Clinical Nutrition Guidelines

Chinese Guidelines for Medical Nutrition Therapy for Patients with Diabetes (2022 Edition)

Nutrition and Metabolic Management Branch of China International Exchange and Promotive Association for Medical and Health Care, Clinical Nutrition Branch of Chinese Nutrition Society, Chinese Diabetes Society, Chinese Society for Parenteral and Enteral Nutrition, Chinese Clinical Nutritionist Center of Chinese Medical Doctor Association

Medical nutrition therapy (MNT) is the foundation of the comprehensive treatment of patients with diabetes. In 2010, the Chinese Clinical Nutritionist Center of the Chinese Medical Doctor Association developed the first Chinese guideline on MNT for patients with diabetes, and it was updated in 2015. Since then, new evidence has emerged in the field of MNT and metabolic therapy in patients with diabetes. The Nutrition and Metabolic Management Branch of the China International Exchange and Promotive Association for Medical and Health Care organized a team of experts from related institutions, including the Clinical Nutrition Branch of the Chinese Nutrition Society, Chinese Diabetes Society, Chinese Society for Parenteral and Enteral Nutrition, and Chinese Clinical Nutritionist Center of the Chinese Medical Doctor Association. Their task was to develop the *Chinese Guidelines of Medical Nutrition Therapy in Diabetes (2022 Edition)* in accordance with the requirements of the *Guidelines for the Formulation/Revision of Clinical Guidelines in China (2022 Edition)* by combining the questions raised and evidence gathered in clinical practices in China, to guide and standardize the clinical MNT.

Key Words: diabetes, medical nutrition therapy, dietary pattern, nutrition support, prediabetes

FOREWORD

The incidence of diabetes has increased at a phenomenal rate over the past 50 years. The International Diabetes Federation in 2019 reported that 463 million people worldwide have diabetes,[1] and the prevalence of maturity-onset diabetes in China has reached 11.2%.[2]

Medical nutrition therapy (MNT) is essential for the prevention and control of diabetes at any stage. Since the American Diabetes Association (ADA) first issued the *Principles of Nutrition and Dietary Recommendations for Patients with Diabetes Mellitus* in 1971,[3] the principles of individualized nutrition therapy for diabetes have been regularly updated.

In 2010, the first Chinese guideline on MNT of diabetes was developed by the Chinese Clinical Nutritionist Center of the Chinese Medical Doctor Association in conjunction with the Chinese Diabetes Society and was updated in 2015.[4] The Nutrition and Metabolic Management Branch of the China International Exchange and Promotive Association for Medical and Health Care initiated the revision of the *Chinese Guidelines of Medical Nutrition Therapy in Diabetes* by organizing experts from the Clinical Nutrition Branch of the Chinese Nutrition Society, Chinese Diabetes Society, Chinese Society for Parenteral and Enteral Nutrition, and Chinese Clinical Nutritionist Center of the Chinese Medical Doctor Association. In accordance with the requirements of the methodology, the branch collected evidence and graded their quality and recommendations (Tables 1 and 2) and also completed the international registration of this guideline by referring to the *Guidelines for the Formulation/Revision of Clinical Guidelines in China (2022 Edition)*[5] and formulated the *Chinese Guidelines of Medical Nutrition Therapy in Diabetes (2022 Edition)*. Each section of this guideline is organized by the basic framework of "Background - Questions - Recommendations - Brief Description of Evidence".[4,6] When the benefits of an intervention outweigh the risks, and the intervention is economically affordable, the intervention is "strongly recommended"; when the benefits are diminished, or the risks increased, the intervention is downgraded to "weakly recommended"; and, conversely, when the risks outweigh the benefits or the benefits are minimal and the economic burden is significant, the intervention is either "strongly not recommended" or "not recommended."

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Manuscript received 29 April 2024. Initial review and accepted 05 May 2024.
doi: 10.6133/apjcn.202406_33(2).0001

Table 1. Information on evidence searches

Information on literature searches	Specific description
Time of literatures	January 1, 2000, to December 31, 2021
Languages	English, Chinese
Databases	Primary databases include Medline, EMBASE, Web of Science, China Biology Medicine disc, etc. Secondary databases include Guideline Clearing House, Cochrane Library, Sum Search, etc.
Screening item	Human
Publication type of literatures	Guideline, meta-analysis, system review, randomized controlled trial, observational study, case report, consensus opinions
Key search terms	diabetes, nutrition, in each chapter, the search terms of related fields are further determined according to the contents

Table 2. GRADE system for grading the strength of evidence and recommendations

Grades	Specific descriptions
High (A)	There is a high level of confidence that the estimated effect size is close to the true effect size and that further research is unlikely to change the confidence level of the estimated effect size.
Medium (B)	There is a medium level of confidence in the estimated effect size, which may be close to the true effect size, but there is still a possibility that both effect sizes are not the same and that further research may change the confidence level of the estimated effect size.
Low (C)	There is a limited level of confidence in the estimated effect size, which may be entirely different from the true effect size, and further research is necessary to change the confidence level of the estimated effect size.
Very low (D)	There is little confidence in the estimated effect size, which is likely to be completely different from the true effect size, and any estimate of the effect size is highly uncertain.
Strongly recommended	Presence of clear indications that the benefits of the intervention outweigh the risks, or the risks outweigh the benefits.
Weakly recommended	The benefits and risks are uncertain, or the evidence, regardless of quality, shows equal benefits and risks.

GRADE refers to the evaluation, formulation, and assessment of grading recommendations

CHAPTER 1: OVERVIEW OF MEDICAL NUTRITION THERAPY

MNT is an individualized nutrition prescription established in line with the patient's medical conditions, lifestyle, and personal factors. It is an indispensable part of the treatment of diabetes, involving nutrition assessment, diagnosis, intervention, and continuous monitoring designed to support changes in long-term lifestyle and modify the interventions as needed.[7, 8] The discovery of insulin as early as 1921 prompted an increase in the amount of carbohydrates in the diabetic diet from 2 to 35% to 40% of the energy supply ratio. After 1970, increased cardiovascular mortality in patients with diabetes led to a 10% decrease in the recommendations for fat intake and an increase in the recommendations for carbohydrates to 55% to 60%.[9] Since 2006, an emphasis on individualized MNT for patients with diabetes has emerged.[10]

In patients with T2DM, intensive lifestyle interventions can reduce the weight of obese individuals.[11] The UK DiRECT study suggested that nutritional interventions in overweight/obese patients with T2DM with strict calorie restriction resulted in a weight loss of at least 15 kg in 24% of patients at one year.[12] In Chinese community-based patients with T2DM who received intensive nutritional management for diabetes for 1-year, significant improvements in fasting blood glucose and HbA1c levels were observed in the intervention group.[13] A systematic review of individualized nutritional interventions for glucolipid metabolism in T2DM involving a total of 928 patients from eight randomized controlled trials (RCTs) indicated that nutritional interventions were effective in improving fasting blood glucose (FBG), postprandial blood glucose (PBG), and insulin resistance index.[14]

These findings showed that the intensive intervention group experienced significant improvements in systolic and diastolic blood pressure, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and urine albumin-creatinine ratio compared to the control group at one year, and the proportion of patients with concomitant blood glucose, lipid, and blood pressure compliance was 23.6%, compared with only 16.0% in the control group.[15] The ability of MNT to significantly improve waist circumference, total cholesterol, and systolic blood pressure has been demonstrated.[16] Similarly, MNT contributes to the cost-effectiveness of comprehensive treatments for diabetes.[17, 18]

CHAPTER 2: EFFECT OF NUTRITION-RELATED ELEMENTS IN NUTRITION THERAPY ON DIABETES

Calorie

The appropriate intake of calories is the basis for preventing the development of diabetes and nutritional therapy for T2DM. The appropriate intake of calories in T2DM depends on multiple factors and needs to be individualized. Calorie-restricted diets are one of the dietary interventions for diabetes. Depending on the degree of restriction, such diets are categorized as low-calorie diets (LCD) and very low-calorie diets (VLCD). In general, LCD refers to a diet with calorie intake controlled in the range of 800–1500 kcal/d, and VLCD refers to a diet with total calorie intake controlled at < 800 kcal/d. These diets

are also divided into short-term (<9 days) or long-term calorie-restricted diets based on the duration of restriction.

Diets can be further categorized as intermittent energy restriction (IER) and continuous energy restriction (CER). On diet-restricted days of IER, calorie supply is typically 0% to 25% of the normal demand (< 800 kcal/day). Compliance with IER in a brief period can reach 93%.[19] Patients who are overweight or have obesity presenting with T2DM should be guided by their healthcare professionals for IER, and particular attention should be paid to the adjustment of medication, frequency of glucose monitoring, and fluid intake.[20]

Q1: What is the appropriate caloric range for patients with diabetes?

Patients with diabetes should receive the individualized calorie balance plan to achieve or maintain the ideal body weight while meeting nutritional needs under different circumstances (B, strongly recommended)

It is recommended that calorie intake be calculated using a universal coefficient method based on 25–30 kcal/kg IBW per day and then adjusted to the individualized calorie criteria based on height, weight, sex, age, activity level, and stress status (Table 3).[2, 21]

Q2: Does LCD/VLCD help in glucose management in T2DM?

1. LCD contributes to the weight and glucose management in overweight/obese patients with diabetes in the short term (< 1 year) (A, strongly recommended)
2. VLCD can help improve FBG, HbA1c, insulin resistance, body weight, and other indicators in T2DM in the short term (C, weakly recommended), but the long-term application of VLCD is not recommended due to the potential for complications such as hypoglycemia (C, strongly recommended)

The results of several RCTs have shown that 4-week to 1-year of interventions with LCD at 800–1100 kcal/day resulted in significant reductions in body weight, FBG, HbA1c, and type and dose of medication in patients who are overweight/obese with T2DM[22-32] without significant adverse effects. The findings of six short-term (≤ 9d) small-sample observational studies indicated that weight, waist circumference, FBG, TG, insulin resistance index, and other indicators were significantly reduced in patients who were overweight/obese with T2DM after VLCD interventions and remained stable during the 3-month follow-up period.[33-38] Three studies of patients who were overweight/obese with T2DM with sample sizes ranging from 11 to 30 provided VLCD interventions for eight weeks and discontinued antidiabetic drugs, resulting in significant reductions in body weight, FBG, and HbA1c.[39-41]

Li Chunrui et al.[34] conducted a 9-day VLCD on 20 patients with T2DM with a body mass index (BMI) of (25.91 ± 2.83) kg/m^2, and 21 hypoglycemia events in 9 cases, with the lowest glucose being 3.1 mmol/L, and six hypoglycemia events occurred on Day 6 of the VLCD. Hyperuricemia events occurred in 16 cases, with mean value of uric acid increased from 322.20 μmol/L to 547.40 μmol/L, and the uric acid began to decrease in 14 cases at the end of the diet restriction and decreased to normal in three cases.

Q3: What is the effect of IER/CER on glucolipid metabolism and body weight in patients with T2DM?

Both IER/CER are favorable for blood glucose and weight management in overweight/obese patients with T2DM, with IER being more favorable than CER for weight management (B, weakly recommended)

A meta-analysis in 2021 included seven studies of 338 patients with T2DM with BMI > 35.65 kg/m^2 and showed that both the IER and standard diet groups were effective in improving blood glucose, with IER being more favorable in weight management.[42] For obese patients with T2DM with a BMI of (35.2 ± 5.0) kg/m^2, calorie intake was 400–600 kcal/day in the IER group and 1100–1500 kcal/day in the CER group on diet-restricted days, with results suggesting that both IER and CER were beneficial for blood glucose/weight management, but no difference was observed between the two groups in the long-term.[43-5] Meta-analysis results showed a similarity between IER and CER dietary patterns in improving fasting insulin, lipids, and hypoglycemia, but IER was more advantageous in terms of weight management.[46]

Carbohydrates

Q4: What are the effects of carbohydrate intake on the control of blood glucose and insulin levels and the risk factors for complications?

A daily carbohydrate energy supply ratio of 45% to 60% is appropriate for diabetes (B, strongly recommended). Carbohydrate-restricted diets are beneficial for blood glucose control in T2DM in the short term (within one year), achieving slight improvements in TG and HDL-C levels, with no identified long-term benefits (B, weakly recommended). Very low-carbohydrate diets are not used for patients with type 1 diabetes mellitus (C, strongly recommended)

A meta-analysis that included 25 RCTs with a total of 2,421 participants showed that significant reductions in HbA1c could be achieved at 3 and 6 months with the low-carbohydrate diet (< 26% energy supply ratio). However,

Table 3. Daily calorie supply for adults with diabetes [kJ/kg (kcal/kg)]

Intensity of labor activities	Underweight	Normal weight	Overweight/obese
High-intensity physical activities (e.g., porters)	188–209 (45–50)	167 (40)	146 (35)
Medium-intensity physical activities (e.g., motorized installation)	167 (40)	125–146 (30–35)	125 (30)
Low-intensity physical activities (e.g., sitting work)	146 (35)	104–125 (25–30)	84–104 (20–25)
Resting state (e.g., bedridden)	104–125 (25–30)	84–104 (20–25)	62–84 (15–20)

after months 12-24, the difference in the effect on glucose was not statistically significant when compared to the balanced diabetic diet with a carbohydrate energy supply ratio of 45%–60% (e.g., including glycemic index [GI] balanced diets, or ADA recommended diets.[47]

In a meta-analysis that included 25 RCTs, only 7 of the 17 related studies demonstrated improvement in lipids.[48] Another meta-analysis that included 33 RCTs and three clinical studies showed that only 5 out of 20 relevant studies reported significant reductions in TG levels, ranging from 0.1 to 1.6 mmol/L.[49]

A meta-analysis that included 23 RCTs with a total of 1,357 participants found no significant difference in quality of life at six months for those on low-carbohydrate diets compared to those on low-fat, low-GI, or Mediterranean diets. However, the quality of life and levels of low-density lipoprotein cholesterol (LCD) were worse after 12 months.[50] In a systematic review investigating adults and children with type 1 diabetes mellitus (T1DM), a carbohydrate-restricted diet was provided for two weeks to compare HbA1c levels, severe hypoglycemic events, and total daily insulin dosage. The results indicated that those with significant improvements in HbA1c were comparable to those without significant changes, the overall effect of which cannot yet be evaluated, and VLCD is not recommended in view of possible safety concerns.[51]

Q5: Do different food sources of carbohydrates have any effect on the control of blood glucose, insulin levels, and complications and their risk factors?

Replacing part of refined grains with whole grain carbohydrates favors the control of blood glucose, TG, and body weight (B, strongly recommended)

An RCT that included 287 patients with T2DM found that low-fat and high-fiber diets achieved significant improvements in FBG, TG, and body weight compared with those in the control group.[52] Another RCT that included 185 patients with T2DM suggested that replacing staple foods with whole grains and legumes (polished rice replaced with 1/3 mixed beans, 1/3 barley, and 1/3 whole grains, three times/day) reduced TG levels by affecting lipoprotein gene expression, producing protective effects on glycemic control and lipid metabolism in T2DM.[53]

Q6: What is the effect of the content and source of dietary fiber (non-supplemental or additional) on glycemic control and complications?

Diets high in dietary fiber (25 - 36 g/day or 12 - 14 g/1000 kcal), especially those that ensure soluble dietary fiber intake (10 - 20 g/day), contribute to the control of blood glucose and reduce all-cause mortality in patients with T1DM and T2DM (B, strongly recommended)

The addition of dietary fiber prolongs gastric emptying time in patients with diabetes, delays glucose digestion and absorption, and improves PBG metabolism and long-term diabetic control. Twenty-eight T1DM patients with a mean age of (28.2 ± 9.5) years were separated into high-fiber diet and low-fiber diet groups, with dietary fiber intake of 36.7 ± 9.4 and 15.4 ± 3.6 g/day, respectively, and the long-term viability of the diets in the high-fiber diet group was identified. The improvement of blood glucose levels and the reduction in the number of hypoglycemic events were seen in comparison to those in the low-fiber diet group after eight weeks of interventions.[54] In a cohort study of 2,108 patients with T1DM, the population was equally divided into three groups according to the amount of total dietary fiber, soluble and insoluble dietary fiber in the diets, the group with the highest intake of total dietary fiber, and the group with the highest intake of soluble dietary fiber had significantly reduced incidence of cardiovascular disease and all-cause mortality relative to the group with the lowest intake.[55] Similarly, a European T2DM cohort study with an average follow-up time of 9.2 years divided the population by total dietary fiber intake into quartiles and found that the group with the highest dietary fiber intake had a significantly reduced risk of death compared to the group with the lowest intake.[56]

Q7: What are the effects of specific carbohydrates (sucrose and fructose) on the control of blood glucose and insulin levels?

Routine sucrose addition is not recommended. The isoenergetic replacement of part of the dietary carbohydrates with sucrose (30–50 g) / increase in carbohydrates had no effect on glycemic control or insulin sensitivity (C, weakly recommended). The isoenergetic replacement of carbohydrates with high doses of additive fructose (> 50g) has an increased risk of TG (C, weakly recommended)

Clinical studies have demonstrated that the magnitude of the blood sugar increase due to sucrose is no greater than that caused by isoenergetic starch. In normal-weight or overweight patients with T1DM, the isoenergetic replacement of part of the dietary carbohydrates with sucrose (27.3 ± 13.5 g) produced no effect on insulin requirements, anthropometric index, body composition, lipids, and blood glucose but increased C-reactive protein level.[57] A UK study in overweight patients with T2DM found that an additional 50 g of sucrose per day did not affect glycemic control or insulin sensitivity, but the intake of other nutrients (e.g., fat) accompanying the consumption of sucrose should still be considered, with care being taken to avoid excessive calorie intake; therefore, the routine addition of sucrose is not recommended for patients.[58] A meta-analysis of T1DM and T2DM identified a 50 g threshold for the effect of replacing sucrose, glucose, or starch with isoenergetic fructose (20–160 g/day) on lipids and body weight, and that excessive amounts could lead to significant increases in TG levels.[59-63]

Fat

Q8: What is the recommended total daily dietary fat and all types of fatty acids for patients with T2DM?

Energy from the recommended total daily dietary fat accounts for 20%–35% of the total energy. It should be emphasized that the quality of fat outweighs its proportion, and restrictions on the intake of both saturated fatty acids and trans-fatty acids are required. It is recommended that the intake of saturated fatty acids not exceed 12% of the total energy, that the intake of trans-fatty acids not exceed 2%, and that polyunsaturated and monounsaturated fatty acids should be increased appropriately to replace part of the saturated fatty acids (B, strongly recommended)

Recommendations should be individualized based on metabolic targets, comorbidities, dietary patterns, and dietary preferences.[64] At the international level, it is now generally recommended that the total fat energy supply ratio be 20%–35%, and it should be emphasized that the quality of fat takes priority over quantity. It is recommended that partially saturated fatty acids (SFA) be replaced with polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA). In countries following the Mediterranean diet, up to 40% of fat energy in the diet is derived from MUFA, with no adverse effects on metabolic results.[65, 66] Researchers have found that a higher SFA intake within a specific range does not increase the risk of major cardiovascular diseases and death, and the median high SFA intake in Asia in this study was 12.1%.[67] Therefore, it is recommended that the energy supply ratio of SFA should not exceed 12%. Studies have revealed that isoenergetic replacement of 5% SFA with PUFA and MUFA reduced the risk of coronary heart disease by 25% and 15%, respectively, whereas a 2% increase in the energy supply ratio of trans-fatty acids increased the risk of cardiovascular disease by 16%.[68, 69] Wang et al.[70] found that isoenergetic replacement of 5% SFA with PUFA and MUFA reduced overall mortality in the population by 27% and 13%. In addition, studies have shown that MUFA-rich diets are recommended in prediabetic populations complicated by fatty liver and in patients with T2DM.[71, 72]

Q9: Do patients with diabetes need to limit cholesterol intake?

Cholesterol intake in patients with T2DM should not exceed 300 mg/day (B, weakly recommended)

A meta-analysis based on 55 RCTs showed a dose-response relationship between dietary cholesterol intake and LDL-C, controlling for differences in fatty acid composition. A multiple regression model with controlled differences in SFA, MUFA, and PUFA showed that for every 100 mg/day increase in dietary cholesterol, LDL-C increased by 0.11 - 0.27 mmol/L, indicating a direct correlation between dietary cholesterol and LDL-C, suggesting that cholesterol intake in patients with T2DM should be no more than 300 mg/day.[73]

Q10: Is supplementation with ω-3 polyunsaturated fatty acid supplementation beneficial in T2DM?

The supplementation with ω-3 polyunsaturated fatty acids contributes to reducing TG levels in T2DM, but the effect on glycemic control is yet unspecified (B, strongly recommended)

A meta-analysis based on 23 RCTs showed that daily supplementation with 3.5 g ω-3 PUFA for an average of 8 weeks in patients with T2DM significantly lowered TG and very low-density lipoproteins but did not have a significant effect on FBG, HbA1c, and fasting insulin.[74] According to a intervention study conducted in China, daily supplementation with 3 g of ω-3 PUFA from animal and plant sources for patients with T2DM combined with dyslipidemia for six months significantly reduced blood TG and TC levels, whereas plant-based ω-3 PUFA improved blood glucose and HbA1c levels.[75] Supplementation with 3 g of ω-3 PUFA daily for 18 months for overweight/obese patients with impaired fasting glucose or impaired glucose tolerance (IGT) is effective in lowering blood glucose and slowing the progression of T2DM.[76] A 24-week supplementation with 520 mg of ω-3 PUFA daily for Mexican patients with T2DM achieved improvements in waist circumference, FBG, HbA1c, and lipid profiles, and increased insulin levels and insulin resistance index.[77]

Protein

Q11: What is the appropriate proportion of protein intake to the total calorie intake in patients with diabetes with normal renal function? Does increased protein intake help to control lipid and blood glucose levels?

Protein intake in patients with diabetes with normal renal function should be 15% to 20% of the total energy (B, strongly recommended). Short-term high protein diet benefits the weight, lipids, and glucose in overweight and obese patients with diabetes (B, weakly recommended)

Daily protein intake should be 15 - 20% of the total energy, as recommended in the *Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition)*.[2] A meta-analysis of 13 RCTs evaluated the effect of a 12-week high-protein diet (energy supply ratio > 25%) on lipid control in patients with T2DM and showed a reduction in TC and TG levels.[78] After a 6-month high-protein dietary intervention in 73 patients with T2DM, lipid distribution improved in both the intervention (35 %) and control (18 %) groups, but the concentration of ApoB was decreased more in the intervention group.[79] A meta-analysis of 18 RCTs showed that high-protein diets for four weeks to 24 months reduced TG levels in patients with diabetes compared to normal protein diets.[80] Another meta-analysis that included 21 RCTs showed better glycemic control in the high-protein diet group.[81]

Vitamins and trace elements

Q14: What is the effect of folic acid supplementation on patients with diabetes?

Folic acid supplementation may favor glucose homeostasis and reduce insulin resistance (C, weakly recommended)

A meta-analysis of 29 RCTs with 22,250 patients showed that interventions using folic acid supplementation alone or in combination with other B-vitamins reduced fasting insulin levels, and homocysteine (Hcy) changes correlated with FBG changes in 11 studies of 834 patients with diabetes.[82] Another meta-analysis that included 183 patients with T2DM from four studies showed that folic acid supplementation (5 mg/day) reduced total plasma Hcy levels and might show a trend toward improved glycemic control.[83] According to a meta-analysis that included a total of 21,081 patients with diabetes from 18 studies aimed at investigating the relationship between folic acid supplementation (0.15–15.00 mg/day) and diabetes, the FBG, insulin resistance, and insulin might be reduced due to the folic acid supplementation, but no significant effect on HbA1c, suggesting that folic acid might have potential benefits on insulin resistance and glycemic control.[84]

Q15: What is the effect of vitamin D supplementation in pre-diabetic and diabetic populations?

There is no evidence of the efficacy of vitamin D supplementation in delaying the onset of diabetes or lowering blood glucose levels in diabetic and prediabetic populations (C, weakly recommended). The supplementation with high-dose vitamin D can have a mild glucose-lowering effect under particular circumstances, but routine vitamin D supplementation for glucose-lowering is not recommended (B, strongly recommended)

Vitamin D levels are negatively correlated with blood glucose levels in patients with diabetes.[85, 86] A randomized, double-blind, placebo-controlled trial (2,423 patients) assessed the efficacy of oral vitamin D3 for the prevention of diabetes, and 508 patients were found to have developed diabetes, indicating that supplementation with vitamin D3 (4,000 IU/day) did not significantly reduce the risk of progression from pre-diabetes to diabetes.[87] A meta-analysis of 20 RCTs with a total of 1,270 patients suggested that vitamin D interventions did not have a significant effect on HbA1c and FBG levels, but inflammatory factors in the vitamin D supplementation group showed specific improvements.[88] Another meta-analysis that incorporated 20 RCTs with a total of 2,703 patients with diabetes also identified that vitamin D supplementation alone failed to improve FBG, HbA1c, and insulin levels; however, subgroup analyses showed that short-term supplementation with high-dose (> 2,000 IU/day) vitamin D had the potential to decrease the level of FBG in populations with vitamin D deficiency.[89]

Q16: How does combined supplementation with multivitamins and minerals affect T2DM development?

Combined supplementation with multivitamins and minerals may be beneficial for glucose and lipid metabolism in obese patients with T2DM, and its efficacy remains to be further investigated (C, weakly recommended)

According to a cross-sectional study of 300 patients with T2DM and 100 healthy controls, levels of multivitamins and minerals (vitamins A, C, and E, and zinc) were lower in the serum of patients with T2DM than in healthy participants. No less than six weeks of supplementation with multivitamins and minerals significantly increased levels of vitamins A and E in the serum while decreasing levels of FBG and HbA1c and potentially reducing complications.[90] Based on a 4-month RCT of 96 patients with T2DM, supplementation with zinc (22 mg/day) in combination with a vitamin-mineral complex (containing vitamins A, D3, and E, magnesium, manganese, copper, and selenium) lowered FBG, HbA1c, and lipid levels in patients with diabetes. In contrast, no improvement was observed in patients supplemented with the vitamin-mineral complex alone.[91] In a study of 20 obese individuals and 10 obese patients with T2DM, B-vitamins combined with selenium-chromium yeast were administered for four weeks of intervention, with results indicating that B-vitamins combined with selenium-chromium yeast might reduce insulin resistance, improve the disorders of glucolipid metabolism, and alleviate fat deposition in the liver without exerting significant effects on liver and kidney functions, and could be put into clinical application as a safe and effective means of metabolic regulation.[92]

Q17: Is chromium supplementation effective for diabetes?

Chromium deficiency may be associated with the development of diabetes mellitus, but there is no consistent evidence of the benefits of routine chromium supplementation for glycemic and lipid control in patients with diabetes (C, weakly recommended)

Chromium is an essential trace element and is the most vital component of glucose tolerance. A cross-sectional study (319 patients) indicated that serum chromium levels were lower in patients with diabetes than in those without diabetes.[93] A meta-analysis that included 13 RCTs with a total of 2,519 patients showed that chromium deficiency increased the risk of developing T2DM.[94] A meta-analysis that included 25 RCTs with a total of 1,641 patients with T2DM showed that supplementation with 150–1000 μg/day chromium or supplementation with 1.28–42.00μg/day chromium yeast was beneficial for glycemic and lipid control in patients with diabetes.[95] However, one meta-analysis that incorporated 10 RCTs with a total of 509 patients with T2DM revealed that supplementation with 42–1000 μg/day chromium preparations reduced HbA1c, but no improvement in FBG and lipid levels was observed.[96] In addition, another meta-analysis that pooled seven RCTs with a total of 387 patients with T2DM revealed that FBG might be reduced by supplementation with 400–1000 μg/day chromium, but HbA1c, lipid, and BMI were not affected.[97] The conclusions from these studies have not been agreed.

Sweeteners

Q18: How do nutritive sweeteners affect the control of blood glucose and insulin?

Short-term intake of small doses of fructose sweeteners or allulose did not elevate postprandial glucose levels in adults with T2DM (D, weakly recommended). Replacement of glucose with xylitol has no significant effect on 2-h postprandial glucose in patients with T2DM with adequate glycemic control (C, weakly recommended)

In the 75 g oral glucose tolerance test (OGTT), some investigators added 5–10 g of fructose or allulose to compare the change in the area under the curve of the OGTT, and the results showed no further increase in post-OGTT blood glucose.[98] According to a randomized trial in 51 patients with T2DM with HbA1c < 7%, under isoenergetic replacement, the use of xylitol-containing desserts with low glycemic load (GL) (xylitol content of 14.3 g/100 g) instead of traditional desserts (sugar content of 33.4 g/100 g) reduced blood glucose by 0.49 mmol/L at 30, 60, and 90 min after meals. However, PBG was not significantly affected.[99]

Q19: How do non-nutritive sweeteners affect glycemic control, insulin levels, and body weight?

Non-nutritive sweeteners such as steviol glycoside, sucralose, aspartame, and saccharin have no significant effect on FBG, HbA1c, and BMI in patients with T2DM (B, weakly recommended)

Several studies have shown that the intake of small doses of non-nutritive sweeteners does not affect glycemic control in patients with T2DM. Some investigators added 400 mg of aspartame or 135 mg of saccharin to unsweetened beverages to observe changes in blood glucose 3 hours after drinking and found that blood glucose levels were not affected at 3 hours compared to unsweetened beverages.[100] An 18-week-long RCT randomizing 62 patients with T2DM to the 2.7 g/day aspartame group and the placebo group showed no statistically significant differences in FBG, PBG, and HbA1c.[101] A study investigating blood glucose and serum C-peptide levels in patients with T2DM four hours after administration of 1,000 mg sucralose found that the difference in changes in blood glucose and C-peptide levels was not statistically significant compared to the control group.[102] A 3-month RCT identified no significant change in HbA1c from baseline in the steviol glycoside group compared to the placebo group.[103]

Q20: How do alcohol and alcoholic beverages affect glycemic control?

Alcohol is not beneficial for glycemic control in patients with T2DM, and alcohol consumption increases the risk of hypoglycemia in patients with T1DM and is therefore not recommended for patients with diabetes (B, strongly recommended)

In a 2-year RCT study, 244 participants were randomly assigned to three groups that consumed 150 mL of mineral water, white wine, or red wine with dinner daily, and all participants followed a Mediterranean diet without calorie restriction, indicating that glycemic control (FBG, HbA1c, and insulin resistance) was improved only in participants with retarded alcohol metabolism compared to those with rapid alcohol metabolism.[104] A meta-analysis that pooled nine studies of short-term RCTs of T2DM identified no difference in blood glucose levels after 0.5, 2.0, 4.0, and 24.0 hours in patients who consumed 16–80 g of alcohol in a single session compared with non-drinking patients. In addition, no difference was observed in HbA1c levels in patients who consumed 11–18 g of alcohol per day compared with non-drinking patients during the follow-up period of 4–104 weeks.[105] However, alcohol consumption carries the risk of inducing hypoglycemia. Sixteen T1DM patients who drank vodka (0.85 g/kg) with dinner reported a 2-fold elevated risk of hypoglycemia, with continuous glucose monitoring suggesting the most pronounced glucose reductions at night and a risk of hypoglycemia persisting through day 2.[106]

Phytochemicals

Q21: What is the effect of phytochemical polyphenols on blood glucose regulation in patients with T2DM?

The phytochemical polyphenols may be beneficial in the management of diabetes and its complications (D, weakly recommended), and proanthocyanidins may be suitable for glycemic control (B, weakly recommended)

According to the results of a meta-analysis that included 20 RCT studies, polyphenol intake might reduce FBG levels in patients with T2DM or those at risk for diabetes (reduced by 0.18 mmol/L, $p = 0.011$).[107] A 12-week RCT in a Chinese population of 160 patients with prediabetes or diabetes revealed that purified anthocyanins were beneficial for the control of blood glucose and lipid levels.[108] A meta-analysis of seven RCTs also showed that glycemic control in patients with T2DM might benefit from supplementation with a specific dose of anthocyanin (9.1–9.8 mg) per day for 8–12 weeks.[109]

CHAPTER 3: DIETARY STRUCTURE

Q23: Does the Mediterranean diet prevent the development of T2DM, improve blood glucose and lipid control, and reduce the risk of cardiovascular diseases?

The Mediterranean diet helps to reduce the risk of T2DM by controlling blood glucose in patients with T2DM and contributing to the increase of HDL-C levels and the decrease of LDL-C and TG levels, thus lowering the risk of cardiovascular diseases (A, strongly recommended)

A Spanish PREDIMED multi-center RCT study in 2014 that included 7,447 non-T2DM participants indicated a 40% and 18% decrease in the risk of T2DM in the olive oil-rich Mediterranean diet group and the nut-rich Mediterranean diet group, respectively, when compared with the low-fat diets.[110] Meta-analyses in recent years have revealed that the Mediterranean diet significantly reduces the risk of T2DM. A 2017 meta-analysis that included 48 studies showed that a Mediterranean diet reduces the risk of developing diabetes.[111] Another systematic review published in 2015 revealed that the Mediterranean diet could reduce HbA1c and FBG levels, improve insulin resistance in T2DM, effectively control glycemia, and prevent cardiovascular diseases in patients with T2DM.[112]

Q24: Does the termination of dietary approaches to stop hypertension (DASH) prevent T2DM? Can improvements in blood glucose and lipid levels in T2DM reduce the risk of cardiovascular disease?

The DASH diets reduce the risk of morbidity and lower fasting insulin levels in patients with T2DM, but no significant improvement was seen in FBG and homeostasis model assessment for insulin resistance (HOMA-IR) (B, weakly recommended)

A meta-analysis in 2014 showed a lower risk of T2DM among those with higher DASH dietary adherence.[113] A 2017 meta-analysis of 16 cohort studies demonstrated that the DASH diet reduced the risk of developing diabetes and that the dietary structure with red meat, processed meats, refined grains, high-fat dairy products, eggs, and fried products as the main elements were positively associated with the development of diabetes (RR value of 1.44), whereas the dietary structure with vegetables, legumes, fruits, poultry, and fish as the main elements was negatively associated with the development of diabetes (RR value of 0.84).[111] A 2013 meta-analysis pooling nine RCT studies showed that the DASH diets for 3–24 weeks significantly reduced fasting insulin, but no improvement in FBG and HOMA-IR was found with the DASH diets.[114]

CHAPTER 4: PROBIOTICS AND PREBIOTICS

The intestinal flora plays a significant role in the development and progression of T2DM.[115] According to the

consensus statement released by the International Scientific Association for Probiotics and Prebiotics (ISAPP), probiotics are living microbial preparations that are beneficial to the health of the host when taken in appropriate doses.[116] Prebiotics are a class of dietary ingredients that are difficult to digest and are absorbed by the body but can be fermented by certain intestinal bacteria.[117] Synbiotics are prepared by mixing probiotics with specific prebiotic substrates with synergistic effects on their growth.[118] These substances may prevent and delay the onset and progression of T2DM[119, 120] by promoting the production of short-chain fatty acids, thus inducing the secretion of intestinal hormones that can affect blood glucose levels.[121, 122]

Q25: How does probiotic supplementation affect glucose metabolism in T2DM?

Specific probiotic supplementation may improve glycemic control in T2DM (B, weakly recommended)

In an RCT study that included 45 patients with T2DM, probiotic fermented milk (containing *Lactobacillus acidophilus* La-5 and *Bifidobacterium animalis subsp. Lactis* BB-12, 1×10^9 CFU) or traditional fermented milk (containing *Streptococcus thermophilus* TA-40) was given for six weeks. Patients consuming probiotic fermented milk had lower HbA1c, TC, and LDL-C levels, and the decrease was significantly greater than that in the traditional fermented milk intervention group.[123] In an RCT, 136 patients with T2DM were administered probiotic capsules (containing *Lactobacillus acidophilus* 12130, *Lactobacillus casei* 12313, *Bifidobacterium animalis subsp. Lactis* 12451, *Bifidobacterium bifidum* 02290, *Bifidobacterium longum* 02129, and *Bifidobacterium infantis* 02120, 1×10^{10} CFU) or placebo, respectively, for 12 weeks, and a significant reduction in fasting insulin was observed with probiotic intervention.[124] In a meta-analysis evaluating the effect of probiotics on glucose homeostasis in patients with T2DM, supplementation with a daily dose of $\geq 1 \times 10^9$ CFU of probiotics lowered HbA1c levels significantly. Multistrain probiotic supplements can improve T2DM better than single-strain probiotic supplements.[125]

Q26: Can supplementation with prebiotics help improve glycemic control in patients with T2DM?

Supplementation with specific prebiotics contributes to improving glycemic control and reducing inflammatory markers in patients with T2DM (C, weakly recommended)

In two RCTs enrolling 49 and 52 patients with T2DM, respectively, patients were administered either inulin (10 g/day) or an equivalent amount of maltodextrin as the placebo for eight weeks of intervention, and FBG, HbA1c, tumor necrosis factor-α (TNF-α), and lipopolysaccharide (LPS) levels were significantly lower in the inulin intervention group than in the placebo group.[126, 127] In an RCT study, 55 patients with T2DM were administered either resistant dextrin (10 g/day) or an equivalent amount of maltodextrin as a placebo for eight weeks of intervention, and fasting insulin was significantly decreased in the resistant dextrin intervention group, but the changes in FBG were not significant.[128] In an RCT study that incorporated 52 patients with T2DM, patients were given either galactooligosaccharide (10 g/day) or an equivalent amount of maltodextrin as the placebo for four weeks of intervention, and the glucose tolerance was not significantly improved in the galactooligosaccharide intervention group. However, the abundance of intestinal *Bifidobacteriaceae* was significantly increased.[129]

Q27: Is supplementation with synbiotics conducive to improving glycemic control in patients with T2DM?

Patients with T2DM may be supplemented with specific synbiotics to improve blood glucose, and the supplementation with synbiotics may better improve metabolism compared to probiotics (C, weakly recommended)

74 patients with T2DM included in an RCT study were administered either synbiotic UB0316 capsules (containing *Lactobacillus salivarius* UBLS22, *Lactobacillus casei* UBLC42, *Lactobacillus plantarum* UBLP40, *Lactobacillus acidophilus* UBLA34, *Bifidobacterium breve* UBBr01, *Bacillus coagulans Unique* IS2, 5×10^{10} CFU, and 100 mg fructooligosaccharide) or placebo for 12 weeks. The synbiotic supplementation group showed a significant decrease in HbA1c and FBG, and HbA1c was significantly lower than that in the placebo group at the endpoint, but the difference in FBG was not statistically significant.[130] Fifty-eight patients with T2DM in another RCT study were given WBF-010 synbiotic capsules (containing three strains of bacteria, including 3.3×10^9 CFU *Clostridium beijerinckii* CBEI, 1.6×10^{10} CFU *Clostridium butyricum* CBUT, 2.0×10^9 CFU *Bifidobacterium infantis* BINF and inulin), WBF-011 synbiotic capsules (1.2×10^9 CFU *Akkermansia muciniphila* AMUC and 9×10^8 CFU *Anaerobutyricum hallii* EHAL added to the formulation WBF-010), or placebo, respectively, for 12-week interventions, and the area under the curve of blood glucose decreased significantly only in the WBF-011 synbiotic supplementation group, to an extent significantly greater than in the placebo group.[131] Eighty-one patients with T2DM in an RCT study were given 120 g/day of synbiotic bread (containing 1×10^8 CFU *of Bacillus coagulans* and 0.07 g of inulin per gram), probiotic bread (1×10^8 CFU of *Bacillus coagulans* per gram), or placebo for eight weeks of intervention, and only the synbiotic bread intervention group experienced significantly greater decreases in fasting insulin levels, HOMA-IR, and islet β cell function index, with an extent significantly greater than that in the placebo group and the probiotic bread intervention groups.[132]

CHAPTER 5: NUTRITION EDUCATION AND MANAGEMENT OF DIABETES

Q29: Does education about diabetes affect the risk of developing diabetes?

Lifestyle interventions guided by diabetes education contribute to improving glucose tolerance, reducing the prevalence or delay the onset of diabetes, and decrease chronic complications of diabetes (A, strongly recommended)

Several large-scale studies conducted in China and other countries have demonstrated the sustainability of lifestyle interventions in slowing down the progression of T2DM in people at high risk of developing IGT or diabetes.[133-138] For example, the results of the Daqing study showed a 43% reduction in 20 years,[133] the DPS study

showed a 43% reduction in 7 years,[137] and the DPPOS study showed a 34% reduction in 10 years.[138]

Studies on T2DM have shown that moderate weight loss (by 5% to 10%) can support improvements in insulin resistance, as well as reductions in blood glucose, lipids, and blood pressure. A study of 1-year Look AHEAD intensive lifestyle interventions revealed that patients lost an average of 8.6% of body weight and experienced a significant reduction in HbA1c and a reduction in risk factors of cardiovascular diseases (including lower blood pressure and TG, and higher HDL-C), with these benefits persisting in year 4 of the study.[139] Similarly, a systematic review and meta-analysis of patients with IGT (six studies) or metabolic abnormalities (one study) revealed that lifestyle changes prevented the development of T2DM in these populations and that active intervention reduced the risk of developing diabetes for many years.[140]

Q30: Does nutrition education and exercise instruction in diabetes affect weight and glycemic control in patients with diabetes?

Comprehensive management that incorporates diabetes nutrition education, diet, and exercise can contribute to weight loss, reduction in waist circumference, HbA1c, and blood glucose levels, as well as increased nutrition knowledge and improved diet quality, with multiple benefits in terms of lipids and blood pressure. (B, strongly recommended)

In studies on general practice and community management of multiple concurrent chronic diseases, it has been suggested that any intervention should consider the patient's values and preferences, and an individualized patient-centered plan that incorporates diabetes-related nutrition, living conditions, and functional status should be developed.[141] A Cochrane review suggested that group education on nutrition therapy was effective in improving FBG and HbA1c levels, increasing the level of knowledge about diabetes, lowering systolic blood pressure and body weight, and decreasing diabetes medication in patients with T2DM.[142] Individualized education is helpful for glycemic control in patients with HbA1c > 8%. The comprehensive treatment team for diabetes should be led by a dietitian/physician familiar with MNT, followed by team members well acquainted with MNT.[10]

Multiple studies have shown that for most overweight and obese patients with T2DM, lifestyle interventions lead to a decrease in body weight and BMI and a significant improvement in blood glucose and HbA1c.[143-149]

Q31: Are diets with a low glycemic index/glycemic load good for patients with diabetes to control their blood glucose levels?

A high GI/GL diet resulted in a remarkable increase in the risk of T2DM in the healthy population. Low GI/GL diets are more effective than high GI/GL diets in controlling FBG, PBG, and HbA1c without increasing the incidence of hypoglycemia events (A, strongly recommended)

A low GI/GL diet helps control blood glucose levels. Low GI diets cause less glucose fluctuations throughout the day than high GI diets. Dietary GI glucose is positively correlated with the area under the curve (AUC).[150] Several studies have shown the effectiveness of low GI/GL diets in reducing HbA1c and FBG.[151, 152] Adherence to low GI/GL diets also benefits patients with diabetes by controlling complications through reasonable glycemic control.[153] A meta-analysis of 15 RCTs with patient numbers ranging from 133 to 6,590 explored the development of T2DM in relation to GI and GL and showed that dietary patterns with higher GI/GL significantly increased the risk of T2DM in healthy male and female populations. For every 10-unit increase in GI value in the 2000 kcal/day diet, the RR (95% CI) for T2DM-GI was 1.27 (1.15–1.40) ($p < .001$, 10 studies); for every 80 g increase in GL, the RR (95% CI) for T2DM-GL was 1.26 (1.15–1.37) ($p < 0.001$, 15 studies).[154] According to a 2018 meta-analysis that included six RCTs, low-GI diets were more effective than high-GI diets in controlling HbA1c and FBG levels in patients with T2DM.[151] Another meta-analysis in 2019 involving 54 RCTs further demonstrated that low-GI diets were effective in reducing HbA1c, FBG, BMI, TC, and LDL-C levels in a wider range of age (adult vs children) and disease groups (IGT, T1DM, or T2DM).[152] Low-GI diets did not increase the probability of hypoglycemic events while improving glycemic control in patients with diabetes; the incidence rate of hypoglycemia was lower in low-GI diets than in high-GI diets.[155]

Q32: Are diets with a low GI/glycemic load good for controlling diabetic complications?

Low-GI diets may be beneficial in managing diabetic complications (C, weakly recommended)

Diabetic complications are closely correlated with glycemic control. The time of day when glucose fluctuations are controlled within the target range (3.9–10.0 mmol/L) is negatively correlated with the degree of fundus lesions,[156] the risk of all-cause mortality,[157] the risk of death from cardiovascular disease,[157] and the carotid intima-media thickness[158] in the patients, suggesting that the daily glucose level is closely related to diabetic complications. An RCT including 201 participants found a 0.16 ng/L decrease in the level of cardiac injury markers (high-sensitivity cardiac troponin I) in the low-GI diet group after six months of treatment.[159] This finding suggests that low-GI diets help in glycemic control in patients with diabetes.[160]

Q33: Does the food exchange serving method help patients with diabetes to control their blood glucose levels?

The food exchange serving method is convenient in practice and helps patients with diabetes control their total energy and blood glucose levels (C, strongly recommended)

The concept of food exchange service was first proposed by the ADA in 1950, based on the nutritional composition of different food categories.[161] The concept in China was developed using 90 kcal (376 kJ) as the unit of exchange. The food exchange serving method, taking isoenergetic foods as the basis, divides different foods into four major categories (eight subcategories) by nature and nutritional composition, with each category containing several units of exchange for different foods.[162] Liu

Cunying et al.[163] reported that the FBG and PBG of patients with diabetes undergoing nutrition therapy in the food exchange serving group were significantly lower than those in the staple food fixation group ($p < 0.01$). Two self-control studies found that FBG and PBG were significantly decreased in patients after using the food exchange serving method $p < 0.01$).[164, 165] A study involving 63 patients with T2DM on different clinical treatment modalities suggested that food selection by the food exchange serving method was effective in reducing FBG and PBG levels.[166]

Q34: Is the food exchange serving method based on a low glycemic load better for glycemic control than the traditional food exchange serving method?

MNT, combined with the low-GL food exchange serving method, is more favorable to glycemic control than the traditional food exchange serving method and helps to improve weight, BMI, and lipid metabolism (B, weakly recommended)

A meta-analysis of 12 studies identified that the combination of the food exchange serving method and education on low-GL diets significantly reduced FBG, PBG, HbA1c, and lipid levels in patients with T2DM ($p < 0.001$).[167] Three case-control studies showed that combining low-GL diets with the food exchange serving method for dietary education in patients with T2DM achieved good clinical results in improving blood glucose and lipid levels ($p < 0.05$).[168-170] Recently, a case-control study of elderly diabetes mellitus patients and a case-control study of gestational diabetes mellitus patients concurrently found that a low-GL diet combined with the food exchange serving method significantly reduced HbA1c and PBG levels compared with conventional dietary intervention and the traditional food exchange serving method ($p < 0.05$).[171, 172]

Q35: Can the use of carbohydrate count in patients with T1DM contribute to glycemic control?

Nutrition interventions based on carbohydrate counting method contribute to improving glycemic control and quality of life in children and adults with T1DM (C, strongly recommended)

A 2015 single-center observational study of T1DM revealed a general increase in awareness rate and a significant decrease in both FPG and PBG after the application of carbohydrate counting.[173] The results of a Turkish study of 110 children with T1DM followed for two years suggested that the carbohydrate counting method achieved reasonable metabolic control without leading to an increase in body weight or insulin demand.[174] Moreover, the increased accuracy of the method by children and their parents contributes to glycemic control.[175, 176] The efficacy of this method in adults with T1DM was more favorable than that in children, and the reduction in HbA1c levels was better than the conventional dietary guidance for diabetes.[177, 178] Bell et al.[179] confirmed this point of view. In patients receiving continuous subcutaneous insulin infusion, the carbohydrate counting method of intervention achieved improved diabetes-specific quality of life scale scores, reductions in BMI and waist circumference, and a marked decrease in HbA1c.[180]

Q36: Is carbohydrate counting helpful for glycemic control in patients with T2DM?

The carbohydrate counting method is effective in lowering blood glucose levels in patients with T2DM (B, weakly recommended)

Several studies have demonstrated that dietary interventions for patients with T2DM using carbohydrate counting can improve blood glucose levels and decrease blood glucose levels in inpatients.[181, 182] A randomized trial verified that the method reduced HbA1c and glycemic variability in patients with T2DM receiving basal insulin therapy without increasing hypoglycemia or BMI.[183] The results of two RCTs in 2016 and 2017 confirmed that the application of the carbohydrate counting method in patients with T2DM was superior to the traditional food exchange serving method in terms of glycemia, blood insulin level, and visceral fat area control.[184, 185] The ability of carbohydrate count to reduce HbA1c and glucose levels in patients with T2DM has been verified by other researchers.[186] The application of the carbohydrate counting method in older patients was also effective in improving glucose and lipid metabolism and delaying the development of renal impairment. After six months of intervention, the levels of FPG, HbA1c, urea nitrogen, creatinine, uric acid, and TG were lower than those in the control group using the traditional food exchange serving method.[187]

CHAPTER 6: SPECIAL POPULATIONS WITH DIABETES

Pediatric and Adolescent Diabetes

Q37: How do different dietary patterns affect glucose and metabolism in pediatric and adolescent patients with T1DM?

The combination of a flexible dietary pattern of low GI and high dietary fiber based on the principles of a balanced diet and regular meals contributes to glycemic management in patients with T1DM (B, strongly recommended). High-fat diets (fat energy supply ratio > 35%) are not recommended for children and adolescents with T1DM, and the balanced diet with a moderately higher proportion of monounsaturated fatty acid intake improves lipid and blood glucose (B, strongly recommended)

Since the 1980s, the overall incidence of diabetes mellitus in children and adolescents and the proportion of pediatric patients with T2DM in China have shown a significant year-to-year increase.[188] MNT, which covers interventions such as diet, exercise, and education, can improve blood glucose and other metabolic markers in children with diabetes.[189, 190] Investigators found that HbA1c was significantly greater in children with T1DM on all-day meals than in those with regular meals (7.7% and 6.1%, respectively, $p = 0.01$) as explored by means of 3-day weighing, dietary records, and mealtime management. A follow-up observation demonstrated that better glycemic management [including indicators such as standard deviation of continuous glucose monitoring data, mean magnitude of glucose, glycemic excursion, and potential of hyperglycemia (> 10.0 mmol/L) vs hypoglycemia (< 2.8 mmol/L)] in children and adolescents with T1DM was correlated with higher healthy eating index scores, whole-plant food density, high dietary fiber, low

GI and other factors.[191] According to a 12-month prospective RCT, a flexible dietary pattern with low GI for patients with T1DM resulted in better HbA1c levels of (8.05 ± 0.95)% and (8.61 ± 1.37)%, respectively ($p = 0.05$) and a lower incidence rate of hyperglycemia (> 15 episodes/month) of 35% and 66%, respectively, compared with the carbohydrate-exchange dietary pattern group ($p < 0.006$).[192]

A 2011 study of adolescents with T1DM demonstrated that for every 1% increase in SFA in the diet, the risk of HbA1c > 7.5% would increase by 53% (OR = 1.53, $p = 0.02$), and the risk of this situation would increase by 30% annually (OR = 1.30, $p = 0.02$).[193] However, some investigators discovered that a 10% increase in n-9 erythrocyte phospholipid fatty acid levels, a marker of increased MUFA intake, was associated with a 0.64% decrease in HbA1c. n-9 erythrocyte phospholipid fatty acid levels were negatively correlated with TC levels (R2 = 0.38, $p = 0.002$) and LDL-C (R2 = 0.21, $p = 0.03$), suggesting that appropriately increased MUFA intake might contribute to improved blood glucose and blood lipid levels.[194]

Q38: What is the impact of protein intake on metabolism and insulin therapy in pediatric and adolescent patients with T1DM?

High-protein and high-fat diets (≥ 25% protein energy supply ratio) are not recommended for pediatric and adolescent patients with T1DM (B, strongly recommended)

Studies revealed that adolescent patients with T1DM on high-protein and high-fat diets developed a greater area under the curve of blood glucose at 12 hours after meals (109.3 and 77.8 mmol/L/12 hours, respectively, $p < 0.05$) and a higher glucose level at 12 hours after meals (8.5 and 5.1 mmol/L, respectively, $p < 0.05$).[195] According to a randomized controlled crossover study, children and adolescents with T1DM on high-protein and high-fat diets required more postprandial correction insulin (1.20 and 0.15 U, respectively, $p < 0.001$), total insulin dosage at one meal (3.48 and 2.70 U, respectively, $p < 0.001$), and significant increase in time to PBG elevation of (364 ± 142) and (185 ± 124) minutes ($p < 0.001$).[196] Another small-sample study that included 11 participants also verified a higher mean insulin demand in adolescent patients with T1DM on high-protein diets (10.3 and 6.7 U, respectively, $p = 0.001$).[197]

Q39: What is the effect of vitamin D on children and adolescents with T1DM?

Vitamin D therapy is conducive to improving blood glucose and lipid levels and reducing the risk of complications in T1DM children and adolescents complicated by vitamin D deficiency; routine monitoring and timely supplementation with vitamin D levels are recommended (C, strongly recommended)

In a prospective study, 30 of 50 children with T1DM complicated by dyslipidemia (medical history of > 2 years) developed vitamin D deficiency. Significant improvements in LDL-C levels were realized after four months of vitamin D treatment (vitamin D3 4000 IU/day) (7.05 and 6.51 mmol/L, respectively, $p = 0.02$).[198] Another prospective study identified that children who received vitamin D treatment (children with a vitamin D deficiency: 800 IU of vitamin D3 orally for three months; children with a vitamin D deficiency: 4000 IU of vitamin D3 and 50 mg/kg of calcium per day for three months) had a significant decrease in HbA1c of (8.83 ± 1.58)% and (10.72 ± 2.22)%, respectively ($p < 0.001$).[199] According to a cross-sectional study in 2016, levels of 25-hydroxyvitamin D were negatively correlated with the severity of diabetic ketoacidosis ($p < 0.05$), with children ≤ 25 nmol/L requiring higher doses of insulin ($p < 0.05$) and having a higher HbA1c level ($p < 0.01$). The level of 25-hydroxyvitamin D significantly increased ($p < 0.001$) and HbA1c significantly decreased after vitamin D treatment (1000 IU/day) ($p < 0.001$).[200] A 2017 study on the improvement of peripheral vascular function in adolescent patients with T1DM with combined vitamin D deficiency demonstrated significant improvement in epithelial function with reactive hyperemia index of (0.58 ± 0.20) and (0.68 ± 0.21), respectively, and significantly decreased urinary inflammatory cytokines/chemokines, epidermal growth factor, TNF-β, IL-10 and other inflammatory factor levels (all $p < 0.05$) after 12–24 weeks of vitamin D3 (1000 or 2000 IU/day) treatment.[201]

Q40: What is the effect of nutritional weight loss interventions on blood glucose levels in overweight and obese pediatric adolescents with T1DM and T2DM?

Overweight and obese children and adolescents with T1DM and T2DM need nutritional weight loss interventions to reduce obesity and improve glucose levels (C, strongly recommended)

A three-country study involving 32,936 pediatric patients with T1DM in Germany, Austria, and the US revealed that higher BMI-Z values were associated with higher HbA1c (8.2%, 8.2%, and 8.4% in normal-weight, overweight, and obese children with T1DM, respectively, $p < 0.001$) and more frequent severe hypoglycemia over one year (2.1%, 2.4%, and 2.8% in normal-weight, overweight, and obese children with T1DM, respectively; $p < 0.001$).[202] A retrospective study revealed that a decrease in BMI one year after the diagnosis of T2DM was positively correlated with lower HbA1c levels regardless of the administration of metformin (r = 0.407, $p = 0.0023$) or treatment with insulin (r = 0.522, $p = 0.0022$).[203]

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is an impaired glucose tolerance (IGT) that occurs during pregnancy and is a common pregnancy complication.[204] The prevalence of GDM in China is estimated to be 14.8%–17.8% and has increased in recent years.[205-207] Many clinical studies have verified that GDM results in severe adverse maternal and infant outcomes.[208] Studies have shown that healthy dietary patterns contribute to the prevention of GDM.[209]

Q41: Is folic acid supplementation during pregnancy beneficial in reducing the risk of GDM?

During preconception and early pregnancy, supplementation with an additional 400 μg of folic acid per day in addition to a balanced diet is beneficial in reducing the risk of GDM, but folic acid supplementation above 800

μg may increase the risk of GDM (B, weakly recommended)

Hcy levels were found to be significantly higher in GDM patients than in the control group, and Hcy was negatively correlated with folic acid levels and positively correlated with insulin resistance, suggesting a possible connection with the development of GDM.[210] A prospective cohort study indicated that 824 patients with GDM were reported among 14,553 pregnant women followed up. The RR value (95% CI) of GDM was 0.83 (0.72–0.95) in women with adequate total folic acid intake (≥ 400 μg/day) compared with those with insufficient intake (< 400 μg/day) ($p = 0.007$), and GDM risk can be reduced by preconception supplementation with an appropriate amount of folic acid.[211] A case-control study including 49,611 GDM and 137,821 healthy women showed that pre-pregnancy intake of folic acid reduced the risk of GDM by 27%, with an adjusted OR (95% CI) of 0.73 (0.69–0.79) ($p < 0.001$).[212] The incidence of GDM among 4,353 women in the Tongji Maternal and Child Health cohort was 8.6%, and the administration of 400 μg/day of folic acid during preconception and early pregnancy has been shown to prevent neural tube defects. However, administration of ≥ 800 μg of folic acid per day from preconception to mid-pregnancy might increase the risk of GDM.[213]

Q42: Is plant protein intake during pregnancy beneficial for reducing the risk of gestational diabetes mellitus?

Both intake and type of proteins should be balanced in the prenatal diet, and the increase of plant proteins such as beans and nuts is beneficial in reducing the risk of GDM (B, strongly recommended)

The binding of plant extensin to glucagon-like peptide-1 (GLP-1) receptors in the human body stimulates insulin secretion from islet cells to significantly lower blood glucose levels.[214] The results of the American Nursing Health Study, which included 15,294 female participants, suggested a 51% reduction in the risk of developing GDM by replacing 5% of animal proteins with plant proteins and a higher intake of animal proteins, especially red meat, was significantly associated with an increased risk of GDM. The risk of GDM is significantly reduced with a greater intake of plant proteins, especially legumes or nuts.[215] A case-control study in China investigated the dietary frequency of 150 pregnant women divided into normal and GDM groups based on the results of OGTT at 24–28 weeks of gestation, suggesting that excessive intake of dietary proteins (especially animal protein) and too low intake of legume proteins during pregnancy might increase the risk of GDM.[216] Daily intake of fish, poultry, eggs, and meat > 200 g and intake of soybeans < 12 g may be risk factors for GDM development.[217]

Q43: How do low-GI diets affect glycemic control in patients with gestational diabetes mellitus?

Low GI diets help glycemic control in GDM (C, weakly recommended)

Some investigators randomly divided 140 patients with GDM into 66 cases in the study group (staple food: low-GI formulation) and 74 cases in the control group (staple food: white rice), and the results showed that the blood glucose of the study group was significantly lower than that of the control group after three meals, suggesting that staple food with low-GI formulations could significantly reduce the PBG of GDM patients, beneficial to the treatment of GDM.[218] In a 12-week RCT consisting of 31 patients in the low-GI treatment group, 31 patients in the control group, and an additional 30 healthy pregnant women in the normal control group, serum metabolomic testing and pregnancy outcome statistics at 36 weeks of gestation revealed that low-GI grain nutrition therapy might significantly improve pregnancy outcomes in GDM by modulating relevant biomarkers.[219]

Q44: Can diabetes-specific nutritional preparations improve the clinical outcomes of patients with gestational diabetes mellitus?

Diabetes-specific nutritional preparations help improve glucose levels and perinatal outcomes and reduce the risks of hypoglycemia and inadequate energy intake in patients with GDM (C, weakly recommended)

Investigators randomized 69 patients with GDM into groups, assigning normal diet plus diabetes-specific nutritional formulations to 32 patients in the study group and normal diet to 37 patients in the control group; the results indicated that the prevalence of premature rupture of fetal membranes, polyhydramnios, and neonatal pneumonia was significantly lower in the study group than in the control group.[220] Other investigators added diabetes-specific formulations rich in slow-release starch to the breakfast of the study group, applied the isoenergetic traditional diet for the control group, and conducted dietary education and dietary management for both groups; they found that the FBG of the study group was significantly lower than that of the control group, suggesting that the diabetes-specific formulations rich in slow-release starch were beneficial for improving the PBG of patients with GDM.[221]

Q45: Do patients with gestational diabetes require dietary fiber supplementation?

Dietary fiber supplementation during pregnancy in patients with GDM helps regulate glucose levels and improve clinical outcomes (B, strongly recommended)

The recommended intake of dietary fiber for patients with diabetes is 25–30 g/day.[4] The investigators randomly divided 112 patients with GDM into two groups to receive basic nutritional treatment, and the study group received additional dietary fiber (9.5 g/day for eight weeks). The results showed that the glycemic control pass rate in the study group was significantly higher than that in the control group, and the incidence of premature rupture of fetal membranes and hyperbilirubinemia in newborns was significantly lower than that in the control group, suggesting that dietary fiber interventions significantly improved the maternal and infant outcomes of patients with GDM.[222] Other investigators randomly divided 206 patients with GDM combined with hyperlipidemia in the middle and late pregnancy into the fortified dietary fiber group (dietary fiber 20 g/day), the resistance exercise group, the combined group, and the control group, among which both FBG and PBG of the dietary fiber

group were significantly lower than those of the control group after interventions, and the incidence rates of preeclampsia, polyhydramnios, preterm delivery, and macrosomia in the combined group were significantly lower than those in the control group, suggesting that dietary fiber combined with resistance exercise was effective in controlling the blood glucose and lipid levels of patients with GDM and improving the pregnancy outcome.[223] Dietary fiber supplementation also prevents excessive weight gain during pregnancy.[224]

Q46: Do patients with gestational diabetes need micronutrient supplementation?

Patients with GDM should maintain good micronutrient intake and supplement with pregnancy-appropriate micronutrient compound preparations when necessary (C, weakly recommended)

Investigators randomized 80 patients with GDM into two groups to receive conventional GDM interventions. The study group received the magnesium-zinc-calcium and vitamin D complex supplements (magnesium 100 mg, zinc 4 mg, calcium 400 mg, and vitamin D 200 IU) twice/day for six weeks and found that the study group developed lower levels of inflammation and oxidative stress during pregnancy. However, the pregnancy outcomes were affected to a lesser extent,[225] which was in line with the results of Jamilian et al.[226] An Iranian investigation of combined magnesium and vitamin E supplementation in 60 patients with GDM found significant improvements in blood glucose and lipid levels after six weeks.[227]

Older people with diabetes mellitus

According to the 7th National Population Census in 2020, 13.50% of the population was aged 65 and over, up 4.63% from the 6th National Population Census, suggesting that the degree of aging in China has further deepened.[228] More scientific and rational nutritional guidance should be provided to older patients with diabetes mellitus.

Q47: What is the appropriate number of calories for older patients with diabetes?

The recommended calorie intake for elderly patients with diabetes is 25–30 kcal/kg/day, which needs to be increased for elderly patients who are malnourished or at nutritional risk (B, strongly recommended)

A U-shaped relationship between calorie intake and mortality in older patients with diabetes has been identified in previous studies, and the optimal calorie intake for older patients with diabetes should be controlled at 25–35 kcal/kg/day.[229] As recommended in the *Clinical Nutrition Guidelines for Geriatrics* of the European Society for Clinical Nutrition and Metabolism, older adults should guarantee a daily calorie intake of approximately 30 kcal/kg, and the use of restricted diets is not recommended for overweight older adults.[230] *The Japanese Treatment Guideline for Diabetes 2019* recommends a calorie intake of 25–30 kcal/kg for older patients, which can be increased for older patients experiencing sarcopenia, frailty, and malnutrition or those at risk for any of these conditions.[231]

Q48: How does increased protein intake affect older patients with diabetes?

Adequate protein intake alleviates frailty and prevents sarcopenia in elderly diabetes patients (B, strongly recommended)

Several elderly nutrition guidelines recommend a protein intake of 1.0–1.2 g/kg/day for elderly diabetics, 1.2–1.5 g/kg/day for patients who are malnourished or at nutritional risk, and at least 1.5 g/kg/day for older people with sarcopenia or cachexia, with the exception of patients with end-stage renal failure.[232] A meta-analysis revealed that adequate protein intake reduces the risk of frailty and sarcopenia in older patients with diabetes.[233]

Q49: Do elderly patients with diabetes need supplementation with vitamins and trace elements?

Elderly diabetes patients should maintain an adequate intake of vitamins and trace elements, especially vitamin D and calcium (C, strongly recommended)

Adequate vitamin D intake reduces the risk of sarcopenia in older patients with diabetes.[234] Given the correlation between low vitamin D levels and diabetic peripheral neuropathy in older people, serum vitamin D levels should be reviewed regularly.[235] The prevalence of vitamin deficiency is higher in patients with diabetes aged > 65 years, and the level of folic acid is significantly associated with grip strength and leg physical strength.[236] Daily calcium intake of 1000–1200 mg is recommended for older patients,[237] and oral vitamin D > 800–1000 IU/day is required for older patients who receive insufficient light exposure.[238]

Prediabetes

Q50: Are lifestyle interventions for prediabetes conducive to delaying the onset of T2DM and its complications?

Lifestyle interventions for prediabetes can delay the onset of T2DM and decrease cardiovascular events, microvascular complications, and cardiovascular and all-cause mortality (A, strongly recommended)

Several large-scale studies have demonstrated that lifestyle interventions in IGT populations can delay the onset of T2DM and decrease the incidence of cardiovascular events, microvascular complications, and cardiovascular and all-cause mortality.[137, 239, 240]

Q51: Does weight loss reduce T2DM in individuals who are overweight/obese with prediabetes?

Overweight and obese prediabetics are recommended to lose 7% to 10% of their body weight to reduce T2DM (B, strongly recommended)

There is a large body of evidence suggesting that overweight/obese prediabetics should be encouraged to lose weight and that a 7% to 10% weight loss is effective in preventing the development of T2DM.[7, 241] Muscle insulin sensitivity and β-cell functions can be further improved by additional weight loss (11%–16% of baseline weight).[242]

Q52: Is precise nutrition therapy beneficial for the glycemic management and prevention of T2DM in the prediabetic population?

Personalized diets that incorporate biological data (e.g., microbiome, genome, and metabolome) and lifestyle factors (e.g., sleep and exercise) of the individuals contribute to the control of PBG in prediabetic, obese and other patients with T2DM and high-risk populations (B, weakly recommended)

In 2015, a research team in Israel developed a machine learning algorithm that could predict the PBG response of an individual based on clinical and flora data, thus combining machine learning with precision nutrition.[243] An RCT in 2021 found better glycemic control effects of 6-month interventions of individualized PBG-targeted diet, a crucial step towards personalized precision nutrition research.[244]

CHAPTER 7: DIABETES-RELATED COMPLICATIONS AND MEDICAL NUTRITION THERAPY

Metabolic surgery and nutrition

Several clinical studies have demonstrated the ability of metabolic surgery to alleviate T2DM and reduce multiple diabetic complications. A 3–15 year follow-up showed that various metabolic surgeries were significantly better than internal medical therapy for T2DM in terms of remission and new-onset rate.[245-247] In addition, dependence on hypoglycemic agents or insulin can be significantly reduced in patients with T2DM.[248]

Q53: Do patients with T2DM require protein supplementation after metabolic surgery?

Protein supplementation is recommended for patients with T2DM according to the *Guidelines for Nutrition Management After Metabolic Surgery*, and postoperative protein intake should be in the range of 60–120 g/day (C, weakly recommended)

A retrospective study in China (244 patients) demonstrated a 1.2% and 8.9% incidence of hypoalbuminemia within one year after SG and RYGB, respectively.[249] The Perioperative Nutrition Guidelines for Bariatric Surgery, published in the US in 2019, suggest that daily protein intake should reach 60 g or 1.5 g/kg IBW.[250] Postoperative protein intake of 60–120 g/day is recommended in the *Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery*.[251] It is recommended that postoperative protein intake should reach 60–120 g/day, depending on height, ideal body weight, and muscle content, combined with the actual situation of Chinese population.

Q54: Do patients with T2DM need iron supplementation after metabolic surgery?

Regular monitoring of iron metabolic markers after metabolic surgery (especially in women and post-RYGB) and timely supplementation in cases of iron deficiency are recommended for patients with T2DM. Supplementation can be provided in the form of ferrous sulfate, ferrous fumarate, or ferrous gluconate accompanied by vitamin C at an oral dose of 150–200 mg/day (B, strongly recommended)

Studies have revealed that the rate of iron deficiency one year after RYGB can be up to 20% (120 patients).[252] The incidence of iron deficiency anemia at two years postoperatively was shown to be higher, reaching 34% in menopausal women and up to 62.5% in nonmenopausal women (184 patients).[253] Another study of Chinese obese patients with T2DM suggested that the 3-year incidence of post-SG or RYGB anemia was 15%, and the incidence of iron deficiency was 20% (20 patients).[254] Therefore, greater attention should be paid to iron metabolism-related indices in non-menopausal women, and patients with T2DM after RYGB metabolic surgery, and iron supplementation is needed once iron deficiency is detected. Supplementation may administer on the doses and dosage forms (ferrous sulfate, ferrous fumarate, or ferrous gluconate accompanied by vitamin C at an oral dose of 150–200 mg/day), as recommended by the *Consensus on Nutritional and Multi-disciplinary Management for Bariatric Surgery*.[255]

Q55: Is it necessary to supplement calcium and vitamin D levels in patients with T2DM after metabolic surgery?

Regular postoperative monitoring of vitamin D levels is recommended for patients with T2DM, with daily prophylactic oral calcium doses of 1200–1500 mg and vitamin D preparations of 3000 IU (C, strongly recommended)

The risk of fracture after metabolic surgery is 1.2 times higher than that in nonoperated individuals owing to osteopenia caused by calcium and vitamin D deficiency.[256] Prospective studies have revealed that the incidence of vitamin D deficiency and hypocalcemia can be as high as 84% and 78%, respectively, six months after SG.[257] For T2DM, it is stated in the *Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition)* that multivitamins and trace elements should be supplemented as appropriate, given that metabolic surgeries may increase the risk of dystrophia.[2] Therefore, the Guideline recommends vitamin D screening and prophylactic supplementation with vitamin D preparations after all metabolic surgeries. Daily oral calcium preparations of 1200–1500 mg and vitamin D preparations of 3000 IU are recommended after SG and RYGB.[4, 258]

Q56: Do patients with T2DM require vitamin B supplementation after metabolic surgery?

Routine monitoring of vitamin B12 levels after metabolic surgery is recommended for patients with T2DM, and oral methylvitamin B12 (1000 μg/day) is recommended for patients presenting with vitamin B12 deficiency until they meet the criteria. Oral supplementation with vitamin B 1100 mg twice/day or thrice/day is recommended for patients with symptoms of vitamin B1 deficiency until symptoms are resolved (C, strongly recommended)

The 2016 Comprehensive Healthy Nutrition Guidelines for Surgical Bariatric Patients of the American Society for Metabolic and Bariatric Surgery were updated to show that within 2–5 years after metabolic surgery, nearly 20% of postoperative RYGB patients and 4%–20% of postoperative SG patients present with vitamin B12 defi-

ciency[259] and that the symptoms cannot be corrected by routine oral administration of common multivitamin preparations.[260] Therefore, vitamin B12 levels should be regularly monitored after metabolic surgery, and in the presence of vitamin B12 deficiency, methylvitamin B12 should be administered orally at 1000 μg/day until the level reaches the criteria.[4, 258] In the case of intramuscular or subcutaneous injections, the dose should be changed to 1000 μg/month.[258] Simultaneous supplementation with oral and intramuscular injections is not recommended.[256] Metabolic surgical procedures predispose patients to vitamin B1 deficiency and thus cause gastrointestinal symptoms such as constipation that present on average five years after surgery, which can be relieved by vitamin B1 supplementation.[261] Therefore, it is recommended that vitamin B1 levels should be regularly monitored after metabolic surgery. Once the deficiency is detected, oral vitamin B (1100 mg twice or thrice daily) should be taken until symptoms are resolved. In cases of severe deficiency, intravenous or subcutaneous supplementation can be administered at a dose of 200–500 mg/day, and the dose should be changed to 250 mg/day after 3–5 days to maintain the treatment for 3–5 days or until symptom resolution. After that, an oral dose of 100 mg/day should be administered for maintenance therapy or until the risk factors are eliminated.[258]

Q57: Do patients with T2DM require vitamin A supplementation after metabolic surgery?

Monitoring vitamin A levels after metabolic surgery is recommended for patients with T2DM, and individuals with vitamin A deficiency should be supplemented with 5,000–10,000 IU/day (C, weakly recommended)

Changes in the anatomy of the gastrointestinal tract after metabolic surgery may affect the absorption of lipid-soluble vitamins (e.g., vitamin A) from the terminal ileum, resulting in an increase in the incidence of vitamin A deficiency one year after metabolic surgery (9.4% and 15.9% after SG and RYGB, respectively).[262] They may be as high as 70% at four years postoperatively.[258] Consequently, regular postoperative monitoring of vitamin A levels and oral supplementation with different doses of vitamin A (5000–10000 IU/day), depending on the type of surgery, is recommended.[258]

Q58: How can patients with T2DM prevent hypoglycemia after metabolic surgery?

High-fiber and low-GI diets or low-carbohydrate and high-protein diets are recommended for patients with T2DM who develop hypoglycemia after metabolic surgery (C, weakly recommended)

Certain obese patients develop hypoglycemia after bariatric surgery, with postprandial hypoglycemia being a more specific postoperative complication after RYGB.[263] High-sugar, low-protein diets are more likely to cause hypoglycemia after RYGB (17 patients).[264] Most hypoglycemic symptoms can be relieved by dietary adjustments. For hyperinsulinic postprandial hypoglycemia, the consumption of substantial amounts of monosaccharides can be avoided with frequent small meals and high-fiber and low-GI diets. Low-sugar and high-protein diets (energy ratio: 30% sugar, 30% protein, and 40% fat) are recommended to minimize glucose fluctuations and prevent hypoglycemia after bariatric surgery (n = 10)[265] for post-RYGB hypoglycemia that is not easy to control through diet or medication, diabetes-specific nutritional preparations may be considered.[266]

Q59: How can perioperative nutritional management promote the positive effects of metabolic surgery in patients with T2DM?

Perioperative glucose monitoring, medication, and diet regulation are effective in controlling blood glucose, reducing surgical risks, and improving surgical prognosis (B, strongly recommended)

Perioperative blood glucose levels are highly variable due to fasting, stress, infection, and glucocorticoid use. Poor preoperative diabetes control (HbA1c level > 7.5%) may predict a reduced diabetes remission rate. In addition, elevated HbA1c levels in patients with diabetes are associated with a high rate of complications, myocardial infarction, and an increased risk of early postoperative infection. An HbA1c level of < 5% indicates possible recurrent episodes of severe hypoglycemia, and adequate adjustment should be conducted before surgery. Therefore, any preoperative pathoglycemia should be treated actively.[267, 268] In the absence of hypoglycemic syncope, it is recommended to control preoperative blood glucose to HbA1c ≤ 8%, FBG ≤ 5.6 mmol/L, and two hours postprandial glucose ≤ 7.8 mmol/L.[269]

Operational difficulties and postoperative complications can be reduced by the application of structured preoperative exercise programs and low-calorie diets (1,350 kcal/day).[270, 271] Blood glucose levels should be tested, and hypoglycemic agents should be adjusted promptly after a change in dietary structure to avoid hypoglycemic episodes. Patients are advised to refeed in stages after surgery, starting with liquids, purees, and soft foods, followed by regular solid foods and water between meals.[272]

Q60: How should patients with T2DM be managed for long-term nutrition after metabolic surgery?

After metabolic surgery, patients with T2DM should be provided long-term nutritional guidance by the professional nutrition team, including formulation of dietary programs, exercise instruction, and assistance in the development of good eating habits and daily routines (B, strongly recommended). For patients with T2DM, grains and fruits with high fiber content should be the primary source of carbohydrates after bariatric surgery, with increased intake of fresh vegetables and decreased intake of high-calorie and high-fat diets (C, weakly recommended)

A small-sample study in China recommended that obese patients with T2DM follow the dietary pattern starting from the second week after SG as follows: In the first stage, low-fat and low-sugar liquid diets (protein ≥ 60 g/day) of 700–900 kcal/day should be adopted, in which a liquid intake of > 2000 mL/day should be guaranteed, along with daily multivitamin supplementation. In the second stage, that is, one month postoperatively, the semi-liquid dietary pattern should be followed for a gradual transition to the normal diet through small frequent meals (6–8 meals throughout the day, with 60–80 g/day of protein) at a fixed quantity on schedule. Finally, in the

later stages, the principle of small frequent meals and sufficient chewing of foods (≥ 12 chews) should be followed as usual. This dietary pattern helps normalize a patient's blood glucose level.[273] Weight loss is negatively correlated with the number of postoperative poor dietary habits (including overeating, multiple meals, and craving for sweets).[274] In terms of food choices, fiber-rich grains are recommended as the basis of diets, low-fat meat, fish, low-fat dairy products, and eggs are preferred sources of protein, and the intake of vegetables and fruits should be increased at a later stage. The intake of grains low in fiber or foods high in saturated fats, trans-fatty acids, cholesterol, sugar, alcohol, and carbonated beverages should be avoided.[275, 276] Foods irritating the stomach, such as ice water, coffee, tea, and alcohol, should not be consumed three months after bariatric surgery. In addition, supplementation with vitamins and trace elements should be routinely performed because of chronic inadequate vegetable and fruit intake after metabolic surgery.[275]

Q61: How should nutrition be managed in patients with poor diabetes remission after metabolic surgery?

The combination of MNT and medication contributes to the control of blood glucose, and revision surgery may be considered for those with refractory hyperglycemia or recurrent metabolic disease, but support from evidence-based medicine is lacking (C, weakly recommended)

Medical treatment for diabetes recurrence after metabolic surgery consists of nutrition therapy combined with medication. MNT provided by registered dietitians and nutritionists can significantly reduce HbA1c levels.[277, 278] Metformin can be used as a monotherapy option for patients with HbA1c < 9% early after metabolic surgery; in the case of HbA1c ≥ 9%, a second medication can be added to help further reduce weight or cardiovascular risk. During the later stages, it is feasible to shift the long-term medication regimen to a combination of metformin and drugs capable of decreasing cardiovascular risk, reducing body weight, and protecting the kidneys, such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) and GLP-1 analogs.[278]

The remission rate of diabetes in patients who underwent gastric pouch or stoma revision and distal bypass revision after RYGB could reach 79% (24 patients) and 100% (11 patients), respectively, but close nutritional management is still required during the perioperative period of revision surgery.[279]

Trauma and perioperative glycemic control

Q62: What is the preferred nutritional support for patients with hyperglycemic stress?

Enteral nutrition is preferred for patients complicated by stress hyperglycemia (B, strongly recommended)

A meta-analysis investigating the effects of parenteral nutrition (PN) and specific enteral nutrition (EN) on blood glucose in patients with acute severe pancreatitis suggested that the incidence of hyperglycemia and insulin demand was lower in patients receiving EN supportive treatment than in patients in the PN treatment group.[280] In trauma patients with comorbid diabetes mellitus, enteral nutrition has been shown to reduce intestinal permeability, improve immunologic function, and restore gastrointestinal function with lower nutritional support costs.[281, 282]

Q63: Can diabetes-specific enteral nutritional preparations be used for patients with stress hyperglycemia?

Diabetes-specific enteral nutritional preparations are appropriate for patients with stress hyperglycemia (B, strongly recommended)

Several studies have shown that diabetes-specific formulations using slow-release starch-modified (tapioca starch, grain starch) carbohydrates or low carbohydrates can improve glycemic control in patients. An RCT study including 80 critical patients complicated by hyperglycemia was separated into two groups and received either standard formulations or diabetes-specific formulations enriched with slow-release starch for ten days, suggesting that enteral nutrition with slow-release starch formulations provided better control of FBG and PBG and reduced the incidence of infection in critically ill patients.[283] In response to post-traumatic stress hyperglycemia, diabetes-specific enteral nutritional preparations are more beneficial in controlling postoperative glycemia than common enteral nutritional preparations.[284, 285] Compared with standard enteral formulations, the use of diabetes-specific formulations in critically ill patients with stress hyperglycemia resulted in a trend toward a modest reduction in mean glucose and a significant reduction in insulin demand.[286] In a study using different nutritional formulations for mechanically ventilated critically ill patients with hyperglycemia, the dosage of insulin required, intensive care unit (ICU)-acquired infections, days of mechanical ventilation, ICU length of stay, and mortality at 28 days after admission, hospital stay, in-hospital mortality, and 6-month mortality were compared among new diabetes-specific formulations, standard formulations, and control diabetes-specific formulations in patients with blood glucose levels maintained at 110–150 mg/dl (glucose target). The results suggested that both diabetes-appropriate formulations reduced insulin demand, improved glycemic control, and reduced the risk of acquired infections relative to standard formulations.[287]

Q64: In what range should glycemic targets be controlled during stress hyperglycemia in critically ill patients?

The initiation of insulin therapy is recommended for critically ill patients with a blood glucose of 10.0 mmol/L, to control blood glucose at 7.8–10.0 mmol/L. The risk of hypoglycemia should be prevented by regular monitoring of blood glucose (hypoglycemia level requiring intervention: < 3.9 mmol/L) (A, strongly recommended)

An RCT (Leuven study) in 2001 revealed that, through continuous intravenous pumping of insulin and close monitoring for tight glycemic control within the normal range (4.4–6.1 mmol/L), termed intensive insulin therapy (IIT), in critically ill patients with stress hyperglycemia, the morbidity and complication rates were significantly decreased.[288] This conclusion was verified in critically ill patients.[289] A multicenter large-sample RCT (NICE-SUGAR study) in 2009 demonstrated that controlling blood glucose below 10.0 mmol/L reduced patient

mortality and the incidence of hypoglycemia (< 2.2 mmol/L) compared with tightly controlled glucose at 4.4–6.1 mmol/L.[290] ADA has also updated its guidance on glycemic management for ICU patients based on the results of the NICE-SUGAR study. According to the clinical Big Data study at Yale University in 2014, after adopting evidence from the NICE-SUGAR study, ICU patients presented a slight decrease in overall glucose levels and significantly lower numbers of hypoglycemia (< 3.9 mmol/L) and severe hyperglycemia (≥ 16.7 mmol/L) events compared with IIT,[291] which also further verified the phase correctness of the NICE-SUGAR study. A reticulated meta-analysis in 2017 that pooled 35 RCTs divided patients into four groups by blood glucose level (< 6.7 mmol/L group, 6.7–7.9 mmol/L group, 8.0–10.0 mmol/L group, and > 10.0 mmol/L group), and the results suggested that the risk of hypoglycemia (< 2.2 mmol/L or hypoglycemia-related symptoms) was significantly higher in the first two groups than in the latter two.[292] In the *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (2021)* published in 2021, it is similarly recommended that patients with sepsis should reach a target blood glucose of 8.0–10.0 mmol/L and that the hyperglycemia levels requiring insulin intervention should be 10.0 mmol/L.[293]

Parenteral and enteral nutrition support

Q65: Are inpatients with diabetes with higher nutritional risk/worse malnutrition than inpatients without diabetes?

Patients with diabetes have a higher incidence of nutritional risks/malnutrition and should be routinely screened and assessed for nutrition (B, strongly recommended)

A cross-sectional investigation in Spain suggested that patients with diabetes scored low on the Mini-Nutritional Assessment Scale (16.5) and Nutritional Risk Index (83.09) and that malnourished patients with diabetes had longer hospital stays (21 and 17 days, respectively).[294] Another prospective study of inpatients with diabetes in the general surgery department also suggested that the prevalence of malnutrition in patients with surgical diabetes was twice as high as in those without diabetes.[295]

Q66: Do diabetes-specific enteral nutritional preparations have a better effect on blood glucose than full-nutrition standard formulations?

Diabetic EN formulations have better effects on insulin demand, FBG, and HbA1c than standard formulations (B, strongly recommended)

A systematic review in 2014 suggested that diabetes-specific EN formulations were superior to standard EN formulations in controlling both PBG and HbA1c.[296] A further meta-analysis in 2019, which included five RCTs with a total of 627 patients, revealed that diabetes-specific EN formulations, in addition to the favorable effects on the above glycemic parameters, presented greater benefits on FBG, with a mean difference of reduction of 1.15 mmol/L.[297] Several randomized prospective studies and meta-analyses have demonstrated the role of diabetes-specific formulations of modified carbohydrates in improving glycemic control and glycemic variability, attenuating insulin resistance, and reducing insulin dosage.[287, 298-300] In most cases, the formulations are improved by replacing all maltodextrin with slow-release starch (tapioca starch, grain starch) and increasing fructose and dietary fiber intake, but the energy supply ratio is controlled within 45%–60%.[4] Alternatively, glycemic improvements can be obtained by increasing MUFA to boost the fat energy supply ratio or increasing the protein energy supply ratio to decrease the carbohydrate energy supply ratio.

Q67: Does the implementation of diabetes-specific enteral nutrition therapy in patients with diabetes improve health economics?

Standardized application of diabetes-specific EN formulations reduces the consumption of healthcare resources (B, strongly recommended)

In a retrospective study involving 93 patients with diabetes, the implementation of diabetes-specific EN preparations for one year resulted in a significant decrease in the number of emergency department visits, days of hospitalization, and use of healthcare resources during the period.[301] Another retrospective study showed that the use of diabetes-specific EN tube feeding had the effects of significantly reduced mortality (from 12.3% to 5.1%), shortened the length of ICU stay, and reduced total ICU treatment expenses ($9,200 and $6,700, respectively).[302] According to a retrospective analysis of nutrition support data from 125,000 hospitalizations of inpatients with diabetes in a premier large-scale research database, the application of diabetes-specific EN tube feeding achieved a per capita reduction in average length of stay of 0.88 days and a cost savings of US$2,586.[303]

Diabetic nephropathy and dialysis period

A large prospective study of 5,032 patients diagnosed with T2DM and followed up showed proteinuria in approximately 40% of patients aged > 15 years and renal impairment in 30% of patients.[304] Relevant Chinese and international guidelines can be used to determine the recommended amount of calories and protein for patients with diabetic nephropathy at various stages in view of the lack of direct clinical study data support.[305-307] The recommended protein intake for hemodialysis patients should be in the range of 1.0–1.2 g/kg/day. For peritoneal dialysis patients without residual renal function, the recommended intake of protein should be kept at 1.0–1.2 g/kg/day and 0.8–1.0 g/kg/day for patients with residual renal function. Further multicenter RCTs are needed to draw relevant conclusions, and it is recommended that the administration of low-protein diets should be monitored and guided by nutritionists (dieticians).[308-311]

Q68: How can malnutrition be prevented in patients with diabetic nephropathy?

Given that patients with diabetic nephropathy are more susceptible to malnutrition when on low-protein diets, malnutrition should be prevented by adequate calorie intake (C, weakly recommended). In patients with diabetic nephropathy who are already malnourished, the implementation of low-protein diets is not recommended, given that the risk of death increases with lower protein intake (C, weakly recommended). Since patients with diabetes

on dialysis usually have a lower daily calorie intake than those without diabetes, the regimen of restricted diets should be used with caution (D, weakly recommended)

A prospective cohort study conducted in 2013 suggested that patients in the low-protein diet group (0.6–0.7 g/kg/day) had low energy intake and were more likely to be malnourished than those in the basal diabetic diet group.[312] A single-center historical cohort study in 2020 involving 449 patients with diabetic nephropathy suggested that reduced dietary protein intake was an independent risk factor for death from malnutrition.[313] A cross-sectional study in 2017 revealed that patients with diabetes undergoing dialysis had a lower daily calorie intake of 3.81 kcal/kg than those without diabetes undergoing dialysis.[314]

Q69: How should the nutritional status of patients with diabetic nephropathy and malnutrition be improved?

Oral nutritional supplementation is preferred in patients with diabetic nephropathy and malnutrition. Nephropathy-appropriate nutritional supplements can improve malnutrition while avoiding the increased use of phosphate binders and electrolyte disturbance (C, weakly recommended)

Eighty malnourished hemodialysis patients were included in an RCT published in 2021, which demonstrated that one consecutive month of oral administration of nephropathic enteral nutritional preparations (370 kcal/day) improved malnutrition inflammation scores and serum albumin levels better than patients in the dietary guidance alone group, without affecting the electrolyte levels.[315] Another RCT in 2008 included 86 moderately malnourished hemodialysis patients, and oral nephropathy-specific nutritional supplements (500 kcal/day) for three consecutive months improved nutritional status and quality of life compared with patients in the non-intervention group, without increasing the need for phosphate binders.[316]

Q70: How can blood phosphorus status be improved in patients with diabetic nephropathy complicated by hyperphosphatemia?

In patients with diabetic nephropathy complicated by hyperphosphatemia, appropriate phosphate binders can be chosen to control high blood phosphorus levels in case dietary adjustments are ineffective (B, weakly recommended)

A 3-year follow-up of 1,726 patients with CKD stages 3-5–investigators found that patients with serum phosphorus levels ≥ 1.39 mmol/L had an increased risk of dialysis and death (HR = 2.04), especially those with diabetic nephropathy.[317] Diets that are low in protein and conducive to limiting the intake of high-phosphorus foods are still needed, but as renal function progresses, appropriate phosphate binders may also be considered when phosphorus metabolism fails to improve by dietary control alone.

Q71: Do patients with diabetic nephropathy require routine supplementation with vitamin D or its analogs?

In vitamin D-deficient patients with diabetic nephropathy, oral supplementation with vitamin D3 is beneficial for improving the serum vitamin D status and dyslipidemia (C, weakly recommended). Since there are no uniform conclusions regarding the ability to improve proteinuria and renal function in patients with diabetic nephropathy, routine use is not recommended (C, weakly recommended)

In an RCT in 2019 that included 50 patients with vitamin D-deficient diabetic nephropathy, oral vitamin D3 (50,000 IU/week) was assigned to patients in the intervention group for eight consecutive weeks, and vitamin D supplementation significantly increased vitamin D status and lowered blood TG, LDL-C, and TC levels in the intervention group compared to those in the control group.[318] A systematic review in 2015 that included four RCT intervention studies suggested that oral administration of vitamin D3 (800–7000 IU/day) or calcitriol (20–40 IU/day) failed to significantly improve the urinary albumin/creatinine ratio in vitamin D-deficient patients with diabetic nephropathy compared with those in the control group.[319] A meta-analysis in 2019 suggested that supplementation with vitamin D or its analogs tended to improve proteinuria in diabetic nephropathy compared to that in the control group, but the difference was not statistically significant.[320] According to another meta-analysis in 2019 that included 20 RCTs with a total of 1,464 participants, supplementation with vitamin D and its analogs was beneficial for 24-hour urinary protein and inflammatory markers in patients with diabetic nephropathy without significant effects on serum creatinine, glomerular filtration rate, and glycemic control.[321]

Diabetes mellitus complicated by disorders of lipid metabolism

Q72: How do different types of dietary fatty acids affect lipid metabolism in patients with T2DM?

Reduction of dietary saturated fat is beneficial for reducing the risk of cardiovascular disease in patients with T2DM. The intake of saturated fatty acids should not exceed 10% of total energy, and that of trans-fatty acids should not exceed 1% of total energy, and the routine use of ω-3 dietary supplements in patients with diabetes to improve dyslipidemia is not yet supported (C, strongly recommended)

In the prevention strategies for cardiovascular disease based on T2DM and pre-diabetic populations, investigators have suggested that the ratio of fat energy supply should be limited to 20%–30%, and the percentage of calorie intake from SFA should be kept ≤ 7%. The composition of fatty acids should be considered in cases where the percentage of calorie intake from fat is > 25%.[322] The *Chinese guidelines for the management of dyslipidemia in patients with T2DM* recommend an intake of SFA of no more than 10% of total energy and trans-fatty acids of no more than 1% of total energy.[323] MUFA, as a better source of dietary fat, should have an energy supply ratio of 10%–20%, and PUFA intake should not exceed 10% of the total calorie intake. It is recommended

to consume fish two to four times a week (especially fish rich in ω-3 PUFA, eicosapentaenoic acid, and docosahexaenoic acid) and nuts and seeds (rich in α-linolenic acid) for the prevention or treatment of cardiovascular disease.[324] The main active ingredients of ω-3 fatty acids are eicosapentaenoic acid and docosahexaenoic acid extracted from fish oil, which, alone or in combination with lipid-lowering drugs (fibrates or statins), can decrease TG by up to 30%–40% with fewer adverse effects and good tolerability. However, high-purity ω-3 fatty acids (2–4 g/day) are required to reduce serum TG levels[325] effectively. Based on current evidence, the routine use of ω-3 dietary supplements in patients with diabetes to improve dyslipidemia is not supported.[322, 325-327]

Q73: What is the effect of dietary cholesterol on the occurrence of cardiovascular events in patients with diabetes?

Patients with diabetes with comorbid lipid metabolism abnormalities may reduce cholesterol intake (C, strongly recommended)

The latest ADA recommendations for lipid management in patients with diabetes suggest that cholesterol intake should be decreased in patients with diabetes with comorbid lipid metabolism abnormalities.[324] The expert consensus on the prevention and treatment of T2DM in patients with comorbid dyslipidemia in China recommends a dietary cholesterol intake of < 300 mg/day.[324] Patients with T2DM may benefit from a reduction in LDL-C by emphasizing the intake of vegetables, fruits, and whole grains (including low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, and nuts) and by limiting the intake of sweets, sugared beverages, and red meat.[326]

Diabetes mellitus combined with neuropathy

Q74: Does supplementation with vitamin B12 derivatives (methylcobalamin) improve neuropathy in patients with diabetes?

The derivatives of vitamin B12 (mecobalamin) improve spontaneous limb pain, numbness, nervous reflex, and conduction disorders in patients with diabetes, and the combination of mecobalamin and α-lipoic acid is more effective than the treatment with mecobalamin alone (C, weakly recommended)

Mecobalamin significantly improves clinical symptoms, signs, and nerve conduction velocities in patients with diabetic neuropathy, and the combination of mecobalamin and α-lipoic acid is more effective in the treatment of diabetic peripheral neuropathy than mecobalamin alone.[328, 329] Plasma vitamin B12 levels were found to be elevated after 12 months of oral administration of 1 mg mecobalamin in patients with diabetic neuropathy, and neurophysiologic indices, motor function, pain scores, and quality of life were all improved.[330]

Q75: Does α-lipoic acid improve diabetic neuropathy?

α-lipoic acid may improve neurosensory symptoms and nerve conduction velocity, as well as neurophysiologic alterations, and alleviate and delay the progression of neurological damages, and oral supplementation is comparable to injection in terms of clinical efficacy (C, weakly recommended)

Several studies have found that α-lipoic acid significantly improves nerve conduction velocity and neuropathy symptoms.[331-333] The results of a 4-year multicenter, parallel RCT showed that α-lipoic acid improved neurophysiological alterations alleviated and delayed the progression of neurological damage, and was well tolerated.[334] A meta-analysis showed comparable clinical efficacy of injected versus oral α-lipoic acid. [335]

Q76: Does vitamin D supplementation improve neuropathy in patients with diabetes?

Supplementation with high-dose vitamin D may be beneficial in improving neuropathy symptoms and quality of life in patients with T2DM (D, weakly recommended)

Several studies have demonstrated the benefits of vitamin D supplementation in improving neuropathy in patients with diabetes.[336-338] A 24-week RCT study showed that participants with vitamin D deficiency/insufficiency treated with vitamin D3 40,000 IU/week experienced a significant decrease in the severity of neuropathy, improvement in skin microcirculation, decrease in IL-6 levels, and an increase in IL-10 levels.[339]

Diabetic foot

Q77: Does supplementation with amino acids with pharmacological action, such as arginine, influence foot ulcer healing in patients with diabetes?

Supplementation with pharmacologically active amino acids (e.g., arginine) may promote the healing of foot ulcers in patients with diabetes (C, weakly recommended)

A study divided 33 patients with a diabetic foot into three groups for treatment of 9–284 days: 11 patients treated with subcutaneous injection of 10 mmol/L arginine in the wound, 11 treated with standard treatment based on soap, water, and iodine, and 11 patients with diabetes without ulcers as the control group. All patients treated with arginine showed improvement in their ulcers, with eight patients presenting complete healing in the wound and another three patients withdrawing from the study due to relocation, with ulcer healing rates of 95%, 90%, and 85%, respectively, before withdrawal. In contrast, the patients in the control group experienced worsening ulcerative lesions.[340]

Q78: Does vitamin D supplementation influence the healing of foot ulcers in patients with diabetes?

Supplementation with high-dose vitamin D may promote healing of foot ulcers in patients with diabetes (C, weakly recommended)

An RCT investigating the effect of vitamin D on foot ulcer healing in patients with diabetes showed that 50,000 U of vitamin D supplementation administered every two weeks for 12 weeks contributed to a more pronounced reduction in the size of foot ulcers in patients with diabetes in the study group.[341] In another RCT, interventions were provided to 64 patients with diabetic foot ulcers with at least one ulcer or ulcer unhealed for at least six weeks by oral administration of high-dose and low-dose vitamin D3, respectively. The high-dose group was administered 170 μg (6,800 IU) of vitamin D3 orally, and

the low-dose group was administered 20 μg (800 IU) of vitamin D3 orally for 48 weeks. The healing rate of ulcers in the high-dose group was significantly greater than that in the low-dosage group.[342] In another RCT with 47 patients with Wagner grade 2 diabetic foot complicated by vitamin D deficiency, 24 patients in the 300,000 IU vitamin D intramuscular injection group and 23 patients in the 150,000 IU vitamin D intramuscular injection group, a significant reduction in ulcer area from baseline in both groups after four weeks was realized and was even more pronounced in the high-dosage group.[343]

Q79: Does zinc supplementation influence foot ulcer healing in patients with diabetes?

Supplementation with zinc may promote healing of foot ulcers in patients with diabetes (D, weakly recommended)

In a randomized, double-blind, placebo-controlled trial involving 60 patients with diabetic foot, 220 mg of zinc sulfate was administered daily to 30 patients in the intervention group, presenting a more significant reduction in the size of foot ulcers in patients with diabetes in the intervention group.[344] Another RCT revealed that zinc supplementation significantly reduced the size of foot ulcers in patients with diabetes.[345]

Q80: Does magnesium supplementation influence foot ulcer healing in patients with diabetes?

Supplementation with magnesium may promote healing of foot ulcers in patients with diabetes (D, weakly recommended)

In a study of 70 patients with diabetic foot, the investigators administered 250 mg of magnesium oxide for 12 weeks to the intervention group, and the results showed a significant reduction in the length, width, and depth of the ulcers in the intervention group compared with the control group.[346] Vitamin E supplementation improves the oxidative stress response and inflammation in the diabetic foot,[347] thus enhancing the effect of magnesium on the healing of diabetic foot ulcers.

Medication and nutrition

Q81: Do GLP-1 receptor agonists contribute to weight loss in patients with T2DM complicated by obesity or overweight?

GLP-1 receptor agonists promote weight loss in patients with T2DM complicated by obesity or overweight (A, strongly recommended)

Several studies have demonstrated the ability of GLP-1 receptor agonists to promote weight loss. A recent reticulated meta-analysis (including 143 RCTs) suggested that the combination of GLP-1 receptor agonists and lifestyle management was effective in promoting weight loss of more than 5%, with weight loss effects superior to those of orlistat, SGLT2i, and metformin.[348] A meta-analysis including 18 RCTs found that GLP-1 receptor agonists promoted the improvement of body weight in overweight/obese patients with T2DM, with a mean weight change of -2.8 (-3.4, -2.3) kg.[349] In addition to improving blood glucose and lowering blood pressure and total cholesterol levels, GLP-1 receptor agonists presented more significant weight loss effects than other interventions, with 1.9 kg weight loss in the GLP-1 receptor agonist group compared to the placebo group (10 RCTs), 4.8 kg weight loss compared to the insulin group (6 RCTs), 3.0 kg weight loss compared to the group administered with other hypoglycemic agents (including metformin or sulfonylureas) (3 RCTs) and 2.0 kg weight loss in the group administered with dipeptidyl peptidase IV inhibitor (DPP-4i) (2 RCTs).[349] Several Chinese guidelines have separately affirmed the role of GLP-1 receptor agonists in delaying gastric emptying, reducing food intake, and lowering body weight and have recommended their use in insulin-resistant patients with diabetes complicated by abdominal obesity.[2, 350]

Q82: Do GLP-1 receptor agonists affect muscle condition in the body?

Combining GLP-1 receptor agonists with calorie restriction and strict lifestyle interventions may lead to a reduction in muscle and fat-free mass in patients with diabetes, but their effects on muscle when used alone are inconclusive (B, weakly recommended)

Based on a small-sample single-arm clinical study, the application of exenatide for 14 weeks in obese patients without diabetes promoted significant weight loss (2.0 ± 2.8 kg) and a reduction in body fat (1.3 ± 1.8 kg) (p = 0.01); however, the fat-free mass also presented a downward trend (0.8 ± 2.2 kg), p = 0.14.[351] Another meta-analysis based on 18 RCTs similarly reported that the application of semaglutide, a GLP-1 receptor agonist, in patients with T2DM reduced the fat-free mass of the body by up to -1.68 (-2.84, -0.52) kg.[352] However, another RCT compared the outcomes of lifestyle intervention + liraglutide and lifestyle intervention alone in obese individuals, and the results showed that despite a decrease in fat-free mass in both groups after the 16-week intervention, the difference between the groups was not statistically significant, suggesting that liraglutide might not produce independent adverse effects on muscle and fat-free mass upon elimination of confounding factors, such as lifestyle intervention and calorie restriction.[353]

Q83: Can SGLT2i reduce body weight?

SGLT2i promotes weight loss in patients with diabetes and a change in body composition characterized by a decrease in body fat (B, strongly recommended)

The diabetes treatment guidelines released by the ADA in 2021 also listed SGLT2i as a first-line hypoglycemic agent for patients with diabetes with comorbid CKD, heart failure, atherosclerotic cardiovascular disease status, or elevated risk.[354]

Clinical evidence from multiple RCTs and meta-analyses suggests that SGLT2i promotes weight loss in patients with diabetes by 3%–5%, with an absolute weight loss of 2.5–3.2 kg.[355-358] MRI, dual-energy X-ray absorptiometry, and bioresistive antibody component analysis in an RCT study of Caucasian populations in East Asia, Japan, Europe, and the United States further revealed that 70%–85% of SGLT2i-induced body weight loss originated from a reduction in body fat, whereas lean body mass and grip strength were maintained without significant reduction.[359-363]

Q84: Does SGLT2i affect the body's bone metabolism?

The effect of SGLT2i on bone metabolism of the body is inconclusive; canagliflozin and dapagliflozin may promote the reduction of bone mineral density and bone loss. The nutritional status of calcium, phosphorus, and vitamin D needs to be closely observed during medication (C, weakly recommended)

The CANVAS large-sample controlled clinical trial, based on the clinical observation of 10,142 patients with T2DM administered canagliflozin or placebo, suggested the potential of canagliflozin in increasing the risk of fracture, with an HR (95% CI) of 1.26 (1.04–1.52), and another subsequent meta-analysis that pooled nine RCTs (including the CANVAS trial) also obtained similar results.[364, 365] In 2015, the Food and Drug Administration (FDA) of the US issued a warning suggesting that canagliflozin might contribute to the loss of body bone density and the increase in the risk of fracture.[366] According to another small-sample RCT (252 patients), dapagliflozin resulted in 7.7% of patients with T2DM experiencing a fracture event compared to placebo over 104 weeks of dosing.[367]

Q85: Do patients with diabetes who are administered SGLT2i need to receive special dietary management?

SGLT2i promotes glucose excretion via the kidneys, achieves feedback reduction in the production of insulin, facilitates glucagon secretion, and tends to accelerate gluconeogenesis and ketoplasia. Avoidance of very low-calorie intake and maintenance of carbohydrate energy supply ratio of no less than 40% of daily dietary energy are recommended to refrain from inducing normoglycemic or hyperglycemic diabetic ketoacidosis (B, weakly recommended)

A meta-analysis incorporated reports of 47 patients with SGLT2i-associated diabetic ketoacidosis (DKA) in the perioperative period. The results showed that multiple factors contributed to the elevated risk of SGLT2i-associated DKA in stress conditions, and in addition to undercapacity, inflammation, infection, surgical stress, a sudden and excessive dosage reduction of combined insulin, and various emergencies (including pulmonary embolism and acute kidney injury), alcohol abuse and insufficient intake of perioperative dietary carbohydrates, such as prolonged preoperative fasting and very low-energy diets in the perioperative period, were also critical inducing factors.[355, 368] Another 3-arm RCT comparing changes in metabolic markers in patients with T2DM administered luseogliflozin and different dietary compositions suggested that patients with low carbohydrates (40% energy supply ratio) had a significant elevation of blood ketone bodies compared to those with high carbohydrates (55% energy supply ratio).[369]

Q86: Does metformin potentially cause vitamin B12 deficiency?

Patients with diabetes who have been taking metformin for the long term (more than two years) or at a dose of more than 1500 mg/day should be routinely screened for vitamin B12 to monitor and prevent vitamin B12 deficiency (A, strongly recommended)

An RCT suggested that long-term use of metformin increases the risk of vitamin B12 deficiency, which can lead to elevated Hcy concentration, and that regular monitoring of vitamin B12 concentration is needed to prevent vitamin B12 deficiency.[370, 371] Older patients with diabetes taking metformin at a dose of more than 1500 mg/day for more than two years are at an increased risk of vitamin B12 deficiency and should be monitored for vitamin B12 levels before and after administration.[372]

In summary, given the importance of the comprehensive treatment and management of diabetes, MNT should be used throughout the care of individuals with diabetes. The implementation of MNT by dietitians or other allied healthcare professionals is effective in reducing body weight, improving glycemic control, preventing and delaying the onset of cardiovascular disease, decreasing the dosage of medication in patients with diabetes, reducing direct healthcare costs, improving quality of life, delaying the onset of T2DM, and even induce the remission of T2DM.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest. The study was funded by Program of National High Level Hospital Clinical Research Funding (2022-PUMCH-B-054).

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