

Effects of Diet and Exercise in Reversing Type 2 Diabetes Mellitus: A Systematic Review

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ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder due to the body's ineffectiveness in responding to insulin. The prevalence of T2DM in Malaysia is increasing from year to year. Besides, diabetes is one of the Non-Communicable Diseases (NCDs) which are the leading cause of premature death due to its complications in Malaysia. Although pharmacological and surgical interventions are available in controlling T2DM, lifestyle modification provides an alternative way to reverse T2DM as the development of diabetes mellitus is highly related to lifestyle. The modifiable risk factors that lead to the causation of diabetes include being overweight or obese, a sedentary lifestyle, and being physically inactive. Losing weight through exercise and diet control is effective in delaying the progression of T2DM. It also improves cardiometabolic disease progression as an increase in insulin sensitivity. Diet and exercise are lifestyle interventions that can reduce weight. Thus, this systematic review aims to study the effectiveness of diet and exercise in reversing T2DM.

Methods & Results: According to PRISMA guidelines, PubMed, Scopus, and Cochrane Library Database were used in this study for searching the related studies. 12 studies that investigated the effectiveness of diet and exercise in reversing T2DM were obtained and reviewed. The main search keywords were linked using the Boolean operator "AND" and "OR". Risk-of-bias assessment was done using JBI critical appraisal tools. Most of the studies reported a significant decline in BMI, fasting plasma glucose, and HbA1c values of intervention groups. There were studies that reported T2DM remission and medication reduction after the intervention.

Conclusion: Diet and exercise effectively reverse T2DM as significant weight loss was achieved. However, the long-term effect should be further evaluated as reviewed studies were limited in duration.

Keywords: Diet, Exercise, T2DM, Reverse & Remission.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) or non-insulin-dependent diabetes mellitus is a chronic metabolic disorder due to the body's ineffectiveness in responding to insulin. It is characterised by a decline in β -cell function leading to a gradual decline in insulin production and the progression to insulin resistance (IR) (American Diabetes Association, 2015). Based on

pathophysiology, the progression of T2DM is due to persistent hyperglycaemia by the presence of both β -cell dysfunction and IR (Galicia-Garcia et al., 2020). According to the World Health Organization (WHO), elevated blood glucose levels are the hallmark of diabetes mellitus, which gradually damages the heart, blood vessels, eyes, kidneys, and nerves. Generally, T2DM is considered a Non-Communicable Disease (NCD) including cancer, cardiovascular disease, and respiratory disease which are the main cause of premature death in Malaysia.

NCD killed approximately 33.2 million people worldwide in 2019, a 28% increase compared to the year 2000. In addition, the most prevalent type of diabetes in Malaysia is T2DM which accounts for over 90% of all adult-onset diabetes mellitus (Clinical Practice Guidelines (CPG) on Management of Type 2 Diabetes Mellitus 6th edition, 2020).

Diabetes accounts for the social and economic burden worldwide. It required a high cost in treating the disease and its complications, especially myocardial infarction (MI), stroke, heart failure, and lower limb amputation. A study reported that approximately RM 2.04 billion yearly is required for the cost of treating diabetes and its complications in Malaysia and RM 1.40 billion was subsidised by the government (Feisul et al., 2017). Based on the finding in 2019 with 10,464 respondents reported by National Health Morbidity Survey (NHMS), the prevalence of raised blood glucose was 18.3% in adults aged more than 18 years. It was also reported in the survey that about 1 in 5 adults in Malaysia have diabetes. The increasing prevalence of raised blood glucose as reported in NHMS suggests a worrisome increase in the number of T2DM patients in Malaysia.

A study by Dodds (2017) showed risk factors that lead to the causation of diabetes were overweight or obese, sedentary lifestyle, being physically inactive, having unhealthy sleep habits, and tobacco use. According to the World Health Statistics report, being overweight and obese is the leading risk factor for NCDs. Besides, according to Dixit et al. (2022), the highest risk factor for T2DM is obesity. Despite genetic factors, being overweight and obese is highly influenced by an unhealthy diet and a sedentary lifestyle that has been practiced nowadays. In addition, a critical consideration in the pathophysiology of T2DM is weight gain. The development and increasing prevalence of both type 1 and type 2 diabetes mellitus is mostly attributed to an increase in weight and body mass (Algoblan et al., 2014).

Increased weight gain also leads to insulin resistance as insulin sensitivity fluctuation is influenced by different lifestyle practices such as the higher amounts of carbohydrates consumed and greater physical activity. It has been demonstrated that weight loss, whether brought on by lifestyle changes, weight-loss medications, or bariatric surgery, can successfully delay the course of T2DM, especially in high-risk prediabetes or metabolic syndrome (Grams & Garvey, 2015). Reversal or remission of T2DM via weight loss was less pronounced in our society due to the lack of education and evidence about it.

Besides, losing weight also improves the cardiometabolic disease progression as an improvement in insulin sensitivity and a decline in cardiovascular disease risk factors, such as reductions in blood pressure, lipids, and inflammation markers were observed. In addition, American Diabetes Association (ADA) consensus statement defined partial or complete remission of T2DM as fasting glucose ≤ 6.9 mmol/L, HbA1c $< 6.5\%$, no anti-glycaemic medication during assessments,

and achieved target at both 12- and 24-month follow-up (Riddle et al., 2021). This characteristic must be followed to elucidate T2DM remission or reversal.

Some recent studies by Dixit et al., (2022) and Sarathi et al., (2017) mentioned that bariatric surgery is effective in achieving remission in T2DM obese patients. Moreover, a study stated that T2DM patients achieve remission after 3 months of the Roux-en-Y gastric bypass (RYGB) procedure. However, performing bariatric surgery to reverse T2DM is very costly, invasive, and high-risk (Dixit et al., 2022). Thus, reversing T2DM via weight loss in lifestyle modification is the potential choice as it is less costly and safer compared to bariatric surgery.

According to CPG Management of Type 2 Diabetes Mellitus 6th edition, T2DM can be prevented with medical nutrition therapy (MNT) with weight loss. Besides, physical activity is also crucial in achieving remission. Increasing exercise levels promote T2DM remission in conjunction with dietary changes (Ried-Larsen et al., 2019). Thus, this systematic review aimed to evaluate the effectiveness of diet and exercise in reversing T2DM.

METHODS

This systematic review was reported based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) statement 2020.

Eligibility Criteria

We included all types of studies except systematic review studies, abstract-only papers, book chapters, thesis, letters, conference papers, a poster, or editorials, which studies the effects of exercise or diet intervention. All types of diet intervention including diet restriction or low-calorie diets, or low-carbohydrate diets were eligible for inclusion. However, the studies that discuss pharmacological intervention or intermittent fasting, or bariatric surgery were excluded. The T2DM or prediabetes population was included while Type 1 Diabetes Mellitus,

Gestational Diabetes, and overt /chronic diabetes mellitus were excluded in this study. We also excluded the smoking population due to differences in regulating insulin levels due to inflammation in smokers' bodies compared to non-smokers. Publication beyond the past 5 years was excluded in this systematic review and only included the articles from the year 2018-2022 publication. Lastly, only the English language was included in the eligibility criteria, while excluding foreign language studies.

Literature Search

The scientific databases which are PubMed, Scopus, and Cochrane Library Database were used in searching articles published from 2018 to 2022. There are 4 main keywords used: diet, exercise, reversing, and type 2 diabetes mellitus. Besides, keywords from the MeSH Database were included in the literature search. Table 1.0 summarised the keyword used in literature searching. In addition, the literature search was done manually through Google Scholar, and the articles are included in the reference list. Lastly, the main search keywords were linked using the Boolean operator "AND" and "OR".

Table 1: Summary of keywords used in the literature search

Main keywords	Text Word
Diet	Diet, Food, Nutrition, Meals, Mediterranean diet, DASH diet, the MIND diet, Low-calorie diet & Diet restriction
Exercise	Exercise, Physical exercise & physically active
Reversing	Reversing, Treating, Treatment & Remission
Type 2 Diabetes Mellitus	Type 2 Diabetes Mellitus, Diabetes Mellitus, Noninsulin-Dependent & Adult-Onset Diabetes Mellitus

Study Selection

All studies obtained from the literature search were combined and imported into the Rayyan website. Rayyan allowed the author to collaborate and manage systematic review research effectively and systematically with the other reviewers. Then, the duplicate studies were detected and removed automatically by Rayyan before the screening of the title and abstract. The author and the coauthors independently reviewed the titles and abstracts of the studies found through the searches. The titles or abstracts of studies that were not related to this research were removed. Following the screening of titles and abstracts, the full-text version of the studies was obtained and analysed to determine whether the studies met the requirements of inclusion criteria or not. If there was a conflict raised regarding eligibility criteria, it was then resolved by a general agreement discussion between the two authors and including the third author if required. All studies that did not meet inclusion criteria were excluded.

Data Extraction

The primary author obtained the study details and outcome data by using the Microsoft Excel file. The study characteristics including study design, publication year, region, intervention duration, and follow-up were extracted from the selected studies. Patient characteristics include sample size, sex, mean age, inclusion and exclusion criteria, baseline data, duration of T2DM, number of participants with glucose-lowering medications, number of initial participants, number of participants withdrawn, and the reason for loss to follow-up also extracted from the 12 studies. Besides, the details of intervention from each study including types of diet and exercise were also extracted. The main details extracted on primary outcome were change from baseline in glycated haemoglobin (HbA1c), Postprandial 2-h glucose, fasting plasma glucose, HOMA-IR, Body Mass Index (BMI), total cholesterol, and anti-glycaemic MES or reduction in medication used.

Risk-of-bias Assessment

JBIs critical appraisal tools were used as the risk-of-bias assessment tools in this research. The selected data were independently reviewed by 2 reviewers (Nadiyah and Naif) to examine the quality of the selected studies. Any conflict was resolved by mutual discussion between the two authors and if necessary, involving the third author. The overall risk of bias for each article was determined and classified into the low, high, and unclear risk of bias. According to Pimsen et al. (2022), JBI scores above 70% were considered high quality, scores between 50% and 70% were of medium quality, and scores below 50% were considered low-quality studies. High-quality studies are considered low risk of bias while low-quality studies have a high risk of bias.

RESULTS

Search Results

The literature search across the database identified 318 studies in total. 6 additional studies were identified via citation search using snowball methods. The PRISMA flow diagram is presented in figure 1. Succeeding a review of the titles and abstracts, any duplicate publications were removed and a total of 238 studies were left. For future analysis, 31 full-text copies were acquired. From 238 studies, 207 studies were excluded. The studies that did not meet the inclusion criteria were excluded. The main reasons for excluded studies were the wrong outcome, wrong intervention, pharmacological intervention, animal study, wrong study design, wrong publication type, and unrelated articles. Other reasons for exclusion were that studies conducted in patients with T2DM, or prediabetes were conducted in other populations including the smoking population, overt or chronic diabetes, Type 1 Diabetes Mellitus, and Gestational Diabetes. Then, 31 full-text studies were reviewed independently by 2 authors to avoid bias, and any disagreements were managed involving the third author. Thus, the total number of studies included in this systematic review was 12, and 3 of them were identified from citation searching via the snowball method.

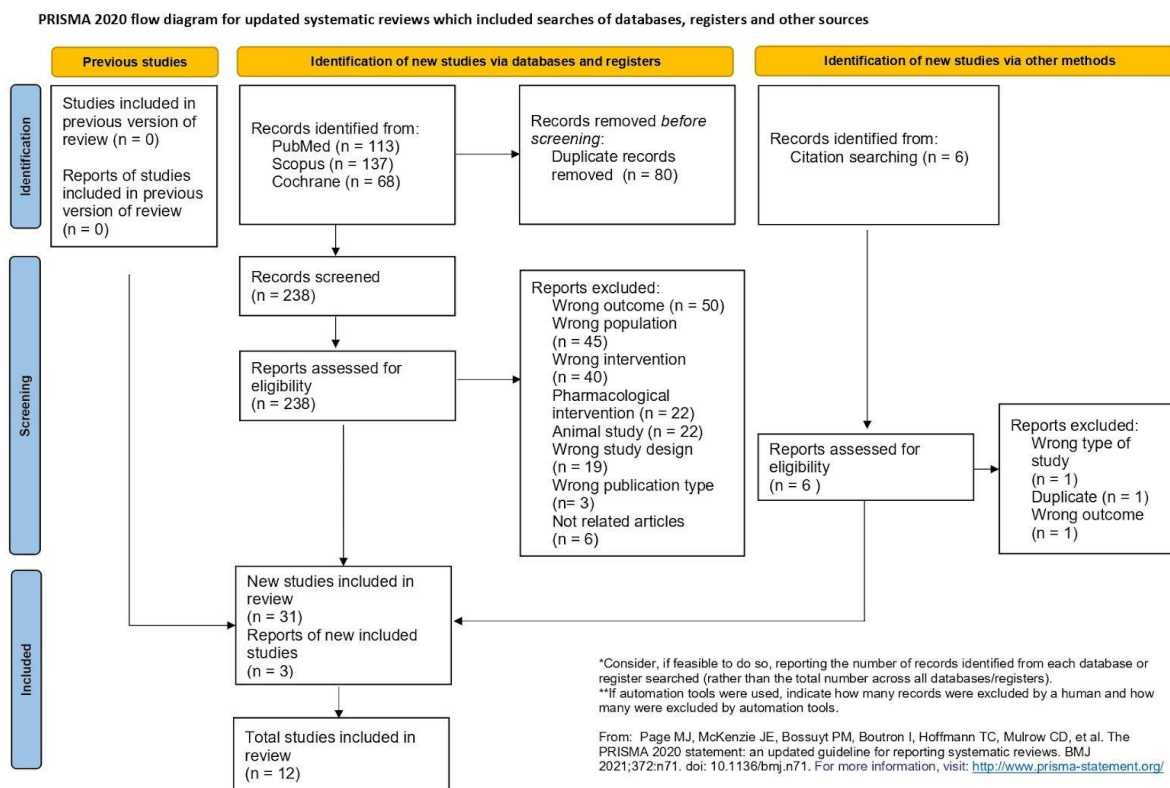


Fig. 1: PRISMA Flow Diagram

STUDY CHARACTERISTICS

A total of 12 studies evaluating the different patterns of diet and exercise in reversing T2DM were included in this systematic review. The reviewed articles were published in the year between 2018-2022. The main characteristics of each study was summarised in Table 2. Five randomised control trials, four case series, one case report, and two cohort studies were identified to be effective in reversing T2DM. Most studies were conducted in Southeast Asia which are Thailand (n=1), China (n=2), and India (n=3). Three studies were conducted in Denmark, one study in Saudi Arabia, one study in California, and one study in The United States of America.

Most of the studies demonstrated a decline in mean HbA1c values following the diet and exercise intervention. Four studies (Skyttee et al., 2019; Wang et al., 2020; Umphonsathi et al., 2021; Dagogo-Jack et al., 2022) demonstrated a very highly significant difference in HbA1c values of the intervention group as the p values <0.001 . One study (Han et al., 2021) reported that mean HbA1c was statistically significant as $p < 0.05$, and one study (Evangelista et al., 2021) described it as statistically highly significant as $p < 0.01$. The remaining studies utilised other glycaemic parameters instead of HbA1c such as peak glucose concentration and fasting plasma glucose values and showed a statistically significant reduction in blood glucose levels of the intervention group. However, there was an exception for one article by Ried-Larsen et al. (2019) where the HbA1c values increased slightly after 24 months following the dietary and exercise intervention.

The majority of the studies reported a significant drop in the body weight and BMI values from the baseline between the intervention and the control group while the two studies showed no significant drop in body weight and BMI values between the group. One study reported the same efficacy in reducing body weight and BMI in both groups. Next, a significant decline in the anti-glycaemic Medication Effect Score (MES) showed in the Low-carbohydrate diet (LCD) group and intermittent very low-calorie diet (VLCD) with advised exercise.

The LCD group was reduced by 1.1 anti-glycaemic MES compared to the low-fat diet group with no changes and the result portrayed a very highly significant difference [$p < 0.001$] (Han et al., 2021). Besides, there is a significant reduction in MES of sulfonylurea and metformin reduction in the intermittent VLCD group after the intervention period. The remaining studies mentioned that the percentage of medication withdrawal after the dietary and exercise intervention was given to the participants.

Risk of Bias Assessment

The overall risk of bias for 12 studies was judged and observed that 5 studies were categorised as low risk of bias, one as high risk of bias, and the remaining 6 studies as unclear risk of bias. The overall risk-bias-assessment was performed using a visualisation tool known as the Risk of Bias Visualization (RoBVIS) tool. The visualised tool was utilised to simplify the domains and overall risk of bias from different studies such as RCT studies, case series studies, case reports, and cohort studies.

Table 2: A summary of included studies in the Systematic Review

First author, year	Types of study (region)	Participants	Intervention	Outcome	Adverse effects
Skytte, 2019	Randomised controlled trial (RCT) (Denmark)	28 (20 male/8 female) mean age: 64 y; BMI: 30.1 kg/m ² ; mean HbA1c: 7.6%; fasting plasma glucose: 9.4 mmol/L; duration of T2DM: 7 y; utilised anti-glycaemic medication: 24; no glucose-lowering medication: 4 Initial participant (n=30) Withdraw participant: relocation (n=1); inability to adhere to diets (n=1)	12 week (6 + 6 w) A: conventional diabetes (CD) diet (n=14); B: carbohydrate-reduced high-protein (CRHP) (n=16). No washout period between the two 6-week periods. 6-week CD + 6-week CRHP and vice versa. A: CD diet: 50% energy carbohydrate, 17% protein, and 33% fat. B: CRHP diet: 30% carbohydrate, 30% protein, and 40% fat; iso-energetic CRHP.	Body weight, Body Mass Index (BMI), or waist circumference: No significant changes in this parameter between the CRHP diet and the CD diet. HbA1c values: CRHP diet treatment was reduced by 0.6± 0.1% compared to CD diet treatment was reduced slightly by 0.1± 0.1%. [p<0.001] Fasting plasma glucose: CRHP diet reduced by 0.71 ± 0.20 mmol/l while the CD diet increased by 0.03 ± 0.23 mmol/l [p < 0.05] Fasting triacylglycerol: CRHP diet reduced by 0.43 (−0.77 to −0.16) mmol/L while the CD diet increased by 0.12 (0.01 to 0.44) mmol/L compared to the baseline [p<0.001] Total cholesterol: CRHP diet reduced by 0.44 ± 0.10 mmol/l compared with CD diet which no changes 0.00 ± 0.10 mmol/l [p < 0.05] Non-HDL-cholesterol: CRHP diet reduced by 0.44 ± 0.10 mmol/l while CD diet reduced slightly by 0.04 ± 0.09 mmol/l [p < 0.05] Magnetic resonance: 1) CRHP diet reduced liver fat fraction by 2.4% (−7.8% to −1.0%) compared to the	Constipation (n=4); sleep disturbance (n=1) Constipation: lower content of dietary fibre in CRHP diet.

				CD diet only reduced by 0.2% (−2.3% to 0.9%) [p < 0.01] 2) CRHP diet reduced pancreatic fat fraction by 1.7% (−3.5% to 0.6%) while the CD diet increased by 0.5% (−1.0% to 2.0%) [p < 0.05]	
Han, 2021	RCT (China)	134 (73 male/61 female); mean age: 51.45 ± 13.42 y; median HbA1c: 7.6% (6.8–9.4%); median fasting plasma glucose: 8 mmol/L (6.3–10.4) mmol/L; postprandial 2-h glucose: 10 mmol/L (7.8–13.5) mmol/L; median duration of T2DM: 3 y (0.3–8.0) y; BMI: 24.5 kg/m² (22.7–27.3) kg/m²; Anti-glycaemic MES: 1.5 (1.1–2.0); oral anti glycaemic medication (n=95); intensive insulin therapy (n=39); GLP-1RA (n=21)	6- month A: low-carbohydrate diet (LCD) group (n= 67); B: low-fat diet (LFD) group (n= 67) A: LCD group: 14% from carbohydrate intake, 28% from protein intake, and 58% from total fat intake. B: LFD group: 53% from carbohydrate intake, 17% from protein intake, and 30% total fat. A&B: Limit saturated fat to <10%; conducted aerobic exercise 3 days a week for 60 minutes every session under professional supervision; received dietary education after the dietary washout period.	BMI values: LCD group reduced significantly by 1.5 kg/m² (−2.0 kg/m², −1.0 kg/m²) while BMI in the LFD group reduced slightly by 0.3 kg/m² (−1.3 kg/m², −0.1 kg/m²) [P<0.001]. HbA1c values: LCD group decreased significantly by 1.8% (−3.3%, −2.0%) compared with the LFD group which reduced steadily by 0.6% (−1.6%, −0.7%) throughout the intervention [p < 0.05]. Fasting plasma glucose values: FBG changed slightly by −0.7 (−2.2, −0.8) mmol/L in the LFD group, and change significantly in the LCD group by −2.0 (−4.0, −2.1) mmol/L [p < 0.05]. Postprandial 2-h glucose values: LCD changed significantly by −3.7 (−5.6, −3.2) mmol/L and LFD group changes slightly by −1.0 (−2.9, −0.9) mmol/L [p < 0.05]. Anti-glycaemic MES: LCD group reduced by 1.1 while in group LFD no changes [p < 0.001].	Indifference in the incidence of hypoglycaemia or ketoacidosis between LCD and LFD groups before and after intervention Adverse event follow-up was not complete.
Ried-Larsen, 2019	RCT (Denmark)	93 (50 male/ 43 female) Initial participants (n=98); loss of contact during follow-up at 3rd and 24-month (n=5) Standard care group: mean age: 56.7 ± 8.3 y; mean HbA1c: 49.7 ± 9.8 mmol/mol; fasting plasma glucose: 9.1 ± 3.1	12- month intervention/24-month from baseline assessments Extension study from 12- month previous study. A: standard care (n=62); B: U-TURN lifestyle intervention (n=31)	BMI values: U-TURN group decreased significantly by 0.45 kg/m² while reduced slightly by 0.31 kg/m² in the standard care group [p = 0.74]. HbA1c values: Increased by 2.7 mmol/mol from 49.1 mmol/mol in U-TURN group during the 24-month follow-up. In comparison, the standard care group increased by 3.2 mmol/mol from 49.7	Adverse events from baseline to 24-month follow-ups were documented.

		mmol/L; postprandial 2-h glucose: 16.3 ± 4.2 mmol/L; duration of T2DM: <10 y; BMI: 32.3 ± 4.4 kg/m²; oral anti-glycaemic medication (n=31) U-TURN group: mean age: 53.5 ± 9.2 y; mean HbA1c: 49.1 ± 9.1 mmol/mol; fasting plasma glucose: 8.4 ± 2.9 mmol/L; postprandial 2-h glucose: 15.4 ± 4.0 mmol/L; duration of T2DM: <10 y; BMI: 31.5 ± 3.9 kg/m²; oral anti-glycaemic medication (n=62)	A&B: Target-driven pharmaceutical therapy; received lifestyle advice every third month by a diabetes nurse. B: Half or one hour of intensive and aerobic exercise for every 5 or 6 days/week under supervision; received tailored dietary plan individually (45%-60% carbohydrate, 15%-20% protein, and 20%-35% fat, with <7% saturated fat); restrict energy intake for the first 4 months of the intervention.	mmol/mol compared to the baseline [p = 0.80]. Fasting plasma glucose values: U-TURN group increased by 0.6 mmol/l while the standard care group increased by 1.2 mmol/l [p < 0.21]. Postprandial 2-h glucose values: Reduced slightly by 0.7 mmol/mol in U-TURN group while reduced by 0.1 mmol/mol in the standard care group [p = 0.43]. Total cholesterol values: There is no significant difference between total cholesterol in the U-TURN group and standard care group as the values after follow-up increased by 0.5 and 0.4 respectively [p = 0.50]. No glucose-lowering medication: For both groups, not available changes.	
Umphonsathi, 2021	RCT (Thailand)	40 (29 female and 11 male) No dropouts Mean age 49.6 ± 7.9 y; mean BMI 30.1 ± 5.9 kg/m²; mean duration of diabetes 4.9 ± 3.1 y; mean $7.4 \pm 1.2\%$ 2 days/week intermittent VLCD Mean age: 49.5 ± 7.2 y; mean HbA1c: $7.5 \pm 0.3\%$; fasting plasma glucose: 156 ± 13.0 mg/dL; postprandial 2-h glucose: 318.2 ± 24.4 mg/dL; duration of T2DM: 5.5 ± 3.0 y; BMI: 29.9 ± 1.6 kg/m²; oral anti-glycaemic medication: metformin: 79%; Sulfonylureas: 29%	20- week A: 2 days per week intermittent very-low-calorie diet (VLCD) (n=14); B: 4 days per week of intermittent VLCD (n=14); C: control group (n=12). A & B: Intermittent VLCD: 55% of carbohydrate intake, 15% of protein intake, and 30% of fat intake; total 600 kcal/day on restricted days; ad libitum food consumption on non-restricted days; reduction by 50% dosages of glucose-lowering medications. C: control group: received a diet of 1500–2000 kcal/day; usual standard diabetes care.	BMI values: No significant differences between the intervention and control group. BMI values decreased by 3.6 ± 0.5 kg/m² in the 4 days/week group, 2.1 ± 0.5 kg/m² in the 2 days/week group and 2.0 ± 0.6 kg/m² in the control group. HbA1c values: Mean HbA1c $\pm$ SEM significantly reduced by $1.2 \pm 0.3\%$ in the 4 days/week group [P < 0.001], reduced by $0.7 \pm 0.3\%$ in the 2 days/ week group [P = 0.042], and reduced the less by $0.1 \pm 0.3\%$ in the control group [P = 0.862]. Fasting plasma glucose values: 4 days per week group had a significant drop by 39.7 ± 12.5 mg/dL and 2 days per week group declined by 25.1 ± 12.5 mg/dL [P = 0.051]. In contrast, the control group reduced by 7.9 ± 13.5 mg/dL [P = 0.56]. Diabetes remission: Both participants in 2	No serious adverse events were observed throughout the intervention. No serious hypoglycaemia was reported.

		4 days/week intermittent VLCD: mean age: 47.6 ± 7.9 y; mean HbA1c: $7.7 \pm 0.3\%$; fasting plasma glucose: 159.6 ± 12.8 mg/dL; postprandial 2-h glucose: 349.2 ± 24.4 mg/dL; duration of T2DM: 3.1 ± 2.8 y; BMI: 31.0 ± 1.6 kg/m²; oral anti-glycaemic medication: metformin: 93%; Sulfonylureas: 57% Control group: mean age: 52 ± 6.0 y; mean HbA1c: $6.9 \pm 0.3\%$; fasting plasma glucose: 145.1 ± 14.0 mg/dL; postprandial 2-h glucose: 306.7 ± 26.4 mg/dL; duration of T2DM: 5.2 ± 3.2 y; BMI: 29.1 kg/m²; oral anti-glycaemic medication: metformin: 100%; Sulfonylureas: 50%	A, B & C: advised to continue usual physical activity; in contact virtually with the endocrinologist to access their compliance; blood glucose monitoring at home.	days/week and the 4 days/week groups achieved 29% of remission. In comparison with a control group with no participants achieved remission [$P = 0.117$]. Withdrawal of Glucose-lowering medications: 64% of the 2 days/week group, 86% of the 4 days/week group, and 58% of the control group were withdrawn glucose-lowering medication. Medication effect score (MES): a significant drop in the mean of sulfonylurea and metformin usage for all groups. HOMA-IR: There are significant improvements in HOMA-IR values in intervention groups. No significant difference in HOMA-IR between the 2 days/week group and the 4 days/ week group at week 20 with a mean difference of 0.1 [$P = 0.924$]; suggesting significant improvement in insulin resistance.	
Evangelista, 2021	RCT (California)	76 (55 male/21 female) No dropout participants Mean age: 57.7 ± 9.7 y; mean weight: 107.8 ± 20.8 kg; 72.4% male High-protein group: Mean age: 57.3 ± 10.1 y; mean HbA1c: $7.2 \pm 1.3\%$; BMI: 36.2 ± 7.1 kg/m²; Total cholesterol: 160.2 ± 41.9 mg/dL	3- month A: High-protein diet (n=33); B: Standard-protein diet (n=43) A: 30% protein, 40% carbohydrates, and 30% fat. B: Standard-protein diet: 15% protein, 55% carbohydrates, and 30% fat. A&B: Received consultation and support from a licensed dietician at 2, 4, 8, and 12 weeks	BMI values: Both diets were equally effective in reducing BMI values, but the high-protein group reduced more by 1.5 kg/m² reduction from the baseline compared to the standard-group only by 1.0 kg/m² [$P = 0.067$]. HbA1c values: High-protein group reduced significantly by 0.7% compared to standard-protein group only by 0.1% [$P = 0.002$]. Total cholesterol: The high-protein group significantly reduced by 16.8 mg/dL compared to the standard-protein group reduced by 0.9	No adverse effect was reported.

		Standard-protein group: Mean age: 58.0 ± 9.6 y; HbA1c: $7.3 \pm 1.8\%$; BMI: 37.3 ± 5.4 kg/m ² ; Total cholesterol: 163.7 ± 39.3 mg/dL	of the study; advised to exercise regularly.	mg/dL [P = 0.031]. Findings demonstrated that both high-protein and standard-protein diets effectively facilitated weight loss and the decrease of visceral fat. However, a high-protein diet portrayed a significant reduction in glycaemic control, lipid profile, and blood pressure.	
Wang, 2020	Case series study (China)	109 Initial participants (n=120); reason participant dropout not mentioned Age > 50 y; BMI: 29.20 ± 3.64 kg/m ² ; HbA1c: $8.94 \pm 1.92\%$; Fasting blood glucose: 11.22 ± 2.78 mmol/L; Oral hypoglycaemic drug/insulin (n=80)	3- month Lifestyle intervention: i) Changing the meal order: Vegetables, meat, eggs, and carbohydrates should be consumed in the following order, with no restrictions on the quantity or variety of carbohydrates. ii) Activity schedule adjustment: Increase the duration of indoor activities after meals such as household chores and slow walking from 30 min to 120 min. iii) Resistance exercise: squatting, standing on heels, standing on toes, resistance band exercise, and plank; 8 to 10 times for 3 to 5 times a week under guidance from a rehabilitation specialist. iv) Reverse abdominal breathing: Breathe in slowly via	BMI values: BMI reduced significantly by 0.68 kg/m ² after intervention [p<0.001]. HbA1c values: HbA1c reduced significantly by 0.88% after the intervention [p<0.001]. Fasting blood glucose values: Fasting blood glucose reduced significantly by 3.16 mmol/L after intervention [p<0.001]. Medication reduction: i) reduced approximately 40% to 60% from the original hypoglycaemic agent based on blood glucose (n=54); ii) tapered and discontinued within 3-months (n=5). No fluctuation in blood glucose after dose reduction and withdrawal.	No adverse effects were discussed in this study

			the nose while squeezing the abdomen, holding the breath for three to five seconds, and then breathe out slowly through the mouth while releasing the abdomen; After two to three rounds of regular breathing, the procedure was repeated, with 10 to 15 cycles per session and three to five times daily. The dosage adjustment is done for subjects who received hypoglycaemic drugs.		
Amer, 2020	Case series study (Saudi Arabia)	180 (43 male/115 female) Initial participants (n=180) (90 each group); At 6-month follow-up (n= 174); At 12-month follow-up; completed 18 months (n=28) Reason of drop out from study: loss to follow-up (n=62); poor compliance (n=55); missing data (n=35) Control group: Age 42.3 ± 11.3 years; BMI: 32.6 ± 5.8 kg/m²; Blood glucose levels: 6.0 ± 0.4 mmol/L; HOMA-IR: 4.1 ± 1.4. ILIG: Age 43.4 ± 7.8 y; BMI: 31.3 ± 6.4 kg/m²; Blood glucose levels: 6.1 ± 0.4 mmol/L; HOMA-IR: 4.3 ± 0.8	18- month A: Intensive lifestyle intervention (ILIG); B: Control group (CG). A: Strict lifestyle changes and personally tailored counselling by nutritionist: received 50%-60% carbohydrate, <30% fat of daily energy, > 15 g/1000 kcal fibre intake and moderate intensity exercise over 150 min/week or 30 min/day, aerobic exercise 30 mins five times/week; at lifestyle modification tailor for every 6-month interval; educational sessions regarding the effect of exercise on blood glucose regulation.	After 12-month intervention: BMI is significantly reduced by 0.7 kg/m² from the baseline in the ILIG group compared to the control group where no significant changes [p=0.07]. Glucose level is significantly reduced by 0.4 mmol/L from the baseline in ILIG compared to the control group [p=0.03]. HOMA-IR is significantly reduced by 0.5 from the baseline in ILIG compared to the control group [p=0.66]. Reversion to normoglycemia: ILIG has a significant incidence of revision compared to the control group where 38 participants (52.1%) reverted to normal status in ILIG group [p=0.02]. After 18-month intervention: Reversion to	No adverse effects were discussed in this study

			B: Received booklets and pamphlets that contain information regarding prediabetes and its prevention. A&B: Education: educate individually about T2DM risk factors, its pathogenesis, and the role of dietary restriction with increased physical activity to delay the progression of T2DM; advised to change lifestyle by a healthy diet and good exercise; educational session every 3 months to emphasise the importance of lifestyle changes in preventing T2DM.	normoglycemia: ILIG reversed 12 patients from 17 patients to normoglycemic and none developed T2DM. Control group: 5 patients out of 11 achieved normoglycemia and 2 developed T2DM. ILIG has better conversion remission compared to the control group [p=0.18].	
Samkani, 2018	Case series study (Denmark)	16 (14 male/2 female) No participants dropped out of the study. Mean age: 65 (43-70) y; BMI: 30 ± 4.4 kg/m²; Median HbA1c: 6.5% (5.5–8.3 %); mean fasting plasma glucose: 8.2 ± 2.0 mmol/l; all treated with metformin monotherapy.	48- hour A: Carbohydrate-reduced high-protein (CRHP) diet; B: Conventional diabetes (CD) diet A: 31% carbohydrate, 29% protein, and 40% fat; higher vitamin D and Ca content B: 54% carbohydrate, 30% fat, and 16% protein; higher fibre content Washout period: 2- to 8 weeks between interventions.	Fasting plasma glucose, insulin, and C-peptide: No differences between the intervention days. Peak glucose concentration: CRHP diet reduced peak glucose concentration significantly after breakfast by 18% (2.1 ± 0.3 mmol/L) [P<0.0001] and by 15% (1.5 ± 0.3 mmol/L) after lunch [P<0.001] compared to CD diet. Peak serum insulin concentrations: After breakfast, the CRHP diet decreased peak serum insulin concentration by 24% (106 ± 45 pmol/l) [P=0.032] and by 21% 90 ± 41 pmol/l [P=0.043] after lunch compared to the CD diet. Peak serum C-peptide concentration: CRHP diet declined peak serum C-peptide	No adverse effect was reported.

				concentration by 24% (713 ± 146 pmol/l) [$P < 0.001$] after breakfast and reduced by 23% (686 ± 179 pmol/l), [$P = 0.002$] after lunch compared to CD diet. Peak Insulin Secretion Rate (ISR): The CRHP diet decreased peak ISR by 23 % (2.3 ± 0.5 pmol/kg per min) [$P < 0.001$] and 26 % (2.6 ± 0.6 pmol/kg per min) [$P < 0.001$] after ingestion of breakfast and lunch, respectively compared to CD diet.	
Dave, 2019	Case series study (India)	45 (30 male/15 female); mean age: 45.1 ± 10.2 y; mean HbA1c: $9.4 \pm 2.5\%$; BMI: 28.9 ± 4.8 kg/m ² ; duration of T2DM: <1 year (n=26), 5 years (n=17), 10 years (n=2); glucose-lowering medication: 43	5-year Lifestyle intervention (LSI) i) Dietary counselling: personalised, individualised, and tailored meal plans according to ADA guidelines ii) Exercise counselling: Increase daily activity and follow a tailored exercise regimen minimum duration of 45 minutes, six days per week ii) Education and monitoring: educate on how to utilise self-monitor fasting blood sugar (FBS) and postprandial blood sugar twice weekly; hypoglycaemia management and awareness of the ADR medication prescribed.	Mean weight loss: significant weight loss observed at one-year intervention compared to after 5 years. Compared to the baseline, after one year of intervention reduced by 7.6 kg while 5 years of intervention reduced by 6.4 kg. Mean HbA1c values: Reduced to $6.0 \pm 0.5\%$ after year one and $6.5 \pm 1.2\%$ at year five. Drop significantly at year one compared to year 5 intervention in all participants. Remission of T2DM: 53.3% (n=24) achieved partial remission and 17.8%(n=8) reached complete remission after one year of intervention. In year five, 26.8% (n=11) of participants achieved partial remission. In comparison, complete remission was sustained by 19.5% (n=8) participants. Glucose-lowering medication reduction: Participants (n=12) treated with three or more oral hypoglycaemic agents (OHAs) have the least chances of achieving T2DM remission; All	No adverse effect was reported.

				participants (n=3) received insulin stopped at the end of year one and year 5.	
Dixit, 2022	Case report (India)	5 Males Duration of T2DM: <1 year (n=2), 1 year (n=1), <5 years (n=2); Range of initial HbA1c: 6.6-12.9%; Glucose-lowering medication (n=1); Ayurvedic medication (n=1); no medication (n=3)	3-month Dietary regimen: 2-OMEX lifestyle modification (meal frequency limitation); received only 2 meals in a day. Exercise routine: Walk at least 4.5 km in 45 minutes daily.	HbA1c values: All patients experienced significant HbA1c reduction to normal values within 3 months; Range of final HbA1c values: 5.7%-6.7%. Medication status: All participants (n=5) discontinue medication within a month.	No adverse effect was reported.
Dagogo-Jack, 2022	Cohort study (America)	223 12 participants from the lifestyle intervention group withdrew from the study; died due to unrelated reasons from this study (n=1) Age: 53.3±9.28 y; BMI: 30.6±6.70kg/m ²	5- year A: Normal glycaemic control group (n=72); B: lifestyle intervention group (prediabetic group) (n=151) A: Passive follow-up B: lifestyle intervention: Counselling session by dietitians: 1) Increased physical activity: moderate-intensity physical activity for 180min/week. 2) weight-based calorie reduction: baseline weight <113.4 kg: restrict calorie intake to 1200–1500 kcal/day (40–50g fat); baseline weight ≥113.4kg: restrict calorie intake to	After 5 years of intervention, participants experienced a decrease in body weight, waist circumference, total fat mass, and trunk fat mass. However, the control group demonstrated an increase in adiposity measures. Mean weight loss: Lifestyle intervention participants reduced by 2.91±6.56kg. Exercise: Less weight loss experienced in 50 min per week or less of physical activity compared to higher exercise activity, but the difference is not statistically significant. Fasting Plasma Glucose values: The lifestyle intervention group reduced by 7.76 ± 10.8 mg/dL compared to the control group which the values is increased slightly by 23 ± 1.43 mg/dL [p=0.0008]. Reversal of T2DM: 2.8% (n=59) reversed from pre-diabetes to normoglycaemic, 50% (n=69)	No adverse effect was reported.

			1500–1800 kcal/day (50–60g fat) Categorised by the pre-diabetes duration before the intervention: 1) < 3 y (n=32) 2) 3-5 y (n=59) 3) >5y (n=47)	maintained in pre-diabetes, and 7.2 (n=10) % progressed to T2DM.	
Goyal Mehra, 2022	Cohort study (India)	150 mean age: 50 y; HbA1c 6.5%-14% Intervention group: mean weight: 76.7 kg; mean HbA1c: 9% ±1.5%	90- day A: Control group B: Sugar. Fit Diabetes Reversal Programme (SDRP) program: personalized intervention program, progressive fitness, and behavioural modification specialized coaches, and nutrition experts. Categorized into age groups: i) 20-35 years (17%) ii) 36 and 50 years (49%) iii) 51 and 65 years (26%) iv) 66 and 80 years (8%)	Mean HbA1c values: Reduced by 1.9% in the SDRP group while increased slightly by 0.05% from the baseline in the control group. Age group 20-35 experienced the greatest reduction (reduced by 2.5%) compared to other age groups. Fasting plasma glucose values: mean fasting plasma glucose reduced significantly by 62.2 ± 51.8mg/dL in the SDRP group while the insignificant drop in the control group by 1.42±25.3mg/dL. SDRP: effective for lowering HbA1c, FBS, and weight in T2DM, and participants between the ages of 20 to 35 had superior results.	No adverse effect was reported.

DISCUSSION

In this systematic review, 12 articles were shown to have information regarding the effectiveness of diet and exercise in reversing T2DM. However, only a few of the articles explored the effects of diet and exercise in patients with long-duration T2DM. Besides, all reviewed articles only include participants with a T2DM duration of fewer than 10 years. Furthermore, only a few studies discussed the same types of diet and exercise interventions, making various types of diet and exercise available in this review. Consequently, the included studies only evaluated the remission of shorter-duration T2DM patients with different approaches of diet and exercise.

Existing reviews suggested diets including low carbohydrate, high protein, very low calorie, 2-OMEX, and diet according to ADA guidelines were able to reverse T2DM as a significant reduction in HbA1c, fasting blood glucose, weight loss and BMI achieved. However, there was an exception in one RCT study by Ried-Larsen et al. (2019) where the HbA1c, fasting plasma glucose, and BMI values were increased after 24 months of follow-up from baseline assessments suggesting a lack of compliance with the prescribed diet. The increased HbA1c values showed that there is no remission or reversibility of T2DM achieved in this study. According to Peng et al. (2021), we can determine that T2DM remission rates were higher in those with shorter T2DM durations and greater weight loss. This is due to the factors of lower severity of T2DM progression in short-duration T2DM patients and hence easily achieved remission. They also mentioned in a study that the chances of achieving partial T2DM decreased with time since diagnosis (Karter et al., 2014).

Different dietary interventions were discussed in the reviewed articles. Most studies focus on the reduction of HbA1c as it is the hallmark of reversing T2DM. Discussing low-carbohydrate diet intervention, (Han et al., 2021) described how a low-carbohydrate environment can maintain low blood glucose levels and eventually reverse T2DM. The study defined low-carbohydrate diets as 14% carbohydrate intake, 28% protein, and 58% total fats. The percentage of carbohydrate intake was defined differently from other studies. The research (Oh et al., 2019), defined low carbohydrates as less than 26% carbohydrate intake while a study by van Zuuren et al., (2018) defined low carbohydrates as $\leq 40\%$ carbohydrates. Even when the low-carbohydrate diet was defined differently, the reviewed study implied the percentage of carbohydrates according to the range.

Low-carbohydrate diets effectively reduced HbA1c, fasting plasma glucose, weight loss, and BMI values based on the reviewed article. They suggested a low carbohydrate environment will lower the demand for insulin-mediated glucose disposal as T2DM is highly related to increased insulin secretion due to impaired insulin metabolism. Besides, it also suggested that carbohydrate restriction will reduce the intestinal absorption of monosaccharides which then leads to a reduction in blood glucose and reduced fluctuation in blood glucose (Han et al., 2021). It is consistent with the study by (Snorgaard et al., 2017) that stated the low carbohydrate diet was able to reduce HbA1c values in the participant compared with standard high carbohydrate diets. It also mentioned that a low carbohydrate diet reduced the greater extent of glucose levels and postprandial excursion compared to high carbohydrate diet groups. To conclude, a low carbohydrate diet was more pronounced to control blood glucose most effectively, lower body weight, and maintain the anti-glycaemic MES if the participants adhere to the diet.

Next, a high-protein diet and carbohydrate-reduced high-protein (CRHP) diet was the second most intervention discussed in the reviewed articles (Skyttee et al. 2019; Evangelista, 2021; Samkani, 2018). CRHP diet to a greater extent reduced the HbA1c values compared to the control groups. Protein plays a vital role in controlling glucose, regulating insulin, and reducing weight and visceral fat. It was also mentioned in a study (Evangelista, 2021) to be effective in increasing metabolism and satiety hormone secretion. It is suggested in other reviewed studies (Skyttee et al. 2019) that a greater reduction of HbA1c in the CRHP diet was due to persistent postprandial blood glucose levels. They also hypothesised that higher content of fat present in a CRHP diet leads to a decrease in gastric emptying and eventually reduces the rate of glucose going to circulation. Samkani et al. (2018) reported that β -cell glucose sensitivity (β -GS) improved in the CRHP diet which is highly related to T2DM remission due to higher protein proportion in the CRHP diet and due to glucagon response. Besides, the satiety score was increased in correlation with the increased release of CCK that was stimulated by high fat and protein content in the dietary intake. The same finding was found in the RCT study in which all participants in the high-protein diet group (n=6) resulted in the remission of T2DM to normal glucose tolerance after 6 months of intervention (Stentz et al., 2022). Thus, a high-protein diet to a greater extent promotes significant weight loss and the consequences are reduced HbA1c values.

Furthermore, intermittent very-low-calorie diet (VLCD) and diet restriction were one of the interventions mentioned in the reviewed articles (Umphonsathi, 2021; Dagogo-Jack, 2022). Both diet interventions show significant diabetes reversal after prescribed lifestyle intervention. Intermittent VLCD intervention effectively improved glycaemic control as one-third of the participants achieved diabetes reversal. This is because intermittent VLCD effectively maintains weight loss and this intervention is suitable for an obese patient who is not able to adhere to continuous VLCD (Umphonsathi, 2021). In comparison with the study by Dagogo-Jack (2022), the dietary intervention was weight-based calorie restriction. The same finding was found that fasting plasma glucose both in the short-duration T2DM and long-duration group in the 8-week very-low-calorie diet declined significantly [$P < 0.001$]. This study (Steven & Taylor, 2015) concluded that over time fat levels in the liver and pancreas would decrease with negative calorie balance, and liver insulin sensitivity and β -cell insulin secretion would return to normal as a result.

The remaining studies (Dave et al., 2019; Amer et al., 2020; Goyal Mehra et al, 2022) utilised, personalised and customised dietary based on participant requirements. All studies reported effective improvements in all parameters including weight loss, HbA1c values, and fasting plasma glucose. Other studies (Jung & Choi, 2017) stated that personalised carbohydrate consumption should be considered, and maintaining a low-calorie intake is still essential for increasing insulin sensitivity and lowering body weight. In addition, in the reviewed studies (Amer et al., 2020) higher participants in Intensive lifestyle intervention (ILIG) changed to normoglycemic from pre-diabetes rather than in the control group. The author suggested the prevention of prediabetes progression in the intervention group due to changes in modified risk factors including body weight, diet, and exercise. As T2DM is very highly genetically variable, a personalised diet approach is suggested to be effective.

In addition to dietary intervention, exercise also contributes to achieving T2DM remission. Most reviewed studies mentioned the results of the exercise were parallel with dietary intervention.

However, there is an exception in two studies (Samkani, 2018; Skytte, 2019) where no exercise interventions were discussed. Other studies discussed exercise intervention differently from general to intensive exercises such as resistance, moderate-intensity aerobic, and advised and educated increased physical activity. According to research (Ried-Larsen, 2019), exercise reduces inflammatory pathways linked to pancreatic β -cell dysfunction and enhances glycaemic control. Besides, remission of diabetes is associated with the amount of weight loss that was sustained after 12 months (Umphonsathien et al., 2021). This is supported by other findings which stated that increased physical activity is an indicator of T2DM remission (Peng et al., 2021).

CONCLUSION

In summary, the findings from the comprehensive review underscore the effectiveness of diet and exercise as pivotal strategies for the reversal of Type 2 Diabetes Mellitus (T2DM). A diverse array of dietary and exercise interventions were investigated, revealing a robust trend towards positive outcomes. Notably, a synthesis of twelve studies highlighted a statistically significant impact in T2DM reversal through the implementation of diet and exercise regimens. The collective data extraction demonstrated a compelling reduction in HbA1c levels, eventually bringing them within the normoglycemic range, thereby achieving T2DM remission. Furthermore, a pronounced and consistent achievement was observed in substantial weight loss and a notable reduction in medication dependence across the majority of the studies. These combined results provide compelling evidence for the efficacy of diet and exercise in the context of T2DM reversal. Yet, a critical consideration emerges regarding the limited temporal scope of the studies, impeding a comprehensive assessment of the long-term sustainability of the observed effects. Furthermore, the enduring implications of abrupt metabolic shifts warrant further elucidation, as these aspects were not consistently addressed in the existing research. As a result, a pressing need for future investigations arises, specifically focused on establishing the enduring effectiveness of sustained diet and exercise interventions in T2DM reversal.

In conclusion, while the current body of research underscores the potency of diet and exercise in reversing T2DM, the lack of longitudinal evaluation and clear insight into the lasting metabolic implications necessitates further inquiry. Subsequent studies that embrace extended durations and more comprehensive metabolic assessments are indispensable for refining our understanding of the enduring impact of diet and exercise in the context of T2DM reversal. Thus, future research is suggested to assess the long-term effectiveness of diet and exercise in reversing T2DM.

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