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Genetic and Transcriptomic Background of Oxidative Stress, and Antioxidative Therapies in Late Complications of Type 2 Diabetes Mellitus: A Systematic Review

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective The purpose of our review is to highlight the crucial role of oxidative stress in the development and severity of late complications in patients with T2DM while providing insight into the underlying genetic mechanisms. We have systematically reviewed published data on various aspects of the role of genetic variability and gene expression levels of oxidative and antioxidative enzymes in the development of late complications of T2DM. We also conducted a comprehensive systematic review of published ran-domized clinical trials that investigated potential antioxidant therapies in patients with late complications of T2DM.

Condition being studied Type 2 diabetes mellitus (T2DM) is one of the most common heterogeneous and devastating chronic metabolic diseases. Macrovascular and microvascular complications play a crucial role in the 15 % in-crease in all-cause mortality and morbidity in this group of patients. We have focused on microvascular and macrovascular late complications of T2DM (DR, DKD, diabetic neuropathy; cerebrovascular disease, CVD, and PVD).

METHODS

Search strategy We have decided to include only scientific articles, indexed by PubMed.
Search terms in both search queries were determined by the agreement of all authors and based on a brief literature review. We have deliberately conducted a broad search strategy to include as many studies as possible.
In 1st search, we used the search query ((type 2 diabetes) OR T2D)) AND (oxidative stress) AND (diabetic complications) AND ((genetics) OR (genomics) OR (genes) OR (poly-morphism) OR (genetic variations) OR (transcriptomics)) to target genetic association studies and transcriptomic studies focusing on genetic variations in

antioxidative enzymes and oxidative stress-related pathways in T2DM and late complications. We have also used the following filters: in the last 10 years, Humans.
For the 2nd search, we performed a PubMed search with the search query (diabetic complications) AND (antioxidants). We have also applied these filters to the search: Randomized Controlled Trial, Meta-analysis, in the last 10 years, Humans.

Participant or population Patients with T2DM late complications.

Intervention No intervention in the 1st search; Administration of non-drug well-described substances with direct antioxidative effect in the 2nd search.

Comparator Any comparator in 1st search; 2nd search: eligible comparators included all of the following: • treatment group(s) vs. control group(s),• > 2 intervention groups (receiving different interventions, one of those antioxidants).

Study designs to be included 1st search: Genetic association study or gene expression analysis; 2nd search: Peer-reviewed randomized controlled trials (RCT).

Eligibility criteria 1st search: We have included clinical studies that focused on association of genetic variants and gene expression levels with T2DM late complications. As we tried to include a broad scope of the reports and since this field is not well researched, we have used a broad search strategy and did not limit the search to specific molecular genetic methods. After performing a broad search, we have filtered the retrieved studies with rigorous selection process. Studies that have not focused on associations with late T2DM complications but on other pathologies or development of the disease, or associations with oxidative stress biomarkers irrespective of T2DM complications were excluded. Moreover, studies on T1DM, T2DM without complications, or multimorbid patients were excluded from further analysis. Furthermore, review articles, systematic reviews, editorials, and reports that have not been written in the English language or could not be accessed in full text were also not included in the final analysis. Genetic association studies and transcriptomic studies, included in the final review, were evaluated separately.; 2nd search: We have included studies that focused on randomized controlled trials using antioxidants as an intervention. Only the randomized controlled trials that focused on the role of antioxidants as an intervention in the population of patients with late T2DM complications were analyzed. As we tried to include a broad scope of the reports and since this field is not well researched, we have used a broad search strategy and relied on filtering study reports with rigorous selection process. Studies that have not focused on late T2DM complications but on other pathologies or development of the disease, were excluded. Moreover, studies on T1DM, T2DM patients without complications, healthy population or multimorbid patients, were excluded from further analysis. Additionally, studies that have not used antioxidants as an intervention but used drugs, vitamins, or other substances with only possible indirect antioxidant mechanism were also excluded (similarly, the studies that have tested the efficiency of poor defined mix of antioxidants or possible antioxidants were ruled out). Furthermore, review articles, systematic reviews, editorials, and reports that have not be written in the English language or could not be accessed in full text were also not included in the final analysis. The studies, included in the final review, have been grouped by type of antioxidant used as an intervention.

Information sources Studies, listed in PubMed.

Main outcome(s)
1st search: Association with T2DM late complications
2nd search: Changes in the state of late complication, or changes of the antioxidant systems (i. e., total antioxidants capacity (TAC)).

Quality assessment / Risk of bias analysis We have conducted a risk of bias assessment for the studies, obtained by the 2nd search and selection process. The risk of bias was analyzed using the Cochrane Risk of Bias tool (RoB2) for randomized controlled studies. Each study has been assigned a judgement of (a) low risk of bias, (b) some concerns, or (c) high risk of bias for each of the five categories, included in the RoB2 tool. Those categories are (1) Risk of bias arising from the randomization process, (2) Risk of bias due to deviations from the in-tended interventions, (3) Missing outcome data, (4) Risk of bias in the measurement of the outcome, and (5) Risk of bias in the selection of the reported result. Based on the risk of bias in named categories, the overall risk of bias was assessed for each study. Risk of bias was conducted independently by two reviewers and any discrepancies in assessment have been resolved with consensus. No automation tools were used in the risk of bias assessment.

Strategy of data synthesis As both searches varied greatly in their purpose and retrieved

studies were extremely non-homogeneous regarding the type of late complications, used intervention, and measured outcomes (different even amongst the same type of late complication), we did not conduct a meta-analysis and have therefore not included summary statistics or effect size estimates in this systematic review. We have carried out narrative data synthesis instead, grouping studies according to the experimental approach (genetic variability, gene expression studies; 1st search) and antioxidants that were used as an intervention (2nd search). We have presented crucial study characteristics, methodology, and findings in the main text and summary tables.

Subgroup analysis No meta-analysis conducted.

Sensitivity analysis No meta-analysis conducted.

Country(ies) involved Slovenia.

Keywords type 2 diabetes mellitus, microvascular complications, macrovascular complications, genetic polymorphisms, transcriptomics, antioxidants, oxidative stress.

Contributions of each author
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Author 2 - Vita Dolžan.
Author 3 - Jasna Klen.