

Diabetes (DM) Type II

Diagnosis/Condition: Diabetes mellitus

Type II Diabetes

Discipline: ND

 ICD-10 Codes:
 E08.9; E09.9; E13.9; E11.9

 Origination Date:
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Type II Diabetes mellitus (T2D) is a disorder in which blood glucose levels are abnormally high due to the development of a resistance to insulin. It was formerly referred to as non-insulin dependent diabetes (NIDDM), although more patients with T2D are utilizing insulin for treatment. The estimated prevalence of diabetes among adults in the United States ranges from 4.4 to 17.9 percent. However, because of the associated microvascular and macrovascular disease, diabetes accounts for almost 14 percent of US health care expenditures.^{2,3} Since the early 1990s, the incidence of T2D has increased in children and adolescents and is linked to the rise in childhood obesity.4 African Americans, Native Americans, and Hispanics who live in the United States have a twofold to threefold increased risk of developing T2D. In 2017, approximately 462 million individuals were affected by type 2 diabetes corresponding to 6.28% of the world's population (4.4% of those aged 15-49 years, 15% of those aged 50-69, and 22% of those aged 70+), or a prevalence rate of 6059 cases per 100,000. The gender distribution is equal, and the incidence peaks at around 55 years of age. Global prevalence of type 2 diabetes is projected to increase to 7079 individuals per 100,000 by 2030, reflecting a continued rise across all regions of the world. More than 1 million deaths were attributed to this condition in 2017 alone, ranking it as the ninth leading cause of mortality. This is an alarming rise when compared with 1990, when type 2 diabetes was ranked as the eighteenth leading cause of deaths. Even though it afflicts individuals later in life, type 2 diabetes ranks seventh among the leading causes of disability and years of life lost (DALYs), jumping ranks from nineteenth position in 1990.⁵ Approximately twenty six percent (26%) of U.S. adults with diabetes reported using some form of Complementary and Alternative Medicine (CAM) in the past year.⁶

OTHER TYPES OF DIABETES

<u>Metabolic syndrome (syndrome X or insulin-resistance syndrome)</u>: thought to be due to developing insulin resistance and can occur in patients with overtly normal glucose tolerance, prediabetes, or diabetes. Diagnosed when a patient has at least 3 of the following 5 conditions:

- 1. Abdominal obesity.
- 2. Elevated triglyceride level.
- 3. Low level of high-density lipoprotein (HDL) cholesterol.
- 4. Elevated blood pressure (BP).
- 5. Fasting glucose value of 100 mg/dL or higher.

<u>Pre-diabetes</u>: glucose levels are too high to be considered normal but not high enough to be labeled diabetes. Fasting glucose levels - between 101 mg/dL and 126 mg/dL or glucose level 2 hours after a glucose tolerance test between 140 mg/dL and 200 mg/dL. Decreasing body weight by 5 to 10% through diet and exercise can significantly reduce the risk of developing future diabetes.

Gestational Diabetes Mellitus (GDM): diabetes diagnosed during pregnancy.

<u>Type I (T1D)</u>: (formerly referred to as insulin dependent diabetes mellitus (IDDM) or juvenile diabetes) - a disorder in which blood sugar (glucose) levels are abnormally high caused by insulin deficiency following destruction of the insulin-producing pancreatic beta cells. Usually developed before age 30. About 10% of all people with diabetes have Type I disease.

Risk Factors

Diabetes risk factors include the following and testing should be considered in these populations:

- Age ≥45 years.
- Overweight (body mass index ≥25 kg/m2).
- Obesity in childhood (≤18 yrs.) even if asymptomatic.
- Family history T2D in a first-degree relative.
- Habitual physical inactivity.
- Higher-risk ethnic or racial group (e.g., African American, Hispanic, Native American, Asian-American, and Pacific Islanders).
- History of delivering a baby weighing >4.1 kg (9 lb) or of gestational diabetes mellitus
- Hypertension (blood pressure ≥140/90 mmHg or on therapy for HTN).
- Dyslipidemia defined as a serum high-density lipoprotein cholesterol concentration ≤35 mg/dL (0.9 mmol/L) and/or a serum triglyceride concentration ≥250 mg/dL (2.8 mmol/L)
- Previously identified A1C ≥5.7 percent, impaired glucose tolerance or impaired fasting glucose.
- History of antidepressant use.⁷
- Vitamin D or magnesium deficiency.
- History of cardiovascular disease (CVD).
- History of statin use.^{8,9}
- Lack of dietary fish and dietary long chain fatty acids.¹⁰

Subjective Findings and History

- Can be asymptomatic.
- Family history of diabetes.

- Polycystic ovary syndrome (PCOS).
- Polyuria, polydipsia.
- Blurry vision or other visual disturbances.
- Hunger, weight loss or weight gain.
- Fatigue.
- Neuropathies/paresthesia.
- Yeast infections/balanitis.
- Abdominal pain.
- Erectile dysfunction.

Complications

Morbidity from diabetes is a consequence of both macrovascular disease (atherosclerosis) and microvascular disease (retinopathy, nephropathy, and neuropathy). In T2D, disease onset is insidious, and diagnosis is often delayed. As a result, diabetic microvascular complications may be present at the time of diagnosis. These can be progressive if blood glucose levels are not well-controlled and include: arteriosclerosis, atherosclerosis, other cardio-vascular disease, strokes, claudication, vision problems (diabetic retinopathy), (poly) neuropathies, limb weakness, skin ulcers and infections (fungal and bacterial), renal failure, injuries and falls, and diabetic ketoacidosis. Acute hypoglycemia can occur and is an urgent medical emergency.

Diagnosis and Differential Diagnosis

- Metabolic Syndrome.
- Pre-diabetes.
- T1D.
- Gestational diabetes.
- Celiac disease.
- Other causes of hyperglycemia.
- Secondary hyperglycemia can be caused by physiological stresses (such as acute infection and trauma) or by various endocrine conditions.

The American Diabetes Association (ADA) criteria for the diagnosis of T2D are any of the following:¹¹

- An HbA1c level of 6.5% or higher*; **or**
- A fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher; fasting is defined as no caloric intake for at least 8 hours, **or**
- A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), **or**
- A random plasma glucose (RPG) of 200 mg/dL (11.1 mmol/L) or higher in a
 patient with classic symptoms of hyperglycemia (i.e., polyuria, polydipsia,
 polyphagia, weight loss) or hyperglycemic crisis

*The American Association of Clinical Endocrinologists recommends that HbA1c be considered an additional optional diagnostic criterion for long term trends, rather than a primary criterion for diagnosis of diabetes.¹²

Objective Findings and Assessment

A workup should be done when a patient presents with symptoms or in asymptomatic patients who present with random serum glucose levels (>140 mg/dL); in all adults with BMI \geq 25 kg/m2; or in adults with hypertension (blood pressure >135/80 mmHg). In individuals without risk factors, routine testing should begin at age 45 years.

Physical Exam (should be performed two to three times yearly), Testing, and Vaccinations.¹³

Management and Physical Exam	Frequency	Comments
Smoking cessation counseling	Every visit	For smokers only
Blood pressure	Every visit	Goal <130/80, or <140/90 14,15,16,17,18(guidelines vary)
Dilated eye examination (fundoscopic)	Annually	Begin at onset of T2D, three to five years after onset of T1D. Examine more than annually if significant retinopathy
Foot examination	Annually	Every visit if peripheral vascular disease or neuropathy is present (include inspection, assessment of foot pulses, reflexes, and testing for loss of protective sensations and vibration)
Skin examination	Every visit	For acanthosis nigricans and insulin injection sites
Thyroid evaluation/palpation	Annually	
Cardiovascular exam and studies		Stress test if indicated or if beginning exercise program
Dental screening	Annually	
Cancer screening	Variable	Some studies have suggested an increased risk of cancer in patients with diabetes, possibly related to the coincident obesity
Psychosocial-Mental Health screening	Variable	Referral as indicated – screen for depression, anxiety, eating disorders, cognitive impairment
Laboratory Studies	Frequency	Comments
Fasting serum lipid profile	Annually	May obtain every two years if profile is low risk.
Antibodies	Once	There is no specific test to distinguish between the two types of diabetes, T1D is

		suggested by the presence of circulating, pancreatic autoantibodies. The absence of pancreatic autoantibodies does not rule out the possibility of T1D. Up to 30 percent of individuals with the classical appearance and presentation of T2D have positive autoantibodies and may have a slowly progressive type of autoimmune diabetes
Blood glucose	Every visit	The patient should check multiple times per day
Insulin and C-peptide levels		High fasting insulin and C-peptide levels suggest T2D. Levels are inappropriately low or in the normal range relative to the concomitant plasma glucose concentration in T1D. At presentation, insulin and C-peptide levels may be suppressed by severe hyperglycemia and illness
HA1C	Every three to six months	Goal <7 percent (may be lower or higher in selected patients)
Microalbuminuria - persistent values between 30 and 300 mg/day (20 to 200 mcg/min)	Annually	Begin three to five years after onset of T1D; protein excretion and serum creatinine should also be monitored if persistent albuminuria is present
Liver function tests (LFTs) and thyroid panel	Annually	
Potassium, serum creatinine and glomerular filtration rate (GFR)	Annually	GFR should be followed closely and nephrology referral based upon National Kidney Foundation guidelines ¹⁹

Plan

The main goal of diabetes treatment is to keep blood glucose levels within the normal range to prevent hypoglycemia and resultant comorbidities. When blood glucose is well controlled, complications are less likely to develop. Maintaining a healthy weight is important. Treatment of high blood pressure and cholesterol levels can prevent other end-organ complications. There should be a major focus on comprehensive cardiovascular risk reduction.

Treatment involves diet, exercise, education, and prescription medications when lifestyle interventions are not effective in reducing blood glucose. A whole systems approach has shown to improve self-monitoring of glucose, diet, self-efficacy, motivation and mood.²⁰ Adjunctive

naturopathic care is consistent with behavior change theory and clinical strategies found most effective in promoting self-efficacy, which may improve clinical outcomes.²¹

If people with diabetes strictly control blood glucose levels, complications are less likely to develop. People with T2D may be able to avoid the need for all medications by achieving and maintaining a healthy weight. Some people who have been unsuccessful in losing weight through diet and exercise may take medications to help them lose weight or may even undergo stomach reduction surgery. Many people with T2D use complementary and alternative medicine as adjunctive treatment.²²

Lifestyle and Dietary Modifications:

- Dietary modification (i.e., low glycemic index diet DASH diet, Bernstein diet).²³
- Meals should be eaten on a regular schedule; long periods between eating should be avoided.
- Weight reduction.24
- Reduced dietary fat and addition of fish to diet.
- Smoking cessation. A meta-analysis of many of the cardiovascular risk reduction trials showed that cessation of smoking had a much greater benefit on survival than most other interventions.²⁵
- Consumption of only moderate amounts of alcohol.
- Tight glycemic control (target A1C <6.5 percent with intensive therapy). ²⁶
- Tight blood pressure control (target <130/80 mmHg).
- Multi-modal Whole Systems Approach. 27,28,29

Manual Adjustments/Manipulation:

• Chiropractic manipulation of musculoskeletal sequelae. 30,31

Acupuncture:

• RCT study suggests that 30 minutes of needling at CV-12 might be useful in reducing blood glucose level in patients with T2DM.³²

Movement and Exercise:

- Exercise helps people control their weight and maintain blood sugar levels within the
 normal range. Because blood sugar levels go down during exercise, patients must be
 alert for symptoms of low blood sugar.
- Light to moderate exercise. 33,34,35,36

Herbal Medicine (Western):

- American Ginseng (Panax quinquefolius). 37,38,39
- Ocimum sanctum (Holy basil). 40,41,42
- Trigonella foenum-graecum (Fenugreek). 43,44
- Cinnamomum cassia (Cinnamon). 45,46,47

- Gymnema sylvestre (Gurmar). 48,49,50
- Mulberry leaf extract.⁵¹
- Salba chia and ginseng.⁵²
- Crocus sativa. 53,54

Supplements and Nutrients:

- Vitamin C.
- Vitamin D.
- Folate.
- Chromium picolinate.55
- Chromium (Polynicotinate). 5657
- Biotin.⁵⁸
- Vanadium Sulfate.
- Magnesium.
- Alpha-lipoic acid (diabetic neuropathy).⁵⁹

Pharmaceuticals (OTC):

• Aspirin: The merits of daily aspirin therapy in patients with macrovascular disease are widely accepted.⁶⁰

Pharmaceutical (Prescription):13

- Oral antihyperglycemic drugs can often lower blood glucose levels adequately in people with T2D, however, they are not effective in T1D (i.e. sulfonylureas, meglitinides. biguanides, thiazolidinediones, glucosidase inhibitors); Oral monotherapy, dual therapy, triple therapy, and combination injectable therapy are all options based upon patient's response based on HA1C and/or blood glucose levels. 13,61,62
- The therapeutic options for patients who fail initial therapy with lifestyle intervention and metformin are to add a second or third oral or injectable agent, including insulin, or a complete switch to insulin.
- Insulin may be necessary in some patients with T2D, particularly those who do not respond to oral therapy after 3 months of treatment.⁶¹
- Angiotensin converting enzyme (ACE) inhibitor therapy regardless of blood pressure;
 Systolic blood pressure should be targeted at <140 mmHg; Diastolic blood pressure goal should be <90 mm Hg; Lower blood pressure targets may be appropriate for certain individuals.
- In all patients \leq 40 years old with diabetes, moderate intensity statin treatment may be considered. Higher doses should be considered in those with increased CVD risk.¹³
- A concise and organized way to evaluate pharmacotherapy options for diabetes is to use the five patient-oriented STEPS criteria: safety, tolerability, effectiveness, price, and simplicity.^{63,64}

Type 2 Management Strategies – Stepwise Approach to Pharmacologic Management of Type 2 Diabetes – 2018⁶⁵

Step 1: According to the ADA 2018 Standards, section 8, Metformin therapy should be started along with lifestyle Management at diagnosis of type 2 Diabetes (unless contraindicated). Metformin is effective, safe, inexpensive and may reduce risk of CV events and death.

Step 2: If A1c target is not achieved after 3 months, consider metformin and any one of the six preferred treatment options based on drug specific effects and patient factors.

If A1c target is still not achieved after 3 months on metformin, and the patient has CV Disease, consider adding a second agent with evidence of cardiovascular risk reduction (based on drug specific effects and patient factors).

These include:

- SGLT-2 Inhibitors empagliflozin (Jardiance) and canagliflozin (Invokana)
- GLP-1 Receptor Agonist liraglutide (Victoza)

Step 3: If A1c target is still not achieved after 3 months, combine metformin plus two other agents for a three-drug combination.

Step 4: If A1c target is still not achieved after 3 months, add combination injectable therapy to the three-drug combination.

For all steps, consider including medications with evidence of CV risk reduction, based on drug specific effects and patient factors. Medication Therapy Based on A1c:

- If A1c is less than 9%, consider monotherapy.
- If A1c is greater than or equal to 9% consider dual therapy.
- If A1c is greater or equal to 10%, or if BG 300 or more, or pt is markedly symptomatic, consider insulin and injectable therapy.

Surgical intervention:

• Bariatric surgery should be considered in patients who are unsuccessful in other weight loss measures.

Referral Criteria

Endocrinologist: Most patients with T2D can be managed by their primary care providers (PCP). If insulin is used or blood sugars are not well controlled, or the PCP is not used to treating diabetes and teaching necessary self-management skills, referral to an endocrinologist is recommended.

- **Diabetic ketoacidosis** a medical emergency, can cause coma and death. Hospitalization, usually in an intensive care unit, is necessary.
- Nonketotic hyperglycemic-hyperosmolar coma is treated much like diabetic ketoacidosis. The levels of sugar in the blood must be restored to normal levels gradually to avoid sudden shifts of fluid into the brain.
- Women of childbearing age pre-pregnancy counseling and planning is important. Prior to pregnancy, glycemic control should be optimized, and both ACE inhibitor and statin medications should be discontinued.

Resources for Clinicians

American Diabetes Association. Standards of Medical Care in Diabetes. Summary of Revisions: . Diabetes Care. 2019;42(Suppl 1):S4-S6.

Davies MJ, D'alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701. This is an excellent resource with useful figures for summary.

Resources for Patients

American Diabetes Association. http://www.diabetes.org/diabetes-basics/type-2/

Clinical Pathway Feedback

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¹ Cory S, Ussery-Hall A, Griffin-Blake S, et al. Prevalence of selected risk behaviors and chronic diseases and conditions-steps communities, United States, 2006-2007. MMWR CDC Surveill Summ 2010; 59:S1.

² Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289:76.

³ Diabetes in America, 2nd, Harris MI (Ed), National Institutes of Health, Bethesda, MD 1995.

⁴ Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. *J Pediatr* 2005; 146:693.

- ⁵Moien Abdul Basith Khan, Muhammad Jawad Hashim, Jeffrey Kwan King, Romona Devi Govender, Halla Mustafa, and Juma Al Kaabi., Epidemiology of Type 2 Diabetes Global Burden of Disease and Forecasted Trends, J Epidemiol Glob Health. 2020 Mar; 10(1): 107–111.
- ⁶ Rhee TG, Westberg SM, Harris IM. Complementary and Alternative Medicine in U.S. Adults with Diabetes: Reasons for Use and Perceived Benefits. *J Diabetes*. 2017; Sep 12.
- ⁷ Type 2 Diabetes Risk With Antidepressants. EASD 2021 meeting presentation(European Assn for Study of Diabetes) presentation
- ⁸ Statin Use linked to Diabetes progression. <u>Mansi IA, et al. *JAMA Intern Med.*</u> 2021;doi:10.1001/jamainternmed.2021.5714.
- ⁹ Statin use raises risks for new-onset diabetes, skin infections. <u>Ko HHT, et al.</u> BJPharmacol. 2019;doi:10.1111/bcp.14077.
- ¹⁰ Wallin A, Di Giuseppe D, Orsini N, et al. <u>Fish consumption, dietary long-chain n-3 fatty acids, and risk of type 2 diabetes: systematic review and meta-analysis of prospective studies</u>. Diabetes Care. 2012;35(4):918-929.
- ¹¹[Guideline] Diagnosis and classification of diabetes mellitus. Diabetes Care. Jan 2010;33 Suppl 1:S62-9.
- ¹² American Association of Clinical Endocrinologists Statement on the Use of A1C for the Diagnosis of Diabetes. Available at https://www.aace.com/files/AACEpositionA1cfeb2010.pdf. Accessed October 13th, 2017.
- ¹³ American Diabetes Association. Position Statement. Standards of medical care in diabetes 2015. Abridged for primary care providers. *Clin Diabetes*. 2015;33(2):97-111.
- ¹⁴ American Diabetes Association. Standards of medical care in diabetes--2012. *Diabetes Care* 2012; 35 Suppl 1:S11.
- ¹⁵ James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–520.
- ¹⁶ Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens. 2014;32:3–15.
- ¹⁷ Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2014;30:485–501.
- ¹⁸ American Diabetes Association. Standards of medical care in diabetes —2014. Diabetes Care. 2014;37(suppl 1):S14–S80
- ¹⁹ National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;60:850–886.
- ²⁰ Bradley R, Sherman KJ, Catz S, et al. Adjunctive naturopathic care for type 2 diabetes: patient-reported and clinical outcomes after one year. *BMC Complement Altern Med.* 2012;12:44.
- ²¹ Oberg EB, Bradley R, Hsu C, et al. Patient-reported experiences with first-time naturopathic care for type 2 diabetes. *PLoS ONE*. 2012;7(11):e48549.
- ²² Chang HY, Wallis M, Tiralongo E, Wang HL. Decision-making related to complementary and alternative medicine use by people with Type 2 diabetes: a qualitative study. *J Clin Nurs*. 2012 Nov;21(21-22):3205-15.
- ²³ Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. *Cochrane Database of Systematic Reviews* 2009, Issue 1.
- ²⁴ Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346:393.
- ²⁵ Yudkin JS. How can we best prolong life? Benefits of coronary risk factor reduction in non-diabetic and diabetic subjects. *BMJ* 1993; 306:1313.
- ²⁶ American Diabetes Association. Standards of medical care in diabetes--2012. *Diabetes Care* 2012; 35 Suppl 1:S11.
- ²⁷ Myers SP, Vigar V. The State of the Evidence for Whole-System, Multi-Modality Naturopathic Medicine: A Systematic Scoping Review. *J Altern Complement Med.* 2019;25(2):141-168.
- ²⁸ Tippens KM, Erlandsen A, Hanes DA, et al. Impact of a Short-Term Naturopathic Whole-Foods-Based Nutrition Education Intervention on Dietary Behavior and Diabetes Risk Markers: A Pilot Study. *J Altern Complement Med*. 2019;25(2):234-240.

- ²⁹ Bairy S, Kumar AM, Raju M, et al. Is adjunctive naturopathy associated with improved glycaemic control and a reduction in need for medications among type 2 Diabetes patients? A prospective cohort study from India. *BMC Complement Altern Med.* 2016;16(1):290.
- ³⁰ Wyatt L, Ferrance R. The musculoskeletal effects of diabetes mellitus. Journal Of The Canadian Chiropractic Association [serial online]. March 2006;50(1):43-50.
- ³¹ Sudano N and Robinson-LeBlanc D. Improved A1 C levels in a patient with insulin-dependent type I diabetes undergoing chiropractic care: A case report. J Pediatr Matern & Fam Health Chiropr: 2011 Fall;2011(4).
- ³² Kumar R, Mooventhan A, Manjunath NK. Immediate Effect of Needling at CV-12 (Zhongwan) Acupuncture Point on Blood Glucose Level in Patients with Type 2 Diabetes Mellitus: A Pilot Randomized Placebo-Controlled Trial. J Acupunct Meridian Stud. 2017;10(4):240-244.
- ³³ Orozco LJ, et al. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2008, Issue 3.
- ³⁴ Nield L, et al. Dietary advice for treatment of type 2 diabetes mellitus in adults. Cochrane Database of Systematic Reviews 2007, Issue 3.
- ³⁵ Thomas D, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2006, Issue 3.
- ³⁶ Balducci S, Haxhi J, et al. Relationships of Changes in Physical Activity and Sedentary Behavior With Changes in Physical Fitness and Cardiometabolic Risk Profile in Individuals With Type 2 Diabetes: The Italian Diabetes and Exercise Study 2 (IDES_2). Diabetes Care. 2022 Jan 1;45(1):213-221.
- ³⁷ Vuksan V, Sievenpiper JL, Wong J, et al. American ginseng (Panax quinquefolius L.) attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals. Am J Clin Nutr. 2001 Apr;73(4):753-8.
- ³⁸ Vuksan V, Sievenpiper JL, Koo VY, et al. American ginseng (Panax quinquefolius L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. Arch Intern Med. 2000 Apr 10;160(7):1009-13.
- ³⁹ Vuksan V, Stavro MP, Sievenpiper JL, et al. Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. Diabetes Care. 2000 Sep;23(9):1221-6.
- ⁴⁰ Gholap S, Kar A. Hypoglycaemic effects of some plant extracts are possibly mediated through inhibition in corticosteroid concentration. Pharmazie. 2004 Nov;59(11):876-8.
- ⁴¹ Agrawal P, Rai V, Singh RB. Randomized placebo-controlled, single blind trial of holy basil leaves in patients with noninsulin-dependent diabetes mellitus. Int J Clin Pharmacol Ther. 1996 Sep;34(9):406-9.
- ⁴² Meta-analysis of the effect of herbal supplement on glycemic control in type 2 diabetes. Suksomboon N, Poolsup N, Boonkaew S, et al. Journal of Ethnopharmacology. 2011;137(3):1328-1333.
- ⁴³ Gupta A, Gupta R, Lal B. Effect of Trigonella foenum-graecum (fenugreek) seeds on glycaemic control and insulin resistance in type 2 diabetes mellitus: a double blind placebo controlled study. J Assoc Physicians India. 2001 Nov;49:1057-61.
- ⁴⁴ Gong J, Fang K, Dong H, et al. Effect of fenugreek on hyperglycaemia and hyperlipidemia in diabetes and prediabetes: a meta-analysis. Journal of Ethnopharmacology. 2016;194:260-268.
- ⁴⁵ Khan A, Safdar M, Ali Khan MM, et al. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care. 2003 Dec;26(12):3215-8.
- ⁴⁶ Costello RB, Dwyer JT, Saldanha L, Bailey RL, Merkel J, Wambogo E. Do Cinnamon Supplements Have a Role in Glycemic Control in Type 2 Diabetes? A Narrative Review. J Acad Nutr Diet. 2016; 116 (11):1794-1802.
- ⁴⁷ Costello RB, Dwyer JT, Saldanha L, et al. Do cinnamon supplements have a role in glycemic control in type 2 diabetes? A narrative review. Journal of the Academy of Nutrition and Dietetics. 2016;116(11):1794-1802.
- ⁴⁸ Shanmugasundaram ER, Rajeswari G, Baskaran K, et al. Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. J Ethnopharmacol. 1990 Oct;30(3):281-94.
- ⁴⁹ Balasubramaniam K, Arasaratnam V, Nageswaran A, et al. Studies on the effect of Gymnema sylvestre on diabetics. J Natl Sci Counc Sri Lanka 1992;20(1):81-89.
- ⁵⁰ Baskaran K, Kizar Ahamath B, Radha Shanmugasundaram K., et al. Antidiabetic effect of a leaf extract from Gymnema sylvestre in non-insulin-dependent diabetes mellitus patients. J Ethnopharmacol. 1990 Oct;30(3):295-300.
- ⁵¹ Riche DM, Riche KD, East HE, Barrett EK, May WL. Impact of mulberry leaf extract on type 2 diabetes (Mul-DM): A randomized, placebo-controlled pilot study. Complement Ther Med. 2017;32:105-108.

- ⁵² Co-administration of viscous fiber, Salba-chia and ginseng on glycemic management in type 2 diabetes: a double-blind randomized controlled trial. Andreea Zurbau 1 2 3, Lea Smircic Duvnjak 4 5, Sasa Magas 4, Elena Jovanovski 1 2, Jelena Miocic 4, Alexandra L Jenkins 2, David J A Jenkins 1 2 6 7 8, Robert G Josse 1 2 6 7 8, Lawrence A Leiter 1 2 6 7 8, John L Sievenpiper 1 2 3 6 7 8, Vladimir Vuksan 9 10 11 12 13 Randomized Controlled Trial.Eur J Nutr. 2021 Sep;60(6):3071-3083. doi: 10.1007/s00394-020-02434-7. Epub 2021 Jan 24.
- ⁵³ Effect of crocin on diabetic patients: A placebo-controlled, triple-blinded clinical trial. Sepahi S, Golfakhrabadi M, Bonakdaran S, Lotfi H, Mohajeri SA.Clin Nutr ESPEN. 2022 Aug;50:255-263. doi: 10.1016/j.clnesp.2022.05.006. Epub 2022 May 18.PMID: 35871933 Clinical T
- ⁵⁴ doi: 10.1016/j.clnesp.2022.05.006. Epub 2022 May 18.PMID: 35871933 Clinical T.
- ⁵⁵ Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348:383.
- ⁵⁶ Urberg M, Zemel MB. Evidence for synergism between chromium and nicotinic acid in the control of glucose tolerance in elderly humans. Metabolism. 1987 Sep;36(9):896-9.
- ⁵⁷ Systematic review and meta-analysis of the efficacy and safety of chromium supplementation in diabetes. Suksomboon N, Poolsup N, Yuwanakorn Journal of Clinical Pharmacy and Therapeutics. 2014;39(3):292-306 ⁵⁸ McCarty MF. High-dose biotin, an inducer of glucokinase expression, may synergize with chromium picolinate to enable a definitive nutritional therapy for type II diabetes. Med Hypotheses. 1999 May;52(5):401-6.
- ⁵⁹ <u>Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy.</u> Ziegler D, Gries FA.Diabetes. 1997 Sep;46 Suppl 2:S62-6. doi: 10.2337/diab.46.2.s62.PMID: 9285502 Review.
- ⁶⁰ Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71.
- ⁶¹ Chamberlain JJ, Herman WH, Leal S, et al. Pharmacologix Therapy for Type 2 Diabetes; Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes. *Ann Intern Med.* 2017;166(8):572-578.
- ⁶² Thrasher J. Pharmacologic Management of Type 2 Diabetes Mellitus. Available Therapies. *Am. J Cardiol.* 2017; 120(1S):S4-S16.
- 63 Steinberg J, Carlson L. Type 2 Diabetes Therapies: A STEPS Approach. Am Fam Physician. 2019;99(4):237-243.
- ⁶⁴ Chamberlain JJ, Doyle-delgado K, Peterson L, Skolnik N. Diabetes Technology: Review of the 2019 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med. 2019.
- ⁶⁵ American Diabetes Association. *Diabetes Care* 2014 Jan; 37(Supplement 1): S14-S80.