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Review Article

# Oral microbiome and metabolome in type 2 diabetes mellitus patients: A systematic review.

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## Abstract

### Introduction
Type 2 diabetes mellitus (T2DM) is one of the leading metabolic disorders worldwide and is associated with multiple systemic complications. Increasing evidence indicates that diabetes alters the composition and metabolic activity of the oral microbiota. The oral microbiome and its associated metabolome may therefore serve as indicators of disease status and for biomarker discovery. This systematic review evaluates the current evidence on alterations in the oral microbiome and metabolome in patients with T2DM.

### Methods
A systematic search was conducted following PRISMA guidelines. Electronic databases, including PubMed, MEDLINE, Scopus, Embase, Web of Science, and LILACS, were searched for studies published between 2020 and 2024. Search terms included "oral microbiome," "metabolome," and "type 2 diabetes mellitus." Eligible studies investigated associations between oral microbial composition and metabolic profiles in T2DM patients. Data extracted included author, year, country, study design, and key outcomes. Study quality was evaluated using the STROBE checklist.

### Results
Four original research studies met the inclusion criteria. The included studies consistently reported alterations in oral microbial composition and metabolic profiles in individuals with T2DM. Changes were observed in bacterial abundance and in metabolite profiles associated with carbohydrate metabolism, inflammatory pathways, and host–microbe interactions. Some studies identified correlations between glycemic control and shifts in microbial diversity and metabolite production. These findings indicate that metabolic changes in the oral environment may influence microbial ecology and disease susceptibility.

### Conclusion
Evidence suggests that T2DM is associated with measurable alterations in the oral microbiome and metabolome. These changes may contribute to oral dysbiosis and may have implications for early detection of metabolic and oral complications.

### Future research
Large-scale longitudinal studies integrating metagenomics and metabolomics are required to validate oral biomarkers and clarify the mechanistic relationship between diabetes, microbial dysbiosis, and metabolic alterations.

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## Introduction

Bacteria, microeukaryotes, viruses, and archaea are part of the complex and incredibly varied human oral microbiota. Although the oral cavity contains a variety of microenvironments, these communities have a complicated and highly structured biogeography that influences metabolic exchange locally. Additionally, the oral microbiota interact with the human host's immune system and play an essential role in both systemic and oral health.

A significant concern for world health is the prevalence of diabetes mellitus and its associated complications. Numerous factors, including population aging, economic growth, urbanization, improper dietary patterns, and sedentary lifestyles, are contributing to the growing diabetes mellitus epidemic. Globally, T2DM and its consequences have significantly increased the burden of death and disability. Diabetes mellitus often manifests years before a diagnosis is made. People with undiagnosed and untreated diabetes mellitus are more likely to experience complications than those receiving treatment; it has been estimated that 45.8% (or 174.8 million cases) of all adult cases of diabetes mellitus are undiagnosed worldwide [22].

Understanding how microbes influence their host's physiology has revolutionized human microbiome research. As culture-independent techniques have advanced, more microbial species within microbial communities are being detected and classified. The composition and genetic makeup of the human microbiome can now be ascertained using technology, shotgun metagenomics, and biomarker sequencing.

Microbes that are normally found in the oral cavity have been detected in various organs, including the brain, placenta, heart, lungs, and small intestine, as well as other distant sites in the body. Specifically, oral bacteria associated with periodontal disease have been connected to several common chronic illnesses, such as high blood pressure and cardiovascular disease. These hidden microflorae can now be accessed through next-generation sequencing (NGS)-based technologies and advancements in sequencing technology.

The impact of diabetes on the oral microbiota has been the subject of numerous investigations. Studies showed that *Treponema denticola*, *Prevotella nigrescens*, *Streptococcus sanguinis*, *Streptococcus oralis*, and *Streptococcus intermedius* were more prevalent in the supragingival plaques of diabetic subjects than in those of non-diabetic subjects [23]. According to an earlier study, the metabolome, Ethanol, taurine, isovalerate, butyrate, and glucose, particularly from saliva, may be a valuable tool for detecting periodontal inflammation. The metabolites, which are produced in oral fluids because of bacterial metabolism or host-induced inflammatory processes, may provide useful biomarkers that can facilitate our understanding of intricate biochemical processes and host-bacteria interactions[29].

Recent advancements in high-throughput technologies have revolutionized our understanding of circulating biomarkers for type 2 diabetes, allowing us to identify these indicators well over a decade before the onset of noticeable symptoms. These biomarkers represent powerful tools for early screening, accurate diagnosis, and effective prognosis of diabetes. Moreover, the involvement of metabolite and protein markers in critical metabolic pathways can offer invaluable insights into the mechanisms driving the development of type 2 diabetes, paving the way for more targeted interventions and preventative strategies [24]. The objective of this systematic review is to evaluate current evidence on the relationship between the oral microbiome and metabolomic profiles in patients with type 2 diabetes mellitus (T2DM). The review was to identify alterations in microbial composition and metabolic signatures associated with T2DM and to assess their potential relevance for biomarker discovery and early detection of disease-related oral and systemic complications.

## Methodology

### Eligibility criteria

Studies were considered eligible if they investigated the relationship between the oral microbiome and metabolomic profiles in patients diagnosed with type 2 diabetes mellitus (T2DM). Original research articles published between January 2020 and December 2024 were included. Observational studies evaluating microbial composition, metabolomic alterations, or their association with glycemic status in T2DM patients were considered eligible.

Exclusion criteria included review articles, editorials, conference abstracts, letters to the editor, and studies not related to the oral microbiome or metabolome in diabetes. Studies lacking sufficient methodological information or not involving human subjects were also excluded.

### Information sources

A comprehensive literature search was conducted using electronic databases including PubMed, MEDLINE, Scopus, Embase, Web of Science, and LILACS. Reference lists of relevant articles were also screened to identify

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additional eligible studies. The final database search was performed in December 2024.

## Search strategy

The search strategy was developed using Boolean operators and relevant keywords. The following terms were used:
"oral microbiome" AND "metabolome" AND "type 2 diabetes mellitus"
Additional combinations included:
"oral microbiome" AND ("metabolome" OR "oral metabolomics" OR "dysbiosis") AND "T2DM"
Filters were applied to restrict results to studies published in English between 2020 and 2024.

## Selection process

The study selection process was conducted in two stages. First, titles and abstracts identified through the database search were screened to remove irrelevant studies. Full texts of potentially eligible articles were then assessed against the inclusion criteria. The selection process followed PRISMA guidelines, and the flow of studies through the screening process is presented in the PRISMA flow diagram.

## Data collection process

Data were extracted from each included study using a standardized data extraction approach. Extracted information included author name, year of publication, country of study, study design, and principal findings related to oral microbiome composition and metabolomic profiles in T2DM patients.

## Data items

The primary outcomes evaluated in this review included:
• Alterations in oral microbial composition in patients with T2DM
• Changes in salivary or oral metabolomic profiles
• Associations between microbial dysbiosis and metabolic biomarkers
Additional variables extracted included study design, geographic location, and characteristics of the study population.

## Study risk of bias assessment

The methodological quality of the included studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist. This tool evaluates study design, data collection methods, reporting transparency, and potential sources of bias.

## Effect measures

Due to the heterogeneity of the included studies and variations in study design, results were summarized using descriptive synthesis rather than quantitative statistical measures. Findings were reported in terms of observed associations between oral microbial profiles and metabolomic alterations in T2DM patients.

## Synthesis methods

A qualitative synthesis approach was adopted to summarize the results. Extracted data were organized into tables summarizing study characteristics and key outcomes. Differences and similarities among the included studies were analysed to identify consistent patterns of microbial and metabolomic alterations associated with T2DM.

## Reporting bias assessment

Given the limited number of eligible studies, a formal statistical assessment of publication bias was not performed. However, potential reporting bias was minimized by searching multiple databases and screening reference lists of relevant publications.

## Certainty assessment

The certainty of evidence was assessed qualitatively based on methodological quality, study design, and consistency of reported findings among the included studies.

## Results

### PRISMA flow chart

The literature search across PubMed, MEDLINE, Scopus, Embase, Web of Science, and LILACS identified 10 records published between 2020 and 2024. After initial screening of titles and abstracts, 6 studies were excluded because they did not meet the eligibility criteria. Reasons for exclusion included studies that were review articles, studies not involving patients with type 2 diabetes mellitus,

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studies not evaluating oral microbiome or metabolomic profiles, and studies lacking sufficient methodological data. Following full-text assessment, 4 studies met the inclusion criteria and were included in the qualitative synthesis. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

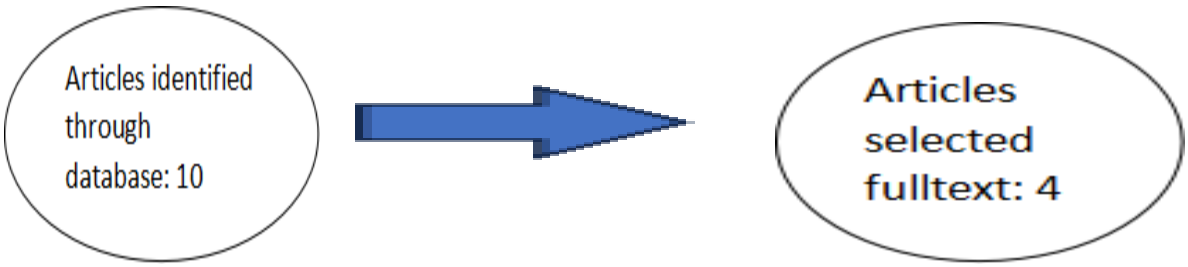


**Figure 1: PRISMA flowchart**

## Study characteristics

Four studies published between 2021 and 2024 were included in the review. The studies were conducted in different geographic regions and primarily used observational study designs. All studies investigated alterations in oral microbial communities and metabolomic profiles in patients diagnosed with T2DM.

Diao et al. analysed the oral microbiome and metabolome in patients with varying glycaemic control and reported reduced periodontal pathogenicity under controlled glycaemic conditions. Fang et al. evaluated the role of multi-omics approaches in identifying biomarkers related to metabolic disorders. Li et al. reported a significant association between oral microbial dysbiosis and altered metabolite profiles in T2DM patients. Almeida-Santos et al. characterised differences in oral microbial composition between diabetic patients and non-diabetic controls.

The main characteristics and outcomes of these studies are summarized in Table 1.

**Table 1. Outcome of the analyzed articles**

| Author | Outcome |
|---|---|
| Diao et al. [1] | Under active blood glucose control, the study found lower periodontal pathogenicity and inflammatory correlation in the oral microecology of T2DM patients. |
| Fang et al. [2] | The authors explored the ways in which genomics, transcriptomics, proteomics, and metabolomics could help identify novel candidate biomarkers. |
| Li et al. [3] | There is a significant correlation between the oral microflora and oral metabolites in T2DM. |
| Almeida-Santos et al. [4] | Differences in microbiome composition compared to non-control diabetics and diabetic controls. |

## Risk of bias in included studies

The methodological quality of the included studies was assessed using the STROBE checklist for observational research. Overall, the included studies demonstrated moderate methodological quality. Most studies clearly described study objectives, population characteristics, and analytical methods. However, some studies had limitations related to sample size and lack of longitudinal follow-up, which may introduce potential bias in the interpretation of results.

## Results of individual studies

Each included study reported alterations in oral microbial composition and metabolomic signatures in individuals with T2DM.

Diao et al. reported that improved glycaemic control was associated with reduced periodontal pathogenicity and decreased inflammatory correlations in the oral microbiome.

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Fang et al. demonstrated that integrated multi-omics approaches, including metabolomics, may help identify candidate biomarkers associated with metabolic disorders.
Li et al. identified significant associations between oral microbial dysbiosis and altered metabolite profiles in T2DM patients, suggesting interactions between host metabolism and microbial communities.
Almeida-Santos et al. observed differences in oral microbiome composition between diabetic patients receiving treatment and healthy individuals.

## Results of syntheses

A qualitative synthesis of the included studies revealed consistent evidence of altered oral microbial composition and metabolic profiles in patients with T2DM. Studies reported changes in bacterial abundance, metabolite production, and host-microbe metabolic interactions. These alterations appear to be influenced by glycaemic control and metabolic status. Due to variations in study design, sample size, and analytical techniques, quantitative meta-analysis was not performed.

## Reporting biases

Formal statistical evaluation of reporting bias was not conducted because only four studies met the inclusion criteria. However, multiple databases were searched to minimize the risk of publication bias.

## Certainty of evidence

The overall certainty of evidence was considered moderate. Although consistent findings were observed across the included studies, the limited number of studies and heterogeneity in methodologies reduced the strength of conclusions.

## Discussion

The human body functions as a complex biological ecosystem that includes not only host cells but also large populations of microorganisms that coexist with the host. These microbial communities form symbiotic relationships with human tissues and participate in many physiological processes that influence both local and systemic health [5]. Increasing recognition of host–microbe interactions has reshaped current understanding of disease mechanisms, particularly in metabolic disorders.
The oral cavity represents one of the most biologically diverse microbial environments in the human body. Current estimates suggest that more than 700 microbial species inhabit the oral ecosystem, with a substantial proportion remaining uncultivated or incompletely characterized [6]. These organisms collectively form the oral microbiome, a term originally introduced to describe the ecological community of microorganisms living in association with the human body and interacting with host biological systems [7].
Microbial communities in the oral cavity consist of bacteria, fungi, viruses, archaea, and protozoa [8]. Despite this diversity, bacterial populations dominate most microbiological studies of the oral environment, and consequently, many investigations focus primarily on bacterial species rather than the full spectrum of microbial organisms present within oral habitats [7]. These microorganisms contribute to oral health by maintaining ecological balance, competing with pathogenic organisms, and modulating immune responses.
Multiple anatomical surfaces within the oral cavity support microbial colonization. Teeth, gingival sulcus, tongue dorsum, buccal mucosa, palate, and saliva create distinct microenvironments that allow the development of specialized microbial communities [7]. These oral niches are connected anatomically with structures such as the pharynx, respiratory tract, and gastrointestinal tract, allowing oral microorganisms to influence systemic physiological processes.
Under normal conditions, oral microorganisms exist in a balanced state characterized by cooperative interactions between microbial species and the host. Commensal organisms play an important protective role by preventing colonization by pathogenic bacteria and maintaining mucosal homeostasis. Disruption of this equilibrium can allow opportunistic organisms to proliferate and initiate disease processes.
The microbial composition of a healthy oral cavity includes several predominant bacterial genera. Gram-positive organisms frequently detected include *Streptococcus*, *Actinomyces*, *Rothia*, *Lactobacillus*, and *Corynebacterium*, whereas gram-negative genera such as *Neisseria*, *Veillonella*, *Prevotella*, and *Fusobacterium* are also commonly present [9]. In addition to bacteria, other microorganisms such as *Candida* species and protozoa, including *Entamoeba gingivalis* and *Trichomonas tenax*, may also colonize the oral cavity [9].
Interactions among oral microorganisms contribute to several biological processes, including immune modulation, maintenance of mucosal integrity, and resistance to pathogen colonization. Oral microorganisms can also enter the systemic circulation through inflamed gingival tissues, thereby linking oral microbial communities with systemic diseases [10]. Evidence

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suggests that alterations in oral microbial composition may contribute to conditions such as dental caries, periodontal disease, and other inflammatory disorders.

Oral biofilm formation represents a critical feature of microbial organization within the oral cavity. Biofilms consist of structured microbial communities embedded in extracellular matrices that adhere to oral surfaces. These structures allow microorganisms to communicate metabolically and respond collectively to environmental changes [11,12].

A balanced oral microbial ecosystem is often described as eubiosis, in which stable host–microbe interactions support physiological homeostasis. In this state, microbial communities contribute to immune system development, protection against pathogens, and regulation of inflammatory responses [7]. Microbial communities in other body sites, including the gastrointestinal tract, also contribute to metabolic regulation, nutrient processing, and energy homeostasis [5].

Disturbances in microbial balance can result in dysbiosis, a condition characterized by alterations in microbial composition that favor pathogenic organisms. Dysbiosis has been implicated in numerous oral and systemic diseases, including periodontal disease, cardiovascular disorders, and metabolic conditions such as diabetes mellitus [13,14]. Environmental and behavioral factors, including diet, tobacco use, alcohol consumption, stress, hormonal changes, and oral hygiene practices, can influence microbial composition within the oral cavity [15].

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. Insulin plays a central role in glucose metabolism by promoting glucose uptake and regulating hepatic glucose production [16,17]. When insulin signaling is disrupted, circulating glucose levels increase, leading to metabolic dysregulation and long-term complications.

Glycemic control in individuals with diabetes is commonly assessed using glycated hemoglobin (HbA1c) levels, which reflect long-term blood glucose concentrations. Diagnostic guidelines generally define diabetes as HbA1c values equal to or exceeding 6.5% [16]. The American Diabetes Association recognizes several major forms of diabetes, including type 1 diabetes, type 2 diabetes, gestational diabetes, and diabetes associated with other specific causes [15].

Type 2 diabetes mellitus (T2DM) represents the most prevalent form of diabetes worldwide and accounts for approximately 90–95% of diagnosed cases. This condition typically develops through progressive insulin resistance accompanied by compensatory hyperinsulinemia. Over time, pancreatic β-cells become unable to maintain adequate insulin secretion, resulting in persistent hyperglycemia [15].

Interactions between diabetes and oral health have been widely investigated. Evidence supports a bidirectional relationship between diabetes and periodontal disease, in which each condition can influence the progression of the other. Early epidemiological observations demonstrated that individuals with severe periodontitis were more likely to exhibit poor glycemic control [7]. Diabetic patients also show an increased susceptibility to periodontal disease, with studies reporting a two- to three-fold higher risk compared with non-diabetic individuals [18].

Several biological mechanisms may explain the association between diabetes and oral microbial alterations. Chronic hyperglycemia can modify immune function and increase susceptibility to infection. Elevated glucose levels in saliva may also provide additional substrates for microbial growth, thereby altering microbial composition within oral biofilms [14]. These changes may promote colonization by pathogenic species and contribute to inflammatory responses within periodontal tissues.

Immune dysregulation is another important factor linking diabetes with oral infection. Impaired immune responses in diabetic individuals may reduce host defense against microbial invasion, increasing the likelihood of chronic inflammatory conditions. Oral pathogens such as *Porphyromonas gingivalis* can activate inflammatory signaling pathways, including TLR-mediated pathways and downstream transcription factors such as NF-κB, ultimately contributing to systemic inflammatory responses [18].

Oxidative stress also plays a key role in the pathophysiology of diabetes and its complications. Increased production of reactive oxygen species can damage cellular structures and disrupt metabolic pathways associated with insulin signaling. Periodontal pathogens may contribute to systemic oxidative stress and inflammatory mediator production, further linking oral infections with metabolic disorders [18].

Diabetes-related inflammatory processes can also influence periodontal tissue metabolism. Alterations in host cell activity, including osteoclast and osteoblast function, may lead to increased production of inflammatory mediators such as tumor necrosis factor and changes in the RANKL/OPG signaling pathway, which contributes to bone resorption in periodontal disease [7].

Metabolic profiling studies have identified several metabolites associated with insulin resistance and diabetes. Branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, have been implicated in metabolic dysregulation and insulin resistance. Altered BCAA

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metabolism may influence pathways such as mTOR signaling and contribute to metabolic complications [19].

Saliva represents an attractive biological fluid for studying microbial and metabolic changes associated with systemic diseases. Sample collection is non-invasive, relatively inexpensive, and suitable for large-scale screening applications [18]. Salivary metabolomic analysis has revealed differences in carbohydrate metabolism, lipid metabolism, and oxidative stress markers between diabetic and non-diabetic individuals [3].

Advances in molecular technologies have significantly improved the ability to study complex microbial ecosystems. High-throughput sequencing techniques, including next-generation sequencing, enable detailed characterization of microbial communities and their functional potential [11]. Initiatives such as the Human Microbiome Project have accelerated host research–microbe interactions and their roles in health and disease [9].

Metabolomics, which involves the comprehensive analysis of small molecules produced during metabolic processes, provides additional insight into biological pathways involved in disease development. Both endogenous metabolites and exogenous compounds can influence metabolic networks within biological systems [19,27]. Integration of metabolomic data with microbiome analysis may therefore provide valuable information regarding host–microbe interactions.

Traditional microbiological techniques rely heavily on culture-based methods, yet many microorganisms cannot be cultivated using conventional laboratory approaches. Molecular techniques based on 16S ribosomal RNA gene sequencing have allowed researchers to identify previously unrecognized microbial species and study microbial diversity more effectively [28]. Metagenomic sequencing provides even greater resolution by analyzing entire microbial genomes and functional gene content [9].

Recent studies evaluating oral microbiota in T2DM have frequently used 16S rDNA sequencing to characterize microbial communities. Although this approach provides valuable information regarding microbial composition, metagenomic sequencing can provide more comprehensive insights into microbial functions and metabolic pathways. Salivary metabolomic studies have demonstrated alterations in carbohydrate metabolism, lipid metabolism, and oxidative stress pathways in individuals with diabetes [3].

Specific microbial taxa may also be associated with metabolic changes. Reduced abundance of *Prevotella nanceiensis* and *Prevotella melaninogenica* has been reported in individuals with elevated glycemic markers such as fasting glucose and HbA1c [15]. These findings suggest that hyperglycemia may influence the oral microenvironment and alter microbial community structure [20].

Metabolomic approaches offer potential for identifying biomarkers associated with metabolic disorders. Because metabolites reflect ongoing biochemical activity, they may provide early indicators of disease processes and physiological alterations [19]. Both endogenous metabolic pathways and external influences, such as diet, can influence metabolomic profiles.

For example, dietary compounds including phosphatidylcholines can be metabolized by gut microorganisms to generate metabolites such as trimethylamine-N-oxide (TMAO), which has been associated with cardiovascular disease risk [19]. Such findings demonstrate the complex interactions between microbial metabolism and host physiological processes.

Although several biomarkers have been proposed for diabetes detection and monitoring, many currently used markers primarily reflect glycemic status rather than underlying disease mechanisms. Identification of additional metabolic and microbial markers may improve diagnostic accuracy and facilitate earlier detection of metabolic disturbances [21].

## Limitations of the evidence and review process

Interpretation of the findings presented in this review should consider several limitations. Only four studies met the inclusion criteria, which restricts the overall strength of the evidence. Differences in study design, sample populations, and analytical techniques also introduce heterogeneity that limits direct comparison between studies. Most available studies are cross-sectional, preventing the determination of causal relationships between microbial dysbiosis and diabetes development.

The review process itself also has limitations. The literature search was limited to studies published between 2020 and 2024 and to English-language publications, which may have excluded relevant research conducted in other languages or earlier periods. In addition, the limited number of studies prevented the performance of a quantitative meta-analysis.

## Implications for clinical practice, policy, and future research

The available evidence indicates that T2DM is associated with measurable changes in oral microbial communities and metabolomic profiles. These findings suggest that oral biological samples may provide useful information

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regarding systemic metabolic status. Saliva-based diagnostic approaches could potentially support early identification of metabolic dysregulation and monitoring of disease progression.

Integration of oral health assessment into diabetes management strategies may improve patient outcomes by recognizing the interconnected nature of oral and systemic health. Public health initiatives addressing diabetes prevention and management may benefit from incorporating oral health evaluation within routine clinical care.

Further research involving large longitudinal cohorts is necessary to clarify the causal relationships between diabetes, oral microbiome alterations, and metabolomic changes. Standardization of analytical methods for microbiome sequencing and metabolomic analysis would also improve comparability between studies. Multi-omics approaches combining metagenomics, transcriptomics, and metabolomics may provide deeper insights into host–microbe interactions and support identification of reliable biomarkers for metabolic disease.

## Conclusion

Type 2 diabetes mellitus (T2DM) is a serious endocrine and metabolic disorder whose aetiology is extremely complex. The oral microflora is a diverse and dynamic ecosystem in the human body. Oral microecological imbalance can cause oral diseases and is closely related to the occurrence and development of systemic diseases such as T2DM. Metabolomics is an attractive method for discovering biomarkers related to the onset and progression of diabetes, due to its ability to provide insights into the molecular processes involved in this condition and its complications. Traditionally, cultivation studies were used, but they have largely been replaced by culture-independent methods, such as 16S rRNA gene-based molecular cloning techniques. These molecular techniques can identify microorganisms that are currently non-culturable.

## Registration and protocol

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review was not prospectively registered in a systematic review registry such as PROSPERO, and a formal review protocol was not published before conducting the study.

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## List of abbreviations

**T2DM** – Type 2 Diabetes Mellitus
**DM** – Diabetes Mellitus
**PRISMA** – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
**STROBE** – Strengthening the Reporting of Observational Studies in Epidemiology
**NGS** – Next Generation Sequencing
**HbA1c** – Glycated Hemoglobin
**ROS** – Reactive Oxygen Species
**BCAA** – Branched Chain Amino Acids
**TLR** – Toll-Like Receptor
**NF-κB** – Nuclear Factor kappa B

## Availability of data, code, and other materials

All data used in this systematic review were obtained from previously published studies. The extracted study data and summary tables used for the qualitative synthesis are available from the corresponding author upon reasonable request. No analytical code or specialized software scripts were used for data analysis in this review.

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## Competing interests

The authors declare that they have no competing interests.

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