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The Effectiveness of Micronutrient Supplementation in the Management of Diabetes among US Adults receiving dietary treatment.

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2020

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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Background: Different researchers have explored the benefits of micronutrients, aiming to clear the uncertainty that engulfs aspects of their role in diabetes dietary therapy. This thesis will review and synthesize existing evidence to establish whether micronutrient supplementation/ intake in diabetes dietary therapy is effective in preventing the progression of the disease or even restoring optimal insulin action to enhance remission in adult populations. Among the notable micronutrients are zinc, potassium, vitamin B-12, and magnesium, which are associated with the homeostasis of glucose metabolism.

Methods: This review employs a clear search protocol to obtain relevant papers from various databases including PubMed/Medline, EMBASE, and Web of Science. To search and identify relevant papers from these databases, the current review employs search strings that combine keywords obtained from the primary research questions by employing Boolean operators (AND/and OR). The current review aims at synthesizing the state of knowledge on the role of four micronutrients (zinc, potassium, magnesium and the vitamin B-12- metformin interaction), which are part of the diabetes management intervention for individuals aged 18 years and above (excluding pregnant women) in the US.

Results: The searches retrieved a total of 1215 articles. Of the 1215 articles, total, 1001 articles were eliminated in the screening phase. The full texts of the remaining 214 articles were subjected to a quality review process. 196 articles were excluded for various reasons including not focusing on adults with type 2 diabetes. In total, 19 studies were included in this review. Although some primary studies examined zinc's importance, they yielded inconclusive results regarding glucose homeostasis and other important outcomes, while others did not find a significant impact; Magnesium levels were found to decrease with certain diabetes risk factors like obesity (Mikalsen et al., 2019) and periodontitis, leading to a decrease in the patient's glycemic status; Reduced potassium intake and low blood potassium concentration result in decreased insulin sensitivity and increased insulin secretion, which increases the risk of T2DM.In addition, research has explored in great detail how metformin use affects serum concentrations of key minerals and vitamins, specifically vitamin B-12. The reviewed studies revealed some notable gaps in the extant literature that require further investigations.

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Chapter I: Introduction

1.1 Background of the Study

1.1.1 Diabetes Prevalence among US Adults

Diabetes is one of the leading causes of mortality among adults in the US. Type 1 and type 2 diabetes presents a major public health concern in the US, affecting over 30.3 million people as of 2015, which is equal to 9.4% of the US population (Xu et al., 2018). In the US, the prevalence of diagnosed cases of diabetes has doubled since the 1990s, affecting large segments of the adult population (Lawrence et al., 2021). Among US adults (18 years or older, excluding pregnant women), the prevalence of diabetes rose from 5.3% in the period between 1976 and 1980 to 11.5% between 2011 and 2014 (Benoit et al., 2019). The increasing diabetes burden is estimated to have had a total economic cost of $327 billion as of 2017, with care for people with diabetes constituting about 24% of the healthcare budget in the country (Benoit et al., 2019). Socio-demographic variables and other factors such as weight status tend to influence the variance of diabetes prevalence.

1.1.2 The Importance of Effective Diabetes Management

Effective management of diabetes is necessary for ensuring that diabetes patients maintain optimal health and do not develop complications associated with the condition. Proper diabetes management includes a combination of lifestyle changes, medications, and at times insulin therapy (Baig et al., 2015). When implemented in the right way, diabetes management interventions may positively influence the health outcomes of patients, including slowing down the progression of the complications associated with the condition through improved glycemic control and even leading to remission. According to Baig et al. (2015), in most cases, diabetes management takes place within the patient's family and social environment, which makes self-care a crucial aspect of effective diabetes management. Micronutrients, which include essential minerals and vitamins, play a critical role in supporting overall health and are considered highly effective interventions in diabetes management.

1.1.3 Micronutrients as a Potential Intervention in Diabetes Management

Chronic hyperglycemia results in elevated oxidative stress as well as the production of pro-inflammatory cytokines that disrupt the signaling pathways of insulin, alter lipid metabolism, the synthesis of proteins, the differentiation of cells, as well as alter the concentrations of micronutrients in the body (Brandão-Lima et al., 2018). Dietary intake of micronutrients can significantly reduce the percentage of glycated hemoglobin (%HbA1c), especially in type 2 diabetes mellitus (T2DM) patients by about 0.3-2% (Brandão-Lima et al., 2018). Researchers have in the recent past established the participation of micronutrients in the synthesis, secretion, as well as the action of insulin (Xu et al., 2018; Brandão-Lima et al., 2018; Lawrence et al., 2021). Among the notable micronutrients are zinc, potassium, vitamin B-12, and magnesium, which are associated with the homeostasis of glucose metabolism.

Zinc intake enhances insulin biosynthesis as a constituent part of the hexameric structure of insulin and enhances its sensitivity to target tissues by stimulating the hormone's receptors (Lawrence et al., 2021). Potassium is essential for the regulation of the voltage-dependent channels in the β-cells of the pancreas, which allow for insulin exocytosis (Brandão-Lima et al., 2018). Magnesium allows for the optimal functioning of the β-cells while also acting as a cofactor for numerous other enzymes that are needed for the metabolism of glucose, including kinase enzymes. These enzymes phosphorylate insulin receptors and enhance the signaling cascade (Brandão-Lima et al., 2018). Drug-nutrient interactions also play a critical role in determining the nutrient requirements and/or the efficacy of the drugs used in the management of diabetes. The interaction between metformin and vitamin B-12 is a common phenomenon in T2DM management (Akindale et al., 2015; Chapman, Darlin & Brown, 2016). As the most commonly prescribed drug for people with T2DM, the impact that metformin use has on micronutrient requirements is of critical concern when seeking to optimize diabetes management outcomes (Chapman et al., 2016). According to Akinlade et al. (2015), metformin is an anti-hyperglycaemic agent that is generally well tolerated by most T2DM patients with only mild gastrointestinal side effects. The drug has been established to have excellent outcomes for the cardiovascular morbidity and mortality among patients with T2DM. Due to the clinical success associated with the drug, some of its side effects tend to be ignored or simply under investigated.

Vitamin B-12, also referred to as cobalamin, is necessary for the full functioning of the haemopoetic, neuro-cognitive as well as vascular systems (Akindale et al., 2015). Long-term use of metformin is associated with decreased levels of vitamin B-12 (Wakeman & Archer, 2020). For instance, metformin is considered to decrease the absorption of vitamin B-12 while at the same time increasing its excretion in the urine. While considering the role that micronutrient supplementation may play in diabetes management, it is equally important to consider how deficiencies such as vitamin B-12 deficiency are influenced by drug-nutrient interactions. T2DM patients taking metformin should also constantly monitor their vitamin B-12 levels and take supplements if deemed necessary to do so.

1.2 Problem Statement

1.2.1 Gaps in Current Diabetes Management Interventions

Micronutrient deficiencies may impair the synthesis, secretion, and signaling pathways of insulin (Dubey, Thakur & Chattopadhyay, 2020). The existing literature, therefore, tends to associate inadequate intake of these micronutrients or their deficiency with the risk of developing T2DM (Dubey et al., 2020; Brandão-Lima et al., 2018). However, there is a dearth of studies that seek to evaluate the relationship between the supplementation of these micronutrients and diabetes management outcomes such as glycemic control among patients with established disease. Additionally, there are no reviews of studies that seek to assess the relationship between the concomitant intake of these micronutrients and outcomes such as glycemic control, the biosynthesis of glucose, as well as the sensitivity of insulin among adults with T2DM. Also, the existing studies tend to focus on evaluating the role of micronutrient intake for patients with established deficiencies while seemingly ignoring those without any deficiencies.

Drug-nutrient interactions, such as metformin-vitamin B-12 interactions, have also not been explored extensively in the extant literature. Most notably, the success of metformin tends to overshadow the necessity of investigating how the drug may result in micronutrient deficiencies that may result in complications for diabetes patients. Also, studies that have sought to explore these drug-nutrient interactions tend to focus essentially on the metformin-vitamin B-12 interaction without considering the whole context of micronutrient supplementation, which includes other important micronutrients, as a way of coming up with holistic diabetes management regimens that balance between drug prescription and micronutrient supplementation.

1.3 Research Objectives and Questions

1.3.1 Research Objectives

The objectives of this systematic literature review are to:

i. Explore the role of the intake of micronutrients (zinc, vitamin B-12, potassium, and magnesium) as potential interventions for diabetes management of adults in the US.

ii. Examine the relationship between micronutrient intakes and glycemic control, insulin biosynthesis, secretion, and signaling pathways.

iii. To specifically investigate how metformin's decreasing the absorption of the crucial micronutrient, vitamin B-12 impacts T2DM patient's diabetes management and examine whether combining different micronutrients intakes (including zinc, potassium, and magnesium) with vitamin B-12 can better combat deficiencies in diabetes management for patients using metformin.

1.3.2 Primary Research Questions

RQ1: What is the role of micronutrients in the management of diabetes among US adults receiving dietary treatment (18+ years, excluding pregnant and lactating women)?

RQ2: What is the relationship between micronutrient intakes and glycemic control, insulin biosynthesis, secretion, and signaling pathways for adults with T2DM?

RQ 3: What is the influence of metformin-vitamin B-12 interactions on the impact of vitamin B-12 supplementation in the management of T2DM?

1.4 Thesis Organization

This thesis is structured into five chapters. The first chapter offers a background on the prevalence of diabetes among US adults and discusses the research problem, the objectives of the study, and the primary research questions. The second chapter is the methodology chapter. It describes and justifies the systematic review search strategy, and the study selection criteria, including the inclusion and exclusion criteria and the quality assessment. It also explores the data extraction and analysis process. The results chapter presents the findings of the SLR process and the analysis of the extracted data while the discussion chapter offers an analysis of the findings based on insights from existing literature. The conclusion chapter summarizes the findings of the study and offers conclusions based on these findings.

Chapter 2: Methodology

2.1 Search Strategy

A systematic literature review (SLR) is a methodology focusing on identifying all research addressing a given question to give a balanced and unbiased summary of the literature (Nightingale, 2009). This systematic review is based on the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as presented by Page et al. (2021). According to Page et al. (2021), the PRISMA standard is a guideline aimed at assisting reviewers to report transparently the justification for the review, the process followed in carrying out the review, and the findings of the review. The current review aims at synthesizing the state of knowledge on the role of four micronutrients (zinc, potassium, magnesium and the vitamin B-12- metformin interaction), which are part of the diabetes management intervention for individuals aged 18 years and above (excluding pregnant women) in the US. The use of the PRISMA approach as the review protocol is necessary in ensuring a transparent approach to reviewing the extant literature on the subject, which is a necessity in evidence-based practice in diabetes care. According to Page et al. (2021), PRISMA 2020 was created for the review of studies that evaluate the effects of certain health interventions without necessarily being limited by these studies' designs. It features four sections, with 27 items, with some of them having subsections. Figure 1 below illustrates the PRISMA 2020 as employed in the current study. The diagram depicts the four stages of the review process and also details the activities involved in each stage.

2.2 Study Selection

This review employs a clear search protocol to obtain relevant papers from various databases including PubMed/Medline, EMBASE, and Web of Science. As noted by Jalali and Wohlin (2012), choosing established databases in conducting a systematic review is informed by concerns of comprehensiveness, rigor, as well as reliability. To search and identify relevant papers from these databases, the current review employs search strings that combine keywords obtained from the primary research questions by employing Boolean operators (AND/and OR). The search strategy is based on the Patient, Intervention, Comparison, Outcome, Study Design (PICOS) approach as described by Eriksen and Fransen (2018). For the three research questions, the search strings employed in searching for the reviews were as follows:

RQ1: (“micronutrient intake” OR “vitamin and mineral” OR “dietary intake”) AND (“diabetes management” OR “blood sugar control”) AND (“US adults” OR “adults with diabetes” OR “non-pregnant adults”)

RQ2: (“micronutrients” OR “vitamins and minerals”) AND (“Type 2 diabetes” OR “adults with T2DM”) AND (“glycemic control” OR “insulin biosynthesis” OR “insulin secretion pathways” OR “insulin signaling”)

RQ3: ("metformin" AND "Vitamin B-12 OR Cobalamin OR micronutrient") AND "metformin-Vitamin B-12 interaction" AND "supplementation") AND ("T2DM" OR Type 2 Diabetes)

This search strategy is not limited to the identification of any specific micronutrients. This allows for a comprehensive view of the role of various micronutrients as explored in the extant literature and also allows for the exploration of drug-nutrient interactions in diabetes management. As such, narrowing down the identified articles to select only those that mention the specific nutrients of interest will be done during the screening stage. The broad search strategy is also necessary for ensuring that a broad range of studies that identify and investigate the role of different micronutrients is arrived at in this review without necessarily focusing on the nutrients of interest.

2.2.1 Inclusion and Exclusion Criteria

The selection of sources adhered to previously defined inclusion and exclusion criteria aimed at enhancing the identification of only the most relevant and recent studies. According to Nightingale (2009), the inclusion/ exclusion criteria also offer a structured and objective way of selecting the most valuable sources that offer the best responses to the research questions by minimizing bias, maintaining consistency, and guaranteeing transparency and the replicability of the literature search process. Inclusion criteria for primary studies to be included in the review included: 1) Randomized Controlled Trials (RCTs), cross-sectional, and cohort studies that featured adult populations (>18 years old excluding pregnant and lactating women) with T2DM; 2) Studies investigating the impact of micronutrient intake or vitamin B-12 supplementation on diabetes management outcomes such as enhanced glycemic control, insulin secretion, biosynthesis and signaling; 3) studies exploring the metformin-vitamin B-12 interaction and those on vitamin B-12 supplementation for patients with T2DM treated with metformin. 4) studies involving patients with comorbidities that may not be related to T2DM, but patients can be at risk of or suffering from along with T2DM. The exclusion criteria included: 1) literature reviews and case reports; 2) studies that do not involve micronutrient intake or vitamin B-12 supplementation; 3) This research will prioritize studies published after the year 2000 to ensure the inclusion of the most current scientific findings, as the research prior to 2000 has been well summarized in Joe M. Chehade's The Role of Micronutrients in Managing Diabetes(2009).; and 4) studies in other languages apart from English.

2.2.2 Screening and Quality Assessment

The screening and assessment of quality to determine the papers to be included in the final review was based on the Cochrane approach for evaluating the quality of evidence. The initial step in the screening involved screening the titles and abstracts of the papers identified in the literature search and determining whether the articles were relevant to the research question (Henderson et al., 2010). Unrelated articles and those that did not meet the inclusion criteria were eliminated at this point. The next screening step involved the full-text screening of the articles, where the papers were downloaded and assessed for eligibility based on the inclusion/exclusion criteria. The full-text screening involved an in-depth assessment of the method, results, and overall content.

The assessment of quality was aimed at evaluating the reliability and validity of the included studies. Based on the Cochrane approach, the assessment of quality involved assessing the risk of bias in the selected articles (Henderson et al., 2010). The process entailed evaluating the randomization process, binding, and other factors that may present bias in the study affecting the reliability and validity of the results. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was employed in assessing the overall quality of evidence based on aspects of the study design, inconsistency, indirectness, as well as publication bias (Gopalakrishnan et al., 2014).

2.3 Data Extraction

The relevant data extracted in this study was based on first author and year of publication, studied micronutrients, study design, demographic information (age, sex), and sample size. The studied diabetes-related outcomes were also recorded, including how they relate to micronutrients being studied. The extracted data are presented and analyzed in the results and discussion chapters respectively.

2.4 Data Analysis

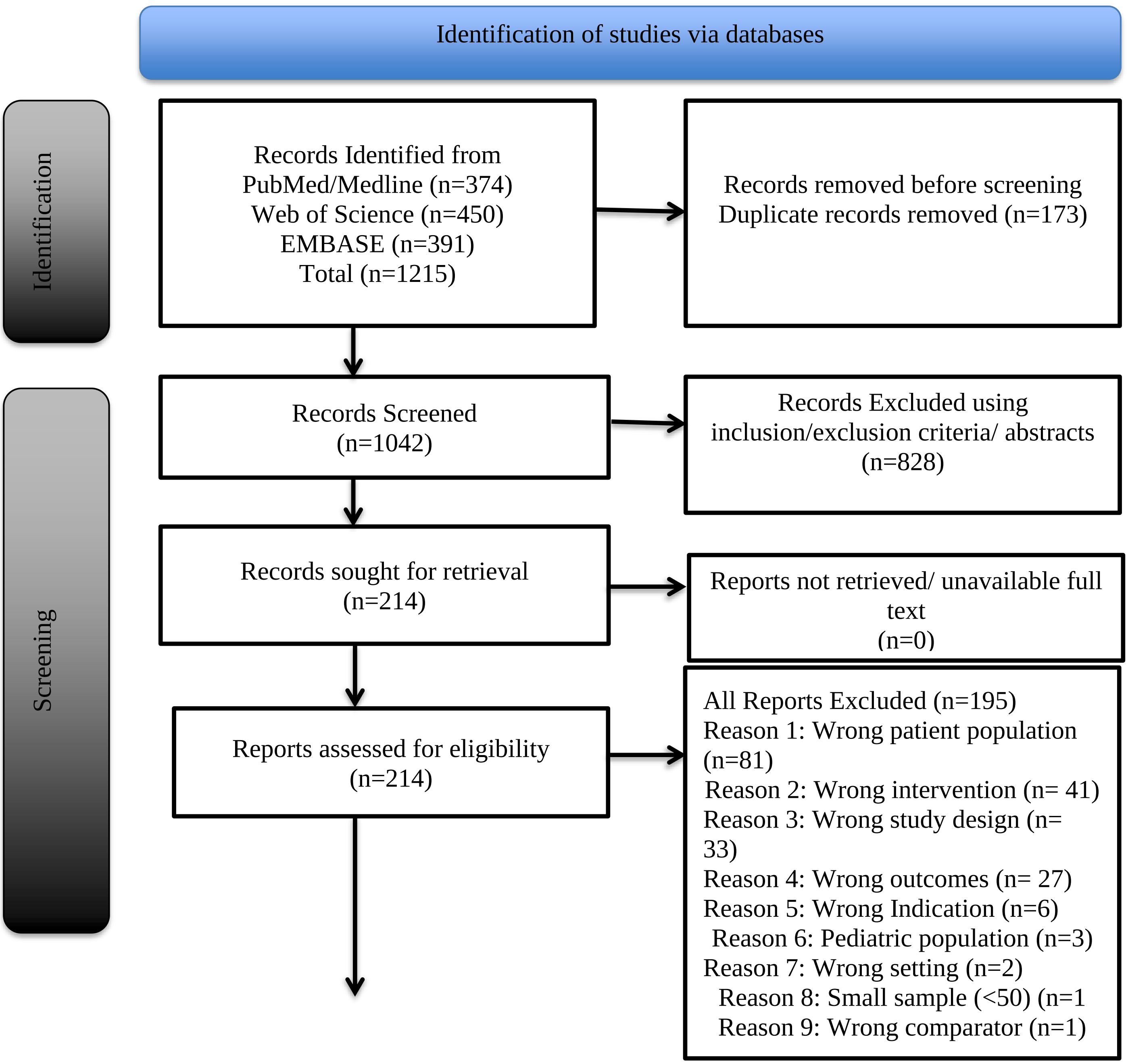
The extracted data were analyzed using the thematic analysis approach. According to Braun and Clarke (2014), thematic analysis is a qualitative data analysis approach involving searching across datasets to identify, analyze, and report patterns of data that offer viable answers to the research questions. The thematic analysis process followed the six steps described by Braun and Clarke (2014). These include familiarizing with the data set, coding, generating themes, reviewing themes, defining and naming the identified themes, and finally, writing the report. According to Braun and Clark (2014), it is necessary to adhere to these steps to eliminate confirmation bias, which may have debilitating consequences on the reliability and validity of the study findings.

Chapter 3: Results

3.1 Search Results and Selection of Studies

The search conducted on Pubmed/Medline, EMBASE, and Web of Science yielded a total of 1215 articles. Of the 1215 articles, 173 articles were excluded since they were duplicated in the different databases. 1042 articles were screened based on the inclusion/exclusion criteria. 644 articles were excluded after scrutinizing their titles and abstracts, A total of 159 articles were excluded because they were literature reviews and case reports; 472 studies that do not involve micronutrient intake or vitamin B-12 supplementation; 13 articles were excluded for wrong patient population including type 1 diabetes and pregnant adults. The full texts of 0 articles were unavailable, and 184 articles were eliminated for not meeting the requirement on publication timelines. In total, 828 articles were eliminated in the screening phase. The full texts of the remaining 214 articles were subjected to a quality review process. 196 articles were excluded for various reasons including not focusing on adults with type 2 diabetes, involving pre-diabetes cases, and not assessing the impact of the studied micronutrients on the management of Type 2 diabetes. In total, 19 studies were included in this review. The study selection process has been illustrated in the PRISMA flow diagram in the methodology chapter (Figure 1).

PRISMA Flow Diagram



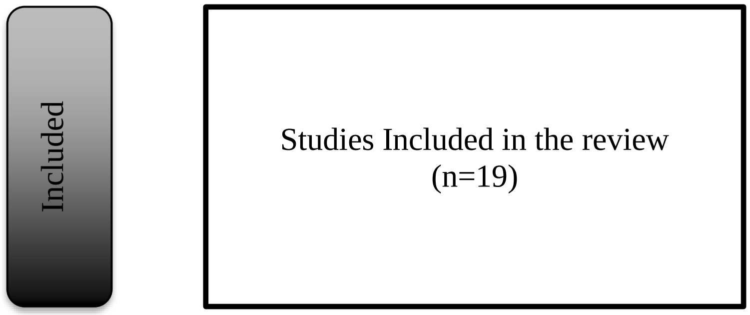


Table 1: Excluded Reasons Table

Reasons	Tags	Number
1. Wrong Patient Population	Pregnant adults/Type 1 DM/Non-diabetics	81
	Pediatric Population	3
2. Inadequate sample size	sample size < 30	1
3. Inappropriate outcome measures	Wrong outcomes	27
4. Inappropriate comparators	Wrong comparator	1
5. Inappropriate indication	Wrong indication	6
6. Inappropriate Study Design	Wrong study design- Review	33
7. Irrelevant intervention	Wrong Intervention	41
8. Wrong Study Setting	Wrong Setting	2
		Total 195

3.2 Characteristics of the Studies

Table 1: Primary studies description table

Author	Study Design	Population	Micronutrient
Kim et al. (2019)	Cross-sectional study	1111 adult (18+) patients with T2DM	Vitamin B12
Park et al., 2016	Cohort	3960 adults with T2DM	Zinc
Alharbi et al. (2018)	Retrospective clinical study	412 adults with T2DM	Vitamin B12
Kancherla et al. (2017)	Retrospective cohort study	13,258 Veterans (50+) with T2DM	Vitamin B12
Farooq et al. (2022)	Cross-sectional study	1600 adult (45+) outpatients with T2DM	Vitamin B12
Aslam et al., 2023	RCT	144 adults with T2DM	Zinc
Lee et al. (2016)	Randomized, placebo-controlled, double-blind, intervention study	36 adult patients with T2DM	Chromium and zinc
Wagh et al., 2020	RCT	412 Adults with T2DM	Potassium
Sundaram et al. (2017)	RCT	120 Adults with T2DM	Zinc, magnesium, copper
Santos et al., 2023a	Cross-sectional	147 Adults with T2DM	Magnesium
Kocyigit et al., 2023	Case-control study	80 Adults with T2DM	Magnesium
Xu et al., 2023	Cohort	3794 Adults with T2DM	Magnesium, zinc
Bahrampour et al., 2023	Case-control study	105 Adults with T2DM	Magnesium, zinc, potassium
Brandao-Lima et al., 2018	Cross-sectional study	95 Adults with T2DM	Magnesium, zinc, potassium
Mikalsen et al.(2019)	studied a group of obese patients with and without diabetes mellitus	92 obese patients (BMI ⩾ 35)	Magnesium
Fan Zhang et al. (2022)	Cross-sectional	2686 participants aged ⩾45 years without diabetes	Mixed dietary B vitamins (B-1, B-2, niacin, B-6, B-12, and dietary folate equivalent)
Genquan Jin, Jingjing Wang, Xiubo Jiang (2021)	Cross-sectional	22,041 U.S. adults aged 20 years and older	Folate, vitamin B-12, and vitamin B-6

Kheriji et al.(2022)	Cross-sectional study	420 participants diabetic (n=106), prediabetic (n=192), and control (n=73)	Mixed dietary vitamins (A, B-12, D)
Perez et al. (2018)	RCT	80 patients with well controlled type-2 diabetes	Zinc

3.3 Summary of the Findings

RQ1: What is the role of micronutrient supplementation in the management of diabetes among US adults receiving dietary treatment (18+ years, excluding pregnant and lactating women)?

Out of the19 reviewed articles, 7 articles (Brandao-Lima et al., 2018; Aslam et al., 2023; Lee et al., 2016; Sundaram et al., 2017; Bahrampour et al., 2023; Wagh et al., 2020; Mikalsen et al., 2018) focused on the role of micronutrients in the management of T2DM.

Table 2: Primary study characteristics (RQ1)

Publication	**Exposure Assessment**	**Outcome Definition**	**Analysis: Measure of Association**	**Results**
Brandao-Lima et al. (2018)	BMI based on WHO cut-off values analyzed at baseline (BMI < 18.5 kg/m^2)- Malnourished (BMI 18.5–24.9 kg/m) normal weight overweight/obese (BMI ≥ 25 kg/m^2 24-hour dietary recalls	The effects of individual and combination intake of micronutrients on glycated hemoglobin percentage (%HbA1c)	multiple linear regression and binary logistic regression analysis	Lower micronutrient intake group (cluster 1) had higher %HbA1c ($p = 0.006$) and triglyceride ($p = 0.010$) levels. High %HbA1c showed an association with cluster 1 (odds ratio (OR) = 3.041, 95% confidence interval (CI) = 1.131; 8.175) and time of T2DM

				diagnosis (OR = 1.155, 95% CI = 1.043; 1.278). Potassium (β = −0.001, p = 0.017) and magnesium (β = −0.007, p = 0.015) intakes were inversely associated with %HbA1c
Aslam et al., 2023	Demographic data, Anthropometric mea-surements, 24-h dietary recall, serum blood glucose analysis, HbA1C, and serum zinc levels recorded at day 0 and at day 60.	Zinc supplementation, age, and blood glucose levels	ANOVA the Tukey test was applied for pair-wise comparison	Final fasting serum glucose levels were significantly lowered in group 1 with ($p < 0.05$) as compared to group 2. Results were significant ($p < 0.05$) in the older age group (51–70 years) as compared to their younger age counterparts (30–50 years) of group2.
Lee et al. (2016)	A cascade-fermented dietary supplement enriched with chromium (100 mg/d) and zinc (15 mg/d), over a period of 12 weeks.	Metabolic control based on levels of glycated hemoglobin (HbA 1c)	Two sample t-test or Mann Whitney U test	No relevant change in the average values during both treatment periods for the test product (0.09%90.4) and placebo (0.01%90.6), respectively. No relevant

				difference was found between verum and placebo treatment (p -0.48)
Sundaram et al. (2017)	Nonsurgical periodontal therapy for 3 months (Blood samples a=obtained at day 0 and day 90)	serum zinc (Zn), magnesium (Mg), and copper (Cu) concentration and glycemic status in type 2 diabetes with chronic periodontitis (CP)	Paired *t*-test and between the groups was analyzed using one-way analysis of variance.	Intragroup for Zn- statistical significance seen after treatment between Groups 1 and 2 and between Groups 1 and 3 (P = 0.04) Individually for Cu, there was statistical significance in the baseline between Groups 1 and 2 and between Groups 1 and 3 (P = 0.041 and 0.042),
Bahrampour et al., 2023	Nephropathy defined as urinary mg of albumin per gram of creatinine (ACR) ≥30 mg/g, using a random spot urine sample. sensitivity 0.001 mg/L; coefficient of variation (CV) 4.5e7.6%]	The risk of diabetic neuropathy as a result of uncontrolled diabetes	Logistic regression was used find the odds ratio (ORs) of DN, and its 95% confi-dence interval (CI) based on the micronutrient patterns in crude and adjusted model	Inverse relationship identified between risk of DN and following mineral patterns and fat-soluble vitamin patterns in adjusted model (ORs = 0.51 [95% CI 0.28–0.95], p = .03) and (ORs = 0.53 [95% CI 0.29–0.98], p = .04), respectively.

Wagh et al., 2020	Vitamin-C and placebo were administered to patients for three weeks at a time	Serum level of post meal and fasting blood sugar levels and HbA1c	Relationship between variables was measured by Pearson's or Spearman's correlation coefficient.	Post meal blood sugar -7.89 ± 2.63 -20.67 ± 2.98 $P < 0.01$ Fasting blood sugar -7.54± 4.87 -21.38 ± 3.44 $P < 0.01$ Plasma Vitamin-C*(μmol/L) 0.18 ± 0.08 5.39 ± 2.25 $P < 0.01$ HbA1c -0.06 ± 0.02 -0.59 ± 0.07 $P < 0.01$
Mikalsen et al. (2018)	Weight loss/ bariatric surgery intervention for diabetic/non-diabetic patients	Serum Mg. HbAIc, PTH, and vitamin D concentrations for diabetic/non-diabetic patients	Chi-square test was used for categorical data. Spearman correlations were used to explore relation-ships between data.	Median serum Mg increased by 5% among diabetic patients and 6% among non-diabetics (continued to increase by 12% after bariatric surgery) HbA1c was reduced from inclusion to 12 months after surgery in both diabetic (− 23%, $p < 0.001$) and non-diabetic patients (− 7%, $p < 0.001$). In the diabetic patients, serum Mg was inversely correlated to HbA1c at inclusion (Spearman's rho

				− 0.31, p = 0.19), and after 8 weeks (rho − 0.52, p = 0.05), but not after bariatric surgery (p > 0.4).

For both normal weight and overweight patients, Brandao-Lima et al. (2018) found that micronutrient intake enhanced the management of important diabetes outcomes including Hemoglobin A1c (HbA1c) and triglyceride levels. Aslam et al. (2023) also found that zinc supplementation resulted in significant reduction in blood glucose levels, which depicts the significant role played by the micronutrient in the regulation of blood glucose levels among T2DM patients.

Sundaram et al. (2017) established a significant relationship between serum zinc, magnesium, and copper concentrations with the glycemic status of patients with T2DM (P=0.04) who had recently undergone periodontal therapy. In managing the progression of diabetic neuropathy among patients with uncontrolled T2DM, Bahrampour et al. (2023) found an inverse relationship between magnesium intake and the progression of diabetic neuropathy. Wagh et al. (2020) found that supplementing vitamin C as part of the dietary therapy for T2DM led to effective management of the condition as depicted in reduced HbA1c, post-meal blood sugar and fasting blood sugar. Mikalsen et al. (2018) found that weight loss therapies, including bariatric surgery results in elevated serum magnesium and eventual reduced levels of blood glucose levels reflecting the significance of the micronutrient in the management of T2DM as well as the prevention of the condition for overweight individuals without the condition. However, Lee et al. (2016) did not find any significant relationship between a placebo and a dietary supplement enriched with zinc and chromium in reducing blood sugar levels and HbA1c.

RQ2: What is the relationship between micronutrient intakes and glycemic control, insulin biosynthesis, secretion, and signaling pathways for adults with T2DM?

Eight studies (Santos et al., 2023; Kherji et al., 2022; Kocyigit et al., 2023; Jin et al., 2021; Xu et al., 2023; Perez et al., 2018; Paiva et al., 2015; Zhang et al., 2022) sought to explore the relationship between micronutrient intakes and glycemic control, insulin biosynthesis, secretion, and signaling pathways for adults with T2DM.

Table 3: Primary study characteristics (RQ2)

Publication	**Exposure Assessment**	**Outcome Definition**	**Analysis: Measure of Association**	**Results**
Santos et al., 2023	Magnesium status and eating patterns were identified using a 24-h recall method	Glycemic control based on serum sugar levels and HbA1c	Logistic regression models were used	T2DM individuals' who presented magnesium deficiency had a higher chance of elevated %HbA1c levels (8.312-fold) and those in the lowest quartile (Q) of the UDP (Q1: $P = 0.007$; Q2: $P = 0.043$) had a lower chance of elevated %HbA1c levels.
Kheriji et al. (2022)	Macro-and micro-nutrient intake	Glucose homeostasis and type 2 diabetes development	Variance analysis using ANOVA was conducted to compare changes in the composition of diet between the three studied groups. Tukey;s post-hoc tests	Micronutrients intake was as positively associated with glucose homeostasis and stable HbA1c levels.

			were also conducted	
Kocyigit et al., 2023	Anthropogenic measurements, BMI for each individual, and biochemical parameters	Metabolic control parameters related to dietary and serum magnesium and calcium	Logistic regression models	-Statistically significant inverse association between HbA1c and serum magnesium ($p < 0.05$). Dietary magnesium intake was inversely associated with HOMA-IR scores ($p < 0.05$) but had a positive association with serum magnesium levels in patients with T2DM ($p < 0.05$).
Jin et al. (2021)	Measurement of Fasting Plasma glucose, HbA1c, and two hours plasma glucose	Association between folate, vitamin B-12, and vitamin B-6 with diabetes outcomes (HbA1c), fasting plasma glucose levels	Logistic regression models and restricted cubic spline models were used to evaluate the associations between dietary folate, vitamin B-12, vitamin B-6 and diabetes.	A linear inverse relationship was found between vitamin B12 and diabetes, and a non-linear inverse relationship was found between dietary folate, dietary vitamin B6 and diabetes 95%CIs (confidence intervals) of diabetes for the highest quartile intakes of folate and vitamin B-6 were 0.65 (0.47–0.90) and 0.61

				(0.42–0.89), the OR with 95% CI of diabetes for the third quartile of dietary vitamin B-12 was 0.76 (0.60–0.97).
Xu et al., 2023	Intake of dietary Cu, Mg, Zn, and Ca 95% (2007-2018)	Risk of diabetic retinopathy (DR) associated to Cu, Mg, Zn, and Ca deficiency	Multivariable logistic regression models and restricted cubic spline models	Higher quartile intake of Ca, Mg, Zn, and Cu was associated with a lower occurrence of DR, the multivariate adjusted ORs (95% CI) were 0.57 (0.38–0.86), 0.48 (0.32–0.73), 0.58 (0.39–0.88), and 0.48 (0.30–0.77), respectively.
Perez et al. (2018)	Insulin sensitivity and beta cell function assessed by a modified Frequently Sampled Intravenous Glucose Tolerance Test (12 hr fast)	Glucose homeostasis as determined by HbA1c and serum zinc concentration	Spearman's correlation coefficient was used; no correction for multiple tests was performed	Positive correlations were observed between EZP and fasting insulin concentration ($\rho = 0.393$, $p = 0.021$) and HOMA-IR ($\rho = 0.386$, $p = 0.024$) in women, and between plasma zinc concentration and HbA1c ($\rho = 0.342$, $p = 0.020$) in men.
Paiva et al. (2015)	Diabetic patients received 600 µg/day CrPic	Fasting glucose concentration as	The Shapiro–Wilk test was performed to	CrPic supplementation reduced the

	supplementation 4 months.	measured by serum HbA1c	evaluate the normality of the distributions Wilcoxon Mann–Whitney rank sum test for differences between control and supplemented group	fasting glucose concentration (−31.0 mg/dL Supplemented group; −14.0 mg/dL control group; $p < 0.05$.
Park et al., 2016	Assessment of insulin resistance (HOMA-IR) (mmol/L) × insulin (mU/L)/22.5.	Toenail zinc levels and diabetes incidence	Toenail zinc- Inductively- Coupled-Plasma Mass Spectroscopy method - Spearman correlation coefficient < 6years= 0.58	Adjusted for confounders hazard ratio of incident diabetes comparing the highest to the lowest quartile of toenail zinc levels was 1.21 (95% CI: 0.90–1.63; $P_{\text{trend}} = 0.20$)
Zhang et al. (2022)	Univariate B vitamins exposure	Relationship between dietary B vitamins intake and insulin resistance	Multivariable logistic regression and Bayesian kernel machine regression	ORs (95% CIs) of insulin resistance 3.06 (1.00-9.37) and 0.42 (0.19-0.93) for the highest quartile of vitamin B-1 and B-12 intake in the middle-aged group when the lowest quartile was the reference

Santos et al. (2023) found that magnesium intake resulted in enhanced glycemic control as depicted in reduced serum sugar levels and HbA1c. Based on this study, individuals with magnesium deficiency tended to have elevated levels of HbA1c by up to 8.312 times compared to those who had normal serum magnesium levels (*P*=0.007). Kocyigit et al. (2023) also found that magnesium levels also had a statistically significant inverse relationship with HbA1c as it enhances important metabolic control parameters. Dietary magnesium intake was also established to have an inverse relationship of HOMA-IR score ($p < 0.05$) and a positive relationship with serum magnesium levels.

Xu et al. (2023) also established that intake of dietary magnesium, zinc, copper, and calcium results in enhanced insulin secretion and biosynthesis, signaling, and glycemic control resulting in reducing occurrence of diabetic retinopathy among patients with T2DM. Jin et al. (2021) found that there is a linear inverse relationship between vitamin B12 and diabetes outcomes such as insulin biosynthesis and glycemic control and also a non-linear inverse relationship between dietary folate, dietary vitamin B6 and diabetes outcomes.

Similar relationships between micronutrient intake/supplementation and important diabetes metrics were recorded by Perez et al. (2018), Kheriji et al. (2022) and Paiva et al. (2015). According to Kheriji et al. (2022) and Perez et al. (2018), micronutrient intake results in enhanced glucose homeostasis, insulin sensitivity and also regulates HbA1c levels, slowing the progression of T2DM symptoms. Paiva et al. (2015) also established that supplementation of chromium picolinate (CrPic) has a significant inverse relationship with fasting blood glucose concentrations and serum HbA1c.

In their study that compared B vitamins intake and insulin resistance in a sample of 1628 individuals with diabetes and 1058 without diabetes, Zhang et al. (2022) established that B-12 intake was negatively related to insulin resistance in the control and the experiment group. They established that mixed dietary B vitamins reduces insulin resistance for both people with T2DM and those without the condition.

RQ 3: What is the influence of metformin-vitamin B-12 interactions on the impact of vitamin B-12 supplementation in the management of T2DM?

Four articles (Kim et al., 2019; Alharbi et al., 2018; Kancherla et al., 2017; Farooq et al., 2022) explore the relationship between metformin use and vitamin B-12 levels and how this impacts the need for vitamin B-12 supplementation in the management of T2DM.

Table 4: Primary study characteristics table (RQ3)

Publication	**Exposure Assessment**	**Outcome Definition**	**Analysis: Measure of Association**	**Results**
Kim et al. (2019)	serum B12 <300 pg/mL using an Unicel DxI 800 analyzer	Serum vitamin B12 levels as quantified using competitive-binding immunoenzymatic assay	Pearson correlation and linear regression analysis to find the linear relationship between the variables. Multivariate logistic regression analysis used to examine the factors related to vitamin B12 deficiency and calculate odds ratios (OR)	<u>Adjusted for confounders</u> a 1 mg increase in daily metformin dose was associated with a 0.142 pg/mL decrease in vitamin B12 (P < .001) <u>Compared with daily dose</u> Adjusted odds ratios for 1000 to 1500, 1500 to 2000, and ≥2000 mg metformin were 1.72 (P = .080), 3.34 (P < .001), and 8.67 (P < .001), respectively.
Alharbi et al. (2018)	Blood specimen Vitamin B12 deficiency was categorized into three groups: mild (118.1–	Prevalence of Vitamin B12 deficiency and	An independent t-test for continuous	B12 deficiency in metformin users was 4.72

	132.8 pmol/L), moderate (88.6–118.1 pmol/L), and severe (< 88.56 pmol/L) deficiency	peripheral neuropathy	data, and the Chi-squared or Fisher's exact test was used for categorical data.	(95% CI, 1.11–20.15, *P* = 0.036) Metformin group - non-metformin group (mild status, 22.3% vs. 15.1%; moderate status, 7.8% vs. 4.3%, respectively
Kancherla et al. (2017)	Serum creatinine test from the test closest to the vitamin B12 test date. Defined as values >2,000 pg/dL) and creatinine (defined as values >25 mg/dL)	The effect of long-term metformin use on serum vitamin B12 levels	multivariable logistic regression, stratified by age, to evaluate the association between metformin use and serum B12 testing	Patients in the exposed groups were also more likely to have borderline deficient B12 concentrations (170-300 pg/dL) compared to their counterparts (29.1% vs. 19.1%, respectively
Farooq et al. (2022)	Vit B 12 assay using the Roche E-170 Vit B12 electrochemiluminescence immunoassay (ECLIA) method	Cumulative metformin intake (grams)and impact on vitamin B12 levels (pmol/l)	Association between cumulative metformin dose and vitamin B12 levels was analyzed using Pearson's correlation coefficient and regression analysis	Pearson's correlation coefficient for cumulative dose of metformin and observed vitamin B12 levels was −0.66, which is statistically significant (p value < 0.001).

Kim et al. (2019) established a significant relationship (*p*<0.001) between a 1 mg increase in daily metformin use with a decrease (0.142 pg/mL) in serum vitamin B-12. Compared to the daily metformin use, they established that the adjusted ratios for 1000 to 1500, 1500 to 2000, and ≥2000 mg metformin were 1.72 (P = .080), 3.34 (P < .001), and 8.67 (P < .001), respectively. Alharbi et al. (2018) also established that metformin users had vitamin B-12 deficiencies of 4.72 (95% CI, 1.11-20.15, p= 0.036) compared to non-metformin users (mild status, 22.3% vs. 15.1%; moderate status, 7.8% vs. 4.3%, respectively).

Kancherla et al. (2017) also established a significant relationship between long-term use of metformin and vitamin B-12 deficiency among individuals with T2DM. They established that patients using metformin were more likely to have borderline vitamin B-12 deficiency (170-300 pg/dL) compared to those not on metformin (29.1% vs. 19.1%, respectively. Farooq et al. (2022) also established a relationship between cumulative metformin intake and declining vitamin B-12 serum levels indicating that individuals on long-term metformin use are more likely to develop vitamin B-12 deficiency compared to non-metformin users. The study established that Pearson’s correlation coefficient for cumulative dose of metformin and observed vitamin B-12 was -0.66 (P<0.001) (Farooq et al., 2022). The established relationship between metformin uses and the decline in vitamin B-12 levels underscores the significance of vitamin B-12 supplementation in the management of the adverse symptoms of T2DM.

Chapter 4: Discussion

This chapter provides an in-depth analysis of the review findings based on how they answer the primary research questions and relevant insights from the extant literature. The chapter is organized into two main parts with the first section discussing the findings based on RQ1 and RQ2 and the second part answering RQ3. Therefore, the first discusses the identified micronutrients, their role in the management of T2DM and their relationship to important metrics such as insulin secretion and functioning, glucose homeostasis, insulin signaling, glycemic control among others. The second part discusses studies that focus on the relationship between metformin use and vitamin B-12 deficiencies and the need for vitamin B-12 in the management of T2DM.

4.1 Role of Micronutrients Intake and Supplementation in Diabetes Management

The review of the selected primary studies identified some notable micronutrients whose role in the management of T2DM cannot be overstated. These include zinc, potassium, and magnesium. The different micronutrients have been established to play a crucial role in enhancing glucose homeostasis, insulin sensitivity, beta-cell function, insulin secretion, and signaling among others. Others play a crucial role in delaying the progress of the adverse impacts of high serum glucose levels, including kidney and cardiac problems among others. This sub-section analyses the selected primary studies with a focus on the identified micronutrients to explore the evidence of the role they play in the management of T2DM and how the intake/supplementation of these micronutrients relates to important diabetes outcomes.

4.1.1 Zinc

Some of the included primary studies explored the importance of zinc as one of the micronutrients whose supplementation has a crucial role in the management of T2DM (Lee et al., 2016; Perez et al., 2018; Sundaram et al., 2017). The analysis of these studies, however, yields inconclusive results, with some establishing zinc as crucial in the management of T2DM by impacting glucose homeostasis and other important outcomes while others found no significant impact on important outcomes. For instance, Lee et al. (2016) conducted a randomized, placebo-controlled study to assess the impact of zinc and chromium supplementation on relevant outcomes for T2DM patients such as glycated hemoglobin levels (HbA1c), fasting blood glucose, fructosamine, and others such as lipid parameters. The participants in the study (n=36), who had T2DM, were placed in either an experiment group or a control group where they were given a cascade-fermented diet supplement containing chromium (100 mg/d) and zinc (15 mg/d) or a placebo with a similar test but lacking the micronutrients (Lee et al., 2016). After 12 weeks of the intervention, the different outcomes were measured (Lee et al., 2016). No significant changes were made in this study and there were no relevant differences in the two treatments for all outcomes (Lee et al., 2016). Therefore, this study does not establish any evidence of the impact of chromium and zinc supplementation on glucose metabolism for patients with T2DM.

Positively, these results could mean that a T2DM patient's zinc levels may not be as severely impacted as other micronutrients and may be dependent on other factors of the patient. However, despite utilizing a randomized, placebo-controlled design and assessing relevant clinical outcomes over a 12-week period, the study did not find significant differences between the experimental and control groups. The findings suggest that, at the doses and formulation tested, zinc and chromium supplementation did not lead to improvements in glycemic control or other important outcomes for T2DM patients. However, the study's limitations, including a small sample size and short duration of intervention, suggest the need for further research with larger sample sizes, longer intervention periods, and potentially different dosages or formulations to better understand the role of these micronutrients in T2DM management. The study had a relatively small sample size (n=36), which may limit the generalizability of the findings. Larger sample sizes are often needed to detect statistically significant differences, particularly in clinical studies involving complex conditions like T2DM. Although the study followed participants for 12 weeks, this may not have been sufficient to observe meaningful changes in glycemic control or other outcomes. Longer intervention periods might be necessary to fully capture the effects of zinc and chromium supplementation on glucose metabolism. The study used a specific dosage and formulation of chromium (100 mg/d) and zinc (15 mg/d), which may not represent the doses used in other studies or recommended in clinical practice. Variations in dosage and formulation could influence the results and lack the statistical power needed to detect true effects or differences between the control and the experiment group.

In their study that measured the association between zinc supplementation on insulin sensitivity and beta cell functioning in patients with well-controlled T2DM, Perez et al. (2018) established that while there were no observable associations between a person's zinc status and markers of glycemic control, there were positive correlations between a person's exchangeable zinc pool (EZP) and fasting concentrations of insulin in women ($p = 0.393$, $p = 0.021$) and HOMA-IR ($\rho = 0.386$, $p = 0.024$) and between serum zinc levels and HbA1c in men. Therefore, like the study by Lee et al. (2016), Perez et al. (2018) did not find any significant associations between a person's zinc status and important glycemic control parameters, especially among people with well-controlled T2DM. However, they found some low-level associations that are also gender-determined (Perez et al., 2018). These studies highlight the need for further research in establishing how zinc supplementation may impact the management of T2DM patients, specifically those who are deficient. However, like Lee et al. (2016), Perez et al. (2018) also employed a small sample size (80 individuals with well-controlled T2DM), which also has serious implications on the reliability, validity, and generalizability of the findings.

T2DM patients with comorbidities or other chronic conditions such as periodontitis who underwent nonsurgical periodontal therapy were found to have increased levels of zinc in the study by Sundaram et al. (2017), which also reflected on their glycemic levels. The study, which assigned 120 participants into three groups of 40 people each (control group, people with controlled T2DM, and people with uncontrolled T2DM) and different parameters, including their micronutrient and glycemic status were taken at baseline and three months after undergoing nonsurgical periodontal therapy (Sundaram et al., 2017). The therapy was established to have a significant reduction in all the patients' clinical parameters. The patient's glycemic status showed a statistically significant reduction ($P < 0.001$) and the patient's zinc and magnesium levels also improved, which may hint at a correlation between the two. Therefore, while the association between serum zinc levels and glycemic control or other outcomes may not be obvious under free-living conditions (Lee et al., 2016), it may be more pronounced under certain conditions, such as when the patient undergoes periodontal therapy. For instance, Sundaram et al. (2017) established that low levels of serum zinc tend to contribute to insulin resistance in patients with periodontitis. The findings of this study also add to the complexity of determining the exact role played by zinc supplementation in the management of T2DM, further indicating the need for more in-depth research to determine the nature of the relationship between different levels of serum zinc and T2DM-related outcomes. The inclusion of a control group of individuals without T2DM and two groups of people with T2DM (controlled and uncontrolled) elevates the statistical power of this study compared to those of Lee et al. (2016) and Perez et al., (2018).

The justification for the inclusion of comorbidities is that the presence of chronic conditions and comorbidities, or the existence of more than one disease, among T2DM patients have the possibility of influencing the effects of micronutrient intake/supplementation, or lack thereof. Moreover, patients with T2DM without proper dietary intake or micronutrient supplementation run the risk of developing a new or recurring disease, such as cardiovascular disease. Therefore, studies examining the relationship between micronutrients in T2DM patients with comorbidities, such as periodontitis and hypertension, deserve inclusion (Nowakowska et al., 2019). All mental and physical diseases, related to T2DM or not, will affect the body and its response to micronutrient intake and supplementation in a variety and perhaps surprising ways, meaning further research is needed on implementing specific treatments to reduce the burden on the increasing number of T2DM patients with comorbidity (Pearson-Stuttard et al., 2022; Shuvo et al., 2023). The positive benefits of zinc levels with T2DM patients undergoing periodontal therapy attest to that.

Regarding the relationship between zinc intake/supplementation and diabetes outcomes, most reviewed studies established a significant relationship. The study by Brandao-Lima et al. (2018), for instance, found that dietary intake of zinc or supplementation for T2DM patients enhanced the functioning and maintenance of beta cells, the biosynthesis of insulin as well as the secretory granules’ maturation (Brandao-Lima et al., 2018). The study also established that zinc also plays a crucial role in inhibiting tyrosine phosphatases through the stimulation of the auto-phosphorylation of insulin receptors. They also established that zinc also plays a critical role in the redox mechanisms where it acts as one of the core components of the superoxide dismutase enzyme, which significantly helps in relieving the oxidative stress that is triggered by hyperglycemia. While the study by Brandao-Lima et al. (2018) does not single out zinc or consider its role independently, it establishes that dietary therapies that include zinc achieve significant results in enhancing the secretion and functioning of insulin and the relieving of oxidative stress.

In the study by Aslam et al. (2023), it was established that an increase in serum zinc through either dietary intake or supplementation played a critical role in delaying the progression of the risks associated with T2DM including cardiovascular disease. This finding is in accordance with those of other reviewed studies that consider the role played by zinc in diabetes management (Brandao-Lima et al., 2018; Sundaram et al., 2017). In the study by Aslam et al. (2023), patients with T2DM presented lower amounts of serum zinc (9.23 µmol/L Vs. 12.46 µmol/L, $p < 0.001$) as compared to individuals without T2DM. This suggests a lower antioxidant capacity for diabetes patients. The reviewed studies emphasized the importance of maintaining high levels of serum zinc as tied to the role it plays in an endogenous antioxidant system and also that zinc plays a crucial role in synthesizing, storing, and secreting insulin (Aslam et al., 2023).

Park et al. (2016) conducted a longitudinal study on toenail zinc concentration and dietary intake of zinc as a way of determining the role that zinc plays in the incidence of diabetes. In the 23 years of follow-up, this study did not establish any statistically significant relationships between toenail zinc or dietary zinc intake and the incidence of diabetes. However, the study also established that in people with T2DM, serum zinc levels were lower compared to those of people without the condition (Park et al., 2016). The authors determined that this observation can be explained by considering how urinary excretion of zinc increases and that the reabsorption of endogenous zinc is also significantly impaired among individuals with T2DM. Therefore, similar to other studies in this review that consider the role played by zinc in diabetes management, the study by Park et al. (2016) also establishes that zinc supplementation among people with T2DM is beneficial in terms of enhancing glycemic control. The same benefits are not realized by people without the condition as Park et al. (2016) do not observe any significant reduction in glucose concentration upon zinc supplementation among healthy individuals. Therefore, based on the findings of this review, while zinc supplementation offers glycemic control benefits for people with T2DM, zinc supplementation for healthy individuals does not have an impact on the incidence of T2DM. The study did not account for confounding factors that may impact the relationship between zinc intake and diabetes onset, which affects the validity and reliability of the findings. Overall, these mixed results from these studies further illustrate the complexity of the role of zinc interactions relating to a patient's sex or comorbidity risk, pushing the need for more research.

4.1.2 Magnesium

Magnesium was also identified in some of the selected primary studies as another important micronutrient that plays a crucial role in the management of T2DM. Certain diabetes risk factors, such as obesity (Mikalsen et al., 2019) or periodontitis (Sundaram et al., 2017) have been found to result in decreased levels of serum magnesium (Mg) levels, which further results in the decline in the patient's glycemic status. These studies, therefore, establish that a normal Mg status is required to control a patient's T2DM-related outcomes, including glycemic status, glucose homeostasis, and insulin secretion, and functioning among others.

Milkasen et al. (2019) studied serum magnesium changes in individuals with obesity, high blood pressure, and T2DM. According to the study, Mg has been identified as a marker for metabolic syndrome in these patient populations. Milkasen et al. (2019) enlisted a patient population (n=92) of people with obesity, both with and without diabetes. Following a weight loss intervention of either dieting or bariatric surgery, they established that the patients who had T2DM had severe Mg deficiency (10/92, <0.75 mmoL/L) and that the median Mg levels for the T2DM patients were lower for the diabetic patients than the non-diabetic participants (P=0.002). Following the weight loss of 10 kg and lifestyle interventions of 8 weeks (about 2 months), Mg levels increased for both the patients with diabetes and those without diabetes by about 5% (Milkasen et al., 2019). For the non-diabetic patients, Mg levels attained a stable level after some time. However, for the patients, the levels of Mg continued to increase significantly. At six months, the Mg levels for the two groups could not be differentiated. This study establishes that while the optimal levels of serum Mg may not be known, the micronutrient is significantly lower for individuals with diabetes compared to any other patient population. Supplementing Mg for T2DM patients is considered to lower the risk of developing cardiovascular and ischemic heart disease in patients with T2DM, which is even more common among individuals with uncontrolled diabetes.

Serum Mg levels were also shown to decrease significantly for T2DM patients suffering periodontitis in the study by Sundaram et al. (2017). Magnesium deficiency is often attributed to poor glycemic control in these patients. Sundaram et al.'s (2017) study establishes that Mg is a critical part of the cellular and subcellular membrane structure and plays a crucial role in enhancing the stability of the membrane. It is also important in carrying out activities of different enzymes that are involved in the oxidation of glucose as well as the secretion of insulin (Sundaram et al., 2017). As such, insulin plays an important role in the regulation of Mg metabolism and at the same time, Mg plays a part in carbohydrate, lipid, and protein metabolism. It is also responsible for activating more than 300 cellular enzymes and takes a leading role in the synthesis of proton and electron transporters in the cell's energy cycle. Patients with T2DM tend to have decreased levels of serum Mg compared to those without the condition. Alongside other micronutrient deficiencies, severely diminished levels of Mg tend to elevate susceptibility to infections, impair the functioning of neutrophils and macrophages, and result in the depletion of antioxidants (Sundaram et al., 2017). Low levels of serum Mg among people with T2DM tend to aggravate insulin resistance, further exposing these patients to the pathogenesis of atherosclerosis. Mg is, therefore, determined to possess an antioxidant property and play an active role in triggering insulin action and facilitating the absorption of glucose within cells. Interestingly, in comparison to the previous studies on zinc, these studies demonstrate that magnesium also lowers the risk of cardiovascular disease. Unlike zinc, however, magnesium decreases significantly for T2DM patients suffering from periodontitis, meaning more data is needed to examine the complexity of micronutrients, such as zinc and magnesium, on insulin sensitivity and secretion.

Santos et al. (2023) attribute magnesium deficiency or hypomagnesemia to poor glycemic control in people with T2DM. They established that magnesium deficiency elevated the percentage of HbA1c by 5.893-fold ($P = 0.041$) (Santos et al., 2023). Especially when coupled with unhealthy eating habits, magnesium deficiency is established as responsible for poor glycemic control, which may result in the progression of diabetes-related complications and increased risks such as chronic kidney disease and cardiac complications.

Brandao-Lima et al. (2018) also establish that magnesium plays a critical role in enhancing glycemic control among people with T2DM. Dietary magnesium intake or supplementation enhances the secretion and sensitivity of insulin and also improves a patient's lipid profile as well as their inflammatory status. Brandao-Lima et al. (2018) established that magnesium supplementation enhanced GLUT4 translocation, which consequently improved metabolic control. Similarly, the findings of Xu et al. (2023) establish an inverse relationship between the intake of magnesium and the risk of T2DM. The researchers determined that hypomagnesemia and low serum magnesium are prevalent among individuals with T2DM, and more so, those with poor glycemic control. Xu et al. (2023) establish that the reduction of magnesium in the plasma results in negative changes in glycemic control considering that the distribution of this micronutrient in the body affects both the secretion and action of insulin.

Studies that address the effect of magnesium supplementation on the management of diabetes also show that this micronutrient is mostly beneficial to T2DM patients who are deficient as compared to healthy individuals (Bahrampour et al., 2023). They show a positive correlation between magnesium supplementation and blood glucose control and the lowering of %HbA1c (Bahrampour et al., 2023). The study by Bahrampour et al. (2023) showed a decline in fasting glucose levels (0.56 mmol/L (95% confidence interval (CI) = −1.10; −0.01) upon magnesium supplementation. As such, based on the study, magnesium supplementation has a more significant impact on blood glucose control among other outcomes for individuals who are deficient.

However, studies that examine the impact of magnesium supplementation on the development of diabetes do not record the same findings (Kocyigit et al., 2023). This observation, according to Kocyigit et al. (2023) can be attributed to normal magnesemia, aspects related to the time of supplementation, and also the assessment of small samples. According to the findings of the study by Kocyigit et al. (2023), magnesium is a crucial part of the enzymes that facilitate glucose metabolism as it attaches to an ATP molecule, giving rise to the Mg-ATP complex that plays a significant role in phosphate transfer reactions. As such, the reviewed studies establish that magnesium plays a central role in enhancing the sensitivity of insulin receptors, improving the functioning of beta-cells, and tyrosine kinases, and also in stimulating proteins and substrates within the insulin signaling cascade (Kocyigit et al., 2023). These functions are mostly impaired among individuals with T2DM, which explains why supplementation is necessary as part of the management of the condition, which involves hypomagnesemia, as opposed to preventing the incidence of T2DM. By controlling for confounders, Kocygit et al. (2023) established the relationship between magnesium intake/supplementation and the enhancement of insulin functioning and glycemic control.

4.1.3 Potassium

The relationship between the dietary intake and supplementation of potassium and diabetes management variables is not extensively explored in the existing literature. Among the primary studies selected for inclusion in this study, only the study by Kherji et al. (2022) considers potassium supplementation, alongside other micronutrients, in seeking to assess its role in the prevention and management of T2DM. The study by Kherji et al. (2022) demonstrated that low dietary intake of potassium and the reduction of the micronutrient’s concentration in the blood resulted in reduced insulin sensitivity and triggered increased compensatory secretion of the hormone and consequently elevates the risk of T2DM. Therefore, this study's results indicate that low serum potassium levels are a significant predictor of the risk of diabetes while establishing a lack of clarity on the impact of dietary potassium on T2DM risk. However, Kherji et al. (2022) also reveals that individuals with the lowest levels of serum potassium and other relevant micronutrients tend to have a two-fold risk of developing T2DM compared to those with higher levels of these micronutrients. Contrary to other studies that suggest that there is no clear link between dietary intake of different micronutrients, including potassium, and the risk of T2DM, Kherji et al. (2022) establish that low dietary potassium intake is directly associated with an increased prevalence rate of T2DM and that supplementation for diabetes patients can increase insulin sensitivity and consequently lead to better glycemic control. For high-risk populations such as obese people, potassium supplementation could ensure adequate presence of the micronutrient in the blood, which may enhance insulin sensitivity and help maintain glycemic control. The inclusion of a sizable sample of both individuals with diabetes and pre-diabetes in this study holds sufficient statistical power to depict the relationship between low serum potassium levels and the risk of developing diabetes for individuals with pre-diabetes.

Kherji et al. (2022) also established that potassium supplementation must be accompanied by dissolvable vitamins, including riboflavin, niacin, vitamin B5, and vitamin D as well as other important micronutrients such as zinc, magnesium, phosphorus, and total iron among others for significant glycemic control to be achieved and to have the most profound impact on the management of diabetes. These micronutrients were determined to activate the functioning of potassium, especially for people with T2DM. Potassium supplementation was also established as capable of delaying the onset of health complications associated with T2DM such as diabetic microvascular angioplasty (Kherji et al., 2022). In the management of T2DM, Kherji et al. (2022) establish the vital role played by potassium and other important micronutrients and vitamins in the regulation of blood pressure, which is a critical aspect of diabetes management considering that T2DM patients have an increased risk of hypertension.

For patients with reduced levels of serum potassium, supplementation emerges as a more effective way of restoring the required levels as compared to dietary intake (Kherji et al., 2022). Therefore, while the reviewed literature affords the assessment of potassium supplementation a marginal focus, the study by Kherji et al. (2022) shows that potassium supplementation is an effective therapy for T2DM patients, especially if they have deficiencies that may result in elevated chances of insulin insensitivity. For at-risk populations such as those with obesity, potassium supplementation may also play a critical role in preventing the risk of developing T2DM. Potassium supplementation, alongside the intake of other important micronutrients and vitamins, may slow diabetic symptom progression and decrease low-grade inflammation that may come because of oxidative stress.

Brandao-Lima et al. (2018) also established that low intake of potassium and the reduction of the micronutrient’s concentration in the blood results in reduced insulin sensitivity, triggering increased compensatory secretion of the hormone and consequently elevating the risk of T2DM. Therefore, this study's results indicate that serum potassium levels emerge as a significant predictor of the risk of diabetes while establishing some level of clarity on the impact of dietary potassium on T2DM risk.

Wagh et al. (2020) revealed that individuals with the lowest levels of urinary potassium have a two-fold risk of developing T2DM compared to those with higher levels of the micronutrient. Contrary to the study by Brandao-Lima et al. (2018), which suggests that there is no clear link between dietary intake of potassium and the risk of T2DM, Wagh et al. (2020) establish that low dietary potassium intake is directly associated with an increased prevalence rate of T2DM and that supplementation for diabetes patients can increase insulin sensitivity and consequently lead to better glycemic control. For high-risk populations such as obese people, potassium supplementation could ensure adequate presence of the micronutrient in the blood, which may enhance insulin sensitivity and help maintain glycemic control. The study by Wagh et al. (2020) also establishes that potassium supplementation has to be accompanied by dissolvable vitamins such as vitamin C to have the most profound impact on the management of diabetes. Potassium supplementation has also been established by Bahrampour et al. (2023) as capable of delaying the onset of health complications associated with T2DM such as diabetic microvascular angioplasty. In the management of T2DM, Bahrampour et al. (2023) establish the vital role played by potassium in the regulation of blood pressure, which is a critical aspect of diabetes management considering that T2DM patients have an increased risk of hypertension.

For patients with reduced levels of serum potassium, supplementation emerges as a more effective way of restoring the required levels as compared to dietary intake (Bahrampour et al., 2023). Therefore, the findings of this review establish that potassium supplementation is an effective therapy for T2DM patients, especially if they have deficiencies that may result in elevated chances of insulin insensitivity. For at-risk populations such as those with obesity, potassium supplementation may also play a critical role in preventing the risk of developing T2DM.

Most of the reviewed studies establish that different micronutrients such as zinc, magnesium, and potassium play a critical role in the management of T2DM by enhancing glycemic control, secretion, synthesis, and functioning of insulin as well as in delaying the progression of the condition and signaling pathways. The findings also establish that since these micronutrients are generally lost at high levels in T2DM patients resulting in deficiencies, supplementation of these micronutrients should be part of the management of these patients. They also offer evidence supporting the claim that supplementing these nutrients in a holistic approach presents more profound benefits to patients with low concentrations or deficiencies compared to normal people without deficiencies.

4.1.4 B Vitamins

Jin, Wang, and Jiang (2021) and Zhang et al. (2022) identified a variety of B vitamins, including B-12 and B-6 among others as crucial micronutrients whose dietary intake and supplementation plays a crucial role in the management of T2DM. Specifically, they associated the dietary intake of these micronutrients with the treatment of insulin resistance as measured using fasting glucose and fasting insulin concentration (Jin et al., 2021; Zhang et al., 2022). The participants in this study had their glucose and insulin levels measured using a hexokinase enzymatic method and a two-site immunoenzymometric assay, respectively. The study by Zhang et al. (2022) emerges as a pioneer in employing the BKMR model to examine the relationship between mixed daily B vitamin intake and the risk of developing insulin resistance, which is a risk factor for developing T2DM.

The findings of Zhang et al.'s (2022) study were three-pronged. Firstly, the researchers identified a negative relational trend between overall dietary intake of B vitamins and insulin resistance for both middle-aged and elderly people. The study also indicated that among middle-aged individuals, the intake of vitamin B-12 and vitamin B-1 was negatively and positively related to insulin resistance, respectively. For the elderly, the increased dietary intake of vitamin B-6 and DFE resulted in a reduction in the odds of developing insulin resistance (Zhang et al., 2022). The final takeaway from this study is also that there exist potential relational effects between dietary intake of vitamin B-12 and other B vitamins such as B-1, B-2, niacin, and DFE on insulin resistance, and especially on the older adult cohort (Zhang et al., 2022).

By employing a multivariate logistic regression, Zhang et al. (2022) found that the level of protection against insulin resistance offered by a single dietary intake of a B vitamin was statistically insignificant for older patients, even considering that their intake of B-2 and B-12 was established as significantly higher compared to that of the middle-aged adults (Zhang et al., 2022). An interesting observation made by Zhang et al. (2022) is that most of the existing multivariate logistic regression analyses tend to include only single B vitamins but fail to consider the overall B vitamin intake as well as the non-linear factors that characterize the complex relations between different B vitamins, which may result in false positives or even false negatives. The bivariate dose-response association within the BKMR model establishes that vitamin B-12 has an interactive effect with other B vitamins, and especially B-1, B-2, DFE, and niacin on insulin resistance, especially for older individuals. This finding reveals why it may not be possible to establish a significant association between a single dietary B vitamin intake and insulin resistance, while at the same time being able to establish that a mixed intake of B vitamins can reduce insulin resistance for older patients.

4.2 Metformin Use and Vitamin B-12 Deficiency

The relationship between metformin use and changes in serum concentrations of important minerals and vitamins, especially vitamin B-12 has been explored in significant depth in the existing literature. For instance, the studies by Farooq et al. (2022), Alharbi et al. (2018) Kancherla et al. (2017) and Kim et al. (2019) focus on exploring this relationship in significant depth. In their study, Farooq et al. (2022), for instance, enlisted a total of 700 patients with T2DM with some of them being on metformin therapy and others not on metformin. The researchers took records of cumulative metformin doses by taking into consideration the history of the dose and the duration of treatment (Farooq et al. (2022). The researchers also took records of serum vitamin B-12 levels, where the participants were placed into different categories based on the serum levels of vitamin B-12 (Farooq et al., 2022). Normal levels were established to be 20 pmoI/L, possible deficiency (150-220 pmoI/L) and definite deficiency (< 150 pmoI/L) (Farooq et al., 2022). The findings of this study established that depending on the length of the duration that a patient has been on metformin, their vitamin B-12 levels decreased by about 11.16% (Farooq et al., 2022). The study established that the metformin-exposed group also has about 45% incidence of clinical neuropathy compared to about 31.8% for the other group. Age of the patient was also identified as a critical determinant of the likelihood of developing clinical neuropathy as older people with T2DMwee found to be more likely to develop clinical neuropathy (59.01 ± 7.14 vs. 49.95 ± 7.47) (p-value < 0.514) (Farooq et al., 2022). Therefore, Farooq et al. (2022) established that cumulatively using metformin in the management of T2DM corresponds with declining levels of serum vitamin B-12. Specifically, the use of metformin for a prolonged period depletes vitamin B-12, contributing immensely to the onset of clinical neuropathy.

Kancherla et al.'s (2018) study that enlisted a sample of veterans aged 50 and above with either T2DMor on long-term use of metformin also confirms the findings of Farooq et al. (2022) and Alharbi et al. (2018). The diabetes status of the patients was determined during outpatient visits, and the long-term metformin use was based on a prescription of ≥500 mg/day for at least six months consecutively (Kancherla et al., 2018). A multivariable logistic regression was employed by both Kancherla et al. (2018) and Alharbi et al. (2018) to determine the intricate nature of the relationship between metformin use and vitamin B-12 deficiency, stratifying the patient records by age, and evaluating the nature of the association between metformin use and serum vitamin B-12 levels. In Kancherla et al. (2018), 37% of the participants in the study were on metformin therapy and had their vitamin B-12 levels measured. For this group, the vitamin B-12 concentration levels were significantly lower (439.2 pg/dL) when compared to those of the individuals without T2DM (522.4 pg/dL) (P=0.0015) (Kancherla et al., 2018). Based on the findings of this study, about 7% of the theT2DM patients who used metformin had vitamin B-12 deficiency (<170 pg/dL) compared to only 3% of the people not having diabetes and not on metformin therapy (P=0.0001) (Kancherla et al., 2018).

Like the study by Farooq et al. (2022) and Alharbi et al. (2018), age was also established as a critical factor determining the increase in vitamin B-12 deficiency among individuals with T2DM and on metformin therapy after adjusting for other confounders such as sex, race, body mass index, and ethnicity among others. Kancherla et al. (2018) and Alharbi et al. (2018), therefore, established that while long-term metformin use has been closely associated with the risk of serum vitamin B-12 deficiency, it is surprising that it is uncommon for those at a greater risk to be monitored to establish B12 deficiency. Given that metformin is often considered an effective first-line therapy for the treatment of T2DM, the potential harm, including the decrease of vitamin B-12 levels, tends to be overlooked. Even for patients treated using metformin, clinical decision support should focus on the promotion of vitamin-12 monitoring among patients under long-term metformin use as a way of addressing the problem and making timely interventions aimed at ensuring constant normal serum vitamin B-12 levels.

Kim et al. (2019) introduce a rather different angle in the study of the relationship between metformin use and vitamin B-12 deficiency among individuals with T2DM by considering how dosage plays a role. In this study, Kim et al. (2019) enlisted a sample of 1111 patients with T2DM who had been on metformin for at least six months. They used a competitive-binding immunoenzymatic assay, whereby deficiency was identified as serum vitamin B-12 <300 pg/mL (Kim et al., 2019). Metformin use, including details on dosage and duration, was recorded based on self-reports from the participants. The study by Kim et al. (2019) confirms the findings of the other related studies, including Kancherla et al. (2018) and Farooq et al. (2022) in highlighting the relationship between the use of metformin therapy and its impact on the balance of micronutrients in the body, and more specifically the associated decline in the concentration of vitamin B-12 in the blood. In this study, Kim et al. (2019) established that a deficiency of vitamin B-12 occurred in about 247 patients (22/2%). The dosage was also considered to play a crucial role in determining the decline in the levels of serum vitamin B-12. For instance, Kim et al. (2019) found that, while adjusting for confounders, an increase in the daily metformin dose of 1 mg resulted in about 0.142 pg/mL decline in serum vitamin B-12 levels ($P < 0.001$) (Kim et al., 2019). Relative to a daily dosage of <1000 mg, for the 1000 mg to 1500mg, 1500 mg to 2000 mg, and ≥2000 mg, the odds ratio were established as 1.72 ($P = .080$), 3.34 ($P < .001$), and 8.67 ($P < .001$), respectively (Kim et al., 2019). This study establishes that metformin dosage, as well as the duration of use, is an important determinant of the declining serum vitamin B-12 levels, which also signals the need for vitamin B-12 supplementation among people with T2DM using metformin.

However, for patients taking vitamin supplements and multivitamins (odds ratio 0.23; $P < 0.001$), Kim et al. (2019) established that the rate at which vitamin B-12 deficiency occurred was slower than for those who did not take multivitamins. This finding reveals the complex nature of the mechanism through which metformin use can result in the decline in serum vitamin B-12 concentration, which is something that is overlooked in other studies on the same topic. According to Kim et al. (2019), the most viable hypothesis explaining this relationship is that metformin tends to interfere with the functioning of calcium-dependent membrane action that oversees the vitamin B-12 internal factor absorption within the terminal ileum. However, how this process could be improved through the supplementation or intake of multivitamins remains underexplored in the existing literature (Kim et al., 2019).

Contrary to the observations made by Farooq et al. (2022) and Kancherla et al. (2018), Kim et al. (2019) did not find any significant correlation between vitamin B-12 deficiency and the length of the duration that one is on metformin therapy. Therefore, while other researchers consider the duration of metformin use as the most significant indicator of vitamin B-12 deficiency among patients with T2DM who have used metformin as a first-line therapy for at least six months, Kim et al. (2019) indicate that metformin doses that are either equal to or greater than 1500 mg/d are the most significant factor. They also emphasized the fact that multivitamin supplementation may have a potentially significant impact when it comes to interfering with the process in which metformin use contributes to the decline in the levels of serum vitamin B-12 concentration. Therefore, while other researchers consider the age of the patient to also indicate the extent to which the use of metformin may result in vitamin B-12 deficiency, Kim et al. (2019) consider these factors to be secondary and possibly insignificant, especially when compared to dosage. Another notable observation that Kim et al. (2019) make is that serum homocysteine levels were also determined to correspond to the levels of vitamin B-12, which may suggest that the deficiency associated with the use of metformin occurs at the level of tissues. However, Kim et al. (2019) also establish that this hypothesis lacks the necessary empirical backing now, meaning that further research is required to elucidate it and make it more scientific. Some of the notable efforts to elucidate this hypothesis have been made by Akindale et al. (2015) but there is still some level of confusion.

The reviewed primary studies identified a wide range of micronutrients that play a crucial role in the management of T2DM. Four of these studies also explored the nature of the association between metformin use and vitamin B-12 deficiency, which is a topic that is currently attracting increasing scholarly attention. Zinc, magnesium, potassium, and B vitamins have been identified to be closely related to diabetes management outcomes such as glucose homeostasis, insulin secretion and functioning, glycemic control, and the slowing of the progression of diabetes-related complications among individuals with T2DM. The use of metformin, especially cumulatively and in daily doses of 1500 mg or more has also been established to enhance the decrease in serum vitamin B-12 levels, resulting in deficiencies. However, supplementation of important micronutrients and vitamins has been established as a viable way of addressing this negative impact of metformin use.

Chapter 5: Conclusion

5.1 Summary of Key Findings

RQ1: Role of Micronutrients Intake and Supplementation in Diabetes Management

The reviewed studies establish that micronutrient intake or supplementation plays a crucial role in the management of T2DM, especially by slowing the progression of the condition and also by preventing the onset of diabetes related diseases such as neuropathy, cardiac, and kidney issues among others. Therefore, considering that patients with T2DM tend to develop micronutrient deficiencies, this study establishes that adopting dietary interventions or supplementation regimes that include different micronutrients is necessary in the management of T2DM patients.

RQ2: Relationship between Micronutrients and Glycemic Control, Insulin Functioning, Glucose Homeostasis

The findings of this study establish that different micronutrients such as zinc, magnesium, potassium, and B vitamins play a critical role in the management of T2DM by enhancing glycemic control, insulin secretion and synthesis, signaling pathways, and functioning as well as delaying the progression of the condition. The findings also establish that since these micronutrients are generally lost at high levels in T2DM patients resulting in deficiencies, supplementation of these micronutrients should be part of the management of these patients. The findings also establish that supplementing these nutrients presents more profound benefits to patients with low concentrations or deficiencies compared to those who have them in sufficient quantities. Supplementation of these micronutrients, therefore, as opposed to solely relying on dietary intake, can have a more profound impact on the management of T2DM.

RQ3: Metformin Use and Vitamin B-12 Deficiency and Supplementation

Long-term metformin use has been established to negatively affect serum vitamin B-12 concentrations among patients with T2DM. This is a concern given the important role that vitamin B-12 plays in enhancing insulin secretion and function. The findings establish that daily metformin dosage and the duration of use are among the most important factors that contribute to vitamin B-12 deficiency. What this finding implies is that patients with T2DM using metformin should take vitamin B-12, either through dietary intake or supplementation as part of the long-term management of the condition.

5.2 Implications of the Review

The implications of this review on praxis are significant, especially for stakeholders involved in the management of diabetes, including healthcare providers, policymakers, and individuals with T2DM. The findings of the review could influence the review of existing clinical guidelines for the management of diabetes, to emphasize more on recommendations on the role of micronutrient intake or supplementation as a core part of nutrition therapy for T2DM patients. The findings of this review could also inform the formulation of patient education and counseling programs aimed at enhancing awareness of the importance of micronutrients in the management of people with T2DM. This may include recommendations for dietary changes, supplementation, or other interventions aimed at optimizing micronutrient intake and improving the overall health of patients. The findings of this study could also inform public health policy, especially the development of policies aimed at improving access to micronutrient supplements and other important resources to people with T2DM.

5.3 Limitations of the Study

This study has some limitations that may impact on the validity of the findings and the generalizability of the study. Among the most notable ones is the heterogeneity of the study designs considering that the selected studies included RCTs, Cohort studies, and cross-sectional studies. Such heterogeneity presents some challenges when it comes to synthesizing the findings of the study as well as drawing definitive conclusions. However, the use of thematic analysis allowed for the identification of common themes and motifs despite the variations in study designs, methodologies, intervention durations, and outcome measures. The heterogeneity of the included primary studies also meant that the quality of evidence in the included studies varied significantly, with some primary studies having a higher risk of bias or methodological limitations. This could have serious ramifications on the reliability and validity of the review's findings. This limitation was mitigated by employing robust quality assessment criteria that ensured that only studies that meet a certain quality threshold were selected.

5.4 Future Research

The reviewed studies revealed some notable gaps in the extant literature that require further investigations. A potential avenue for future research is the elucidation of the mechanism through which metformin use contributes to vitamin B-12 deficiency and how using micronutrient and multivitamin supplements may solve the issue. While some scholars have made decent attempts in exploring this area, there is still some level of uncertainty that requires to be cleared through further research. Researchers could also focus on exploring if the deficiency of certain micronutrients may trigger other deficiencies and how such an issue should be handled through dietary therapy or supplementation. It is necessary to conduct more clinical trials on metformin use, vitamin B-12 deficiency, and the role of micronutrients in the management of diabetes. Clinical trials can help elucidate the mechanism by which metformin contributes to vitamin B-12 deficiency. This is critical because understanding the biological pathways involved can lead to more targeted therapies that minimize adverse effects while maximizing therapeutic benefits. There is a significant gap in the research regarding the efficacy of micronutrient and multivitamin supplements in preventing or mitigating the vitamin deficiencies caused by long-term metformin use. Clinical trials can provide rigorous data on whether these supplements can effectively counteract the deficiencies and under what conditions. While it's recognized that micronutrients play a critical role in diabetes, the specific micronutrients or trace elements that could enhance diabetes management outcomes remain unclear. Clinical trials can help determine which micronutrients are most beneficial and how they contribute to the management of diabetes. Solid, evidence-based data from clinical trials can inform and refine clinical guidelines and policies. This includes recommendations for routine screening for micronutrient deficiencies in patients taking metformin and guidelines for supplementation. In summary, more clinical trials are necessary to fill the current gaps in our knowledge about the interaction between metformin use, micronutrient deficiencies, and diabetes management. Such trials are crucial for developing more effective, holistic, and personalized treatment strategies for diabetes patients.

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