relevant study. These included studies will undergo analysis to examine markers of pulmonary vascular function and fibrosis in both T2DM and prediabetes populations. Through meta-analysis, we aim to assess pooled mean differences in these markers, shedding light on potential associations with metabolic disorders. This protocol serves as a guide for systematically exploring articles investigating pulmonary vascular function and fibrosis within diabetic and prediabetic states. The outcomes generated from this protocol will direct future research efforts.

Discussion

Principal Findings:

The systematic review and meta-analysis are designed to assess the impact of T2DM and prediabetes on pulmonary vascular function and the development of pulmonary fibrosis. The review aims to synthesize existing evidence to clarify whether metabolic dysregulation in T2DM and prediabetes contributes to pulmonary vascular abnormalities and fibrosis.

The expected outcomes of this study include identifying significant associations between T2DM, prediabetes, and impaired pulmonary vascular function. We anticipate elevated levels of markers indicative of endothelial dysfunction, such as MDA, ET-1, and Ang-2, in individuals with T2DM and prediabetes. These markers suggest endothelial impairment, which may be a critical mediator of pulmonary vascular dysfunction in metabolic disorders. Comparatively, existing literature highlights similar trends, with studies indicating that T2DM is associated with systemic endothelial dysfunction extending to the pulmonary vasculature [15, 16].

Additionally, we expect to find increased levels of fibrotic markers, including IL-6, SP-A, and MMPS, in individuals with T2DM and prediabetes. This would support the hypothesis that metabolic disorders accelerate the progression of pulmonary fibrosis. Previous research corroborates these findings, indicating that chronic inflammation and oxidative stress in T2DM contribute to fibrogenesis in various tissues, including the lungs [17].

Limitations:

This systematic review and meta-analysis may face several limitations. The heterogeneity of the included studies, in terms of population demographics and measurement techniques, could affect the generalizability of the findings. Additionally, the observational nature of most included studies limits the ability to infer causality. Potential publication bias and the varying quality of studies, as assessed by the STROBE checklist, could influence the results. Finally, the exclusion of non-English language studies might lead to the omission of relevant data.

Conclusions:

The anticipated findings from this systematic review and meta-analysis are expected to highlight the significant impact of T2DM and prediabetes on pulmonary vascular function and the development of pulmonary fibrosis. These results could underscore the need for heightened clinical awareness and

early intervention strategies to mitigate pulmonary complications in individuals with metabolic disorders. The broader implications of this study suggest that addressing endothelial dysfunction and chronic inflammation in T2DM and prediabetes could potentially reduce the burden of pulmonary diseases. Future research should focus on longitudinal studies to establish causality and explore targeted therapies to preserve pulmonary vascular health in metabolic disorders.

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Authors' Contributions

NM, ND, AS, and AK were responsible for brainstorming, designing the study, and drafting the protocol. NM, AS, and AK were responsible for reviewing the eligible study and final draft of the manuscript. Funders had no role in developing the protocol.

Conflicts of Interest

None declared.

Data Availability Statement

No extra data is available since it is a protocol for systematic review.

Abbreviations

Type 2 diabetes mellitus (T2DM), Malondialdehyde (MDA), Endothelin-1 (ET-1), Angiopoietin-2 (Ang-2), (IL-6), Surfactant protein-A (SP-A), Matrix metalloproteinases (MMPs), Corona virus (COVID-19, Grading of Recommendations Assessment, Development, and Evaluation (GRADE), Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA).

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Supplementary Files

Untitled.
URL: http://asset.jmir.pub/assets/4e0cb3566418ab7f16513dd20906892c.docx

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CONSORT (or other) checklists

Checklist.
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