Lifestyle Approaches and Glucose Intolerance

Abstract: *Glucose intolerance is a global health concern that encompasses glucose metabolism abnormalities such as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes (T2D). There is an urgent need to focus on the prediabetes (ie, IGT and IFG) stage before the disease actually occurs. The progression from IGT to T2D can be prevented or delayed by modifying the lifestyles in high-risk individuals, and these health benefits are well documented in various ethnicities with prediabetes across the world. Specifically, consuming a healthy diet (high in polyunsaturated fatty acids, monounsaturated fatty acids, fiber, and whole grains), losing weight, quitting smoking, consuming alcohol in moderation, and increasing physical activity can improve glucose tolerance and reduce the risk of T2D. Also, pharmacological agents and botanicals can be used to manage glucose intolerance if the implementation of lifestyle changes is challenging. Pharmacological treatments have been successful in managing glucose intolerance; however, they have adverse effects. Also, more research on botanicals is warranted before a definitive recommendation can be made for their use in managing glucose intolerance. To make progress on this worldwide*

problem, efforts are needed to improve the awareness of prediabetes, increase promotion of healthy behaviors, and improve the availability of evidence-based lifestyle intervention programs to the community.

Keywords: diet; physical activity; diabetes prevention; lifestyle; glucose intolerance

developed nations, but also in undeveloped nations and the disease has been recognized as a global burden. According to the International Diabetes Federation, approximately 382 million adults had diabetes worldwide in the year 2013, and this number is expected to escalate to 592 million by the year 2035 (55% increase).² People with diabetes have a 1.7 times higher rate of

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Introduction

Glucose intolerance constitutes a major public health concern and refers to a spectrum of glucose metabolism abnormalities such as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes (T2D). Approximately 28.9 million adult Americans (12.3% of adults) have diagnosed diabetes, with T2D accounting for about 90% to 95% of diagnosed diabetes.¹ The diabetes epidemic is not only prevalent in

dying from cardiovascular disease than people without diabetes.¹ The health complications of diabetes (ie, nephropathy, neuropathy, retinopathy, and nontraumatic lower amputations) can seriously affect an individual's quality of life with the disease. Also, it can affect their families because of premature illnesses, mortality, and financial debt.³

To circumvent the health complications of T2D and its related financial burdens, primary prevention

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before the disease actually occurs is warranted. *Prediabetes* is a term used for individuals with IFG and/or IGT, which represents intermediate metabolic states between normal glucose tolerance and T2D.³ According to the United States National Health and Nutrition Examination Survey (NHANES; years 2009-2012), 37% of adult Americans (51% of those aged 65 years or older) have prediabetes.¹ Globally, 316 million adults had prediabetes in the year 2013, and this number is expected to increase by 49% in the year 2035 (471 million people).² Prediabetes is a key stage in the natural history of T2D because these people have an increased risk of developing T2D. It is estimated that 20% to 70% of individuals with prediabetes who do not lose weight, change their dietary habits, and/or engage in moderate physical activity will progress to T2D within 3 to 6 years.⁴⁻⁶ Consequently, a high-risk population represents an important target population for lifestyle modification interventions aimed at preventing diabetes.

The increase in T2D is related to lifestyle changes that have resulted in obesity, unhealthy eating habits, and physical inactivity.^{7,8} Therefore, changes in lifestyle should have the potential to postpone or prevent the development of T2D in high-risk individuals. Several studies have reported beneficial effects of lifestyle modification intervention programs in high-risk populations, especially those with IGT.⁴⁻⁶ The American Diabetes Association (ADA) currently recommends structured programs targeting lifestyle changes such as moderate weight loss (7% of body weight) and physical activity (150 min/wk) to individuals with prediabetes.⁹ Also, the medical nutrition therapy should be individualized (given as needed) and include reducing intake of calories, consuming dietary guideline recommendations for fiber and whole grains, and limiting or avoiding sugar-sweetened beverages.⁹ This review will focus on diabetes prevention and the relevant lifestyle interventions, including diet and exercise modifications, that have

salutary effects on improving glucose tolerance and preventing diabetes in high-risk individuals. Additionally, the relative importance of individual modifiable risk factors for T2D will be identified and reviewed.

Lifestyle Modification and Risk of T2D

Worldwide evidence from well-known landmark clinical studies in China,⁵ Finland,⁴ and the United States⁶ suggest that lifestyle changes can help prevent the development of T2D in individuals with IGT. IGT was diagnosed based on the criteria from the World Health Organization (WHO)¹⁰ or ADA¹¹ for glucose concentrations 2 hours after a 75-g oral glucose load. The lifestyle interventions in these studies focused on modest weight loss, dietary modification, and increased physical activity. The primary outcome measure was the rate of progression from IGT to T2D over a defined period of time (approximately 3 to 6 years) in the intervention group versus the comparison group. Also, the lifestyle interventions have long-term effects on the risk of T2D.¹²⁻¹⁴

It is important to note that other randomized controlled clinical trials, such as the Indian Diabetes Prevention Programme (IDPP),¹⁵ Japanese Trial,^{16,17} Malmo Sweden Study,¹⁸ and Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht (SLIM),^{19,20} have also researched lifestyle interventions and diabetes prevention. Analogous to the landmark studies' findings, these studies reported that implementation of lifestyle interventions reduced the diabetes incidence in Asian Indians, Japanese, Swedish, and Dutch individuals with IGT.¹⁵⁻²⁰ Furthermore, the lifestyle intervention groups showed improvements in glucose tolerance (postload glucose concentrations were reduced) and insulin sensitivity, and reduced hyperinsulinemia and body weight. It is apparent that diabetes can be prevented or at least delayed through lifestyle modifications in various ethnicities with prediabetes across the world.

China Da Qing Diabetes Prevention Study

The Da Qing Study randomized (by clinic) 577 Chinese adults with IGT (WHO criteria) to a control group or any of 3 treatment interventions (diet, exercise, or diet plus exercise).⁵ These individuals had a mean age of 45 years and body mass index (BMI) of 26 kg/m². The dietary intervention focused on increasing vegetables, reducing consumption of alcohol and simple sugars, and encouraging overweight individuals (BMI ≥25 kg/m²) to lose weight. The exercise group was instructed to increase their daily activity by the equivalent of 20 minutes of moderate activity, such as brisk walking, and the diet plus exercise group was asked to follow both the exercise regimen and dietary modification. After adjustments for differences in baseline BMI and fasting glucose, the intervention groups showed a 31% (diet only), 46% (exercise only), and 42% (diet plus exercise) significant reduction in the risk of developing T2D when compared with the control group at the 6-year follow-up period. Thus, the effectiveness of the diet intervention were similar to the exercise intervention and an additive effect was not present when the interventions were combined (diet plus exercise). Interestingly, in a multivariate analysis that controlled for age and clustering by clinic, individuals in the lifestyle intervention group (all 3 interventions combined) had a 51% lower incidence of diabetes at the 6-year evaluation period and a 43% lower incidence over the 20-year period (14 years after the intervention ceased) when compared with the control group.¹³ These results demonstrate that the benefits from a lifestyle modification intervention can be maintained long-term after the active intervention period has ceased.

Finnish Diabetes Prevention Study

The Finnish Diabetes Prevention Study randomized 522 middle-aged (mean age = 55 years) and overweight/obese (mean BMI = 31 kg/m²) individuals with IGT (WHO criteria) to either the intensive

lifestyle intervention or control groups.⁴ The lifestyle intervention provided individualized counseling focused on achieving a weight loss goal of 5% or more of total body weight, reducing fat intake, increasing fiber intake, and increasing physical activity (30 minutes per day of moderate exercise). At 4 years, the cumulative incidence of T2D was 11% in the intervention group and 23% in the control group. Overall, the incidence of diabetes was 58% lower in the intervention group than in the control group. Three years following the active intervention (7-year follow-up), the incidence of diabetes was still lower in the intervention group (4.3 per 100 person-years) when compared with the control group (7.4 per 100 person-years), indicating a 43% reduction in the relative risk of T2D.¹² It is important to note that the impact of lifestyle changes in reducing the incidence of diabetes was maintained for at least 3 years following the discontinuation of the intensive lifestyle intervention.

The Diabetes Prevention Program (DPP)

To date, one of the largest randomized controlled clinical trials is the US DPP.⁶ This study was conducted in 3234 adults (mean age = 51 years; mean BMI = 34 kg/m²) with IFG and IGT (ADA criteria). The individuals were randomized to 1 of 3 groups, which included placebo, metformin (results reviewed in the pharmaceutical section), or intensive lifestyle intervention. Here, 68% of the participants were women, and 45% were from minority groups that have an increased risk of developing T2D. The 2 major goals of the DPP lifestyle intervention were a minimum of 7% weight loss through a low-calorie and low-fat diet and a minimum of 150 min/wk of physical activity similar in intensity to brisk walking. After an average follow-up period of 2.8 years, the intensive lifestyle intervention had a 58% reduction in the incidence of T2D when compared with the placebo group. Furthermore, reversion to normal glucose tolerance occurred in approximately 30% of the individuals in the lifestyle

intervention arm, as compared with approximately 18% in the control arm (fasting and postload glucose concentrations). Lifestyle changes worked particularly well for participants aged 60 years and older, thus, reducing their diabetes risk by 71%. Approximately 5% of the lifestyle intervention group developed diabetes each year during the study period compared with 11% of those in the placebo group. Also, 50% of the lifestyle intervention group achieved the goal of at least 7% weight reduction, and 74% met the goal of at least 150 min/wk of moderately intensive activities. Although weight loss was a predictor of reduced diabetes incidence in the lifestyle intervention group, improvements in insulin sensitivity and insulin secretion may also be independent predictors of a beneficial outcome.²¹

Delay or prevention of T2D by lifestyle intervention can persist for at least 10 years in US adults. The long-term effect of the DPP lifestyle intervention was assessed 7 years later following the intervention (10-year follow-up). The DPP Outcomes Study (DPPOS) found that diabetes incidence was reduced by 34% in the lifestyle intervention group when compared with the placebo group.¹⁴ Also, high-risk individuals who achieved normal glucose regulation status at least once during the DPP clinical trial had a 56% lower risk of diabetes compared with individuals with consistent prediabetes during the subsequent follow-up in DPPOS.²²

Translation and Cost-effectiveness of Lifestyle Modification in the Community

Lifestyle modification interventions are effective in reducing diabetes risk. However, for this approach to be broadly implemented, it must be translated into community-based settings that are accessible and affordable. A significant body of evidence has demonstrated that effective lifestyle-based interventions can be successfully implemented in the YMCA and other community-based

settings.²³⁻²⁵ These lifestyle interventions can also be implemented in disparate populations that are medically underserved, minority groups, and those living in rural and urban communities.²⁶⁻²⁹ However, Kahn and Davidson³⁰ reported that there is a lack of strong evidence that diabetes can be delayed or prevented in a community setting, and more research is needed before implementation of a lifestyle modification intervention to the community. In regard to the cost-effectiveness of the lifestyle interventions, Eddy et al³¹ suggested that the lifestyle modification programs may be too expensive for health care plans or a national program to implement. However, other studies have found that implementing lifestyle interventions to prevent or delay T2D in glucose-intolerant individuals have favorable cost-effectiveness ratios.³²⁻³⁵

Modifiable Risk Factors for T2D

Obesity

Excess body weight is an important modifiable risk factor for individuals with a high-risk of developing T2D. The incidence of T2D rises as obesity prevalence increases.³⁶ One of the many important benefits of weight loss is diabetes prevention. In the Finnish Diabetes Prevention Study and DPP clinical trials, the lifestyle modification interventions resulted in weight loss and reduced risk of T2D in individuals with IGT.^{4,6,16,18} During the first year of the Finnish Diabetes Prevention Study,⁴ the participants' body weight decreased on average by 4.2 kg in the intervention group and 0.8 kg in the control group. Most of the weight reduction was maintained during the second year, and by the end of the second year the mean weight loss was approximately 3.5 kg in the intervention group and approximately 0.8 kg in the control group. During the 4-year follow-up assessment, a sustained weight reduction in participants with IGT resulted in insulin sensitivity improving by 64%, whereas insulin sensitivity deteriorated

by 24% with weight gain.³⁷ Additionally, insulin sensitivity was inversely correlated with body weight.³⁷ In a similar study (DPP),⁶ the lifestyle intervention group had a significantly greater average weight loss (5.6 kg) than the metformin (2.1 kg) and placebo (0.1 kg) groups. The individuals in the lifestyle intervention had a 16% average reduction in risk of T2D per kilogram of weight loss.³⁸ Also, studies of diabetes prevention in Japan¹⁶ and Sweden¹⁸ confirmed the benefit of lifestyle modification programs, and the weight loss was associated with the diabetes risk reductions.

Severe obesity can be difficult to treat through lifestyle modification alone. When lifestyle modification interventions are insufficient, then bariatric surgery can be used to achieve weight-loss goals. There is evidence suggesting that bariatric surgery can be successful in preventing diabetes. In the Swedish Obese Subjects (SOS) intervention study,³⁹⁻⁴¹ obese individuals underwent adjustable or nonadjustable banding, vertical-banded gastroplasty, or gastric bypass operations. The bariatric surgery group had greater weight loss, lower blood glucose and insulin levels, and lower incidence of diabetes when compared with the control group (no surgery group).⁴⁰ The mean changes in body weight after 2, 10, 15, and 20 years were -23%, -17%, -16%, and -18% in the surgery group and 0%, 1%, -1%, and -1% in the control group, respectively.³⁹ Bariatric surgery reduced the long-term incidence of diabetes by 78% in obese individuals.⁴¹ These results certainly suggest that severe obesity can be treated with bariatric surgery and that weight loss results in a marked reduction in the incidence of diabetes. However, individuals should be cautious when undergoing weight loss surgery because of increased morbidity and mortality rates from the surgical procedure.

Unhealthy Eating Habits

Although obesity is an important risk factor for T2D,³⁶ eating habits are also believed to play a role in the development of T2D. Dietary

modification, including a reduction in total calories and fat (also saturated fat) and an increase in fiber and whole grains, has been successful in reducing the risk of T2D.⁵ Similar results were found when diet modification was combined with physical activity (ie, lifestyle intervention).^{4,6} However, there is evidence suggesting that neither total fat nor carbohydrate, as proportions of total energy intake, play a major part in the development of T2D,^{8,42-44} thus suggesting that the quality of fat and carbohydrates may be more important than the quantity. Also, emerging evidence found that dietary patterns (ie, combination of different foods or food groups) may be associated with diabetes.^{45,46}

Dietary Pattern. Investigating the role of complete dietary patterns on the risk of diabetes is just as important as studying isolated foods or nutrients. Also, dietary patterns represent the most prevalent nutritional practices found in the assessed populations. The rationale for this concept is that synergistic or antagonistic effects may exist between the different food components.⁴⁷

Dietary patterns, such as the Western, prudent, and Mediterranean diets have been explored. In a systemic review of epidemiological studies,⁴⁸ the dietary patterns (ie, prudent and Mediterranean diets) high in fiber-rich food items such as vegetables, fruits, whole grains, seeds, and nuts plus white meat sources were protective against the incidence of T2D. However, a dietary pattern (ie, Western diet) rich in processed and red meat, refined cereals, and saturated fatty acid (SFA) increased the risk of T2D. In a prospective cohort study in US adults,^{45,46} the Western dietary pattern was associated with an increased risk of T2D, and the prudent dietary pattern was associated with a modestly lower risk of T2D. Additionally, the traditional Mediterranean diet has been found to exhibit many health benefits, such as reducing the risk of T2D and improving insulin sensitivity.⁴⁹⁻⁵¹ These health benefits are attributable to the rich

source of monounsaturated fatty acid (MUFA) in the Mediterranean diet.⁵¹

Quality of Carbohydrates. There are 4 important qualitative features of dietary carbohydrates that are relevant to diabetes, and they include fiber, whole grains, glycemic index (GI) and glycemic load (GL), and simple sugars in beverages (SSB). Several studies have provided evidence for reduced risk of diabetes and fasting insulin levels, and increased insulin sensitivity with increased intake of dietary fiber.⁵²⁻⁵⁵ Also, prospective cohort studies found that individuals who consumed whole grains were less likely to develop T2D than those who rarely consumed whole grains.^{56,57} In the Insulin Resistance Atherosclerosis Study,⁵⁸ a higher intake of whole-grain-containing foods was associated with improved insulin sensitivity and decreased insulin concentrations.

GI is the blood glucose response after consuming a carbohydrate-containing test food relative to a carbohydrate-containing reference food, usually glucose or white bread.⁵⁹ GL is a product of GI, and it takes into account the amount of carbohydrate eaten.⁶⁰ Thus, GL provides an indication of glucose available for energy or storage following a carbohydrate-containing meal. It is postulated that a diet higher in GI and GL increases glycemia, insulinemia, and risk of developing diabetes.^{43,44,61-63} In China, where white rice is a staple, the Shanghai Women's Health Study found that women with the highest GI and GL diets had a 21% and 34%, respectively, higher risk of developing T2D when compared with their counterparts with the lowest GI and GL diets.⁶⁴ Some investigations, however, were unable to confirm the relationship between GI and GL load with insulin sensitivity and insulin secretion.⁵⁵

Beverages containing simple sugars (eg, soft drinks, nondiet colas, sodas) and sugar-enriched fruit juices are examples of high-GI foods that are consumed in significant amounts globally. Observational studies have

shown that consuming SSB relates to an increased risk of diabetes after adjusting for various confounders.⁶⁵⁻⁶⁹ In a meta-analysis, Malik et al⁷⁰ found that individuals who consumed a higher amount of SSB (1-2 servings/d) had a 26% greater risk of developing diabetes than those individuals who never or rarely (1 serving/month) consumed SSB.

Quality of Fat. Analogous to dietary carbohydrates, the quality of fat (ie, SFA, trans fatty acid (TFA), polyunsaturated fatty acid (PUFA), and MUFA) is also relevant to diabetes prevention or glycemic control. The data on SFA and TFA intake are inconsistent. Intervention studies in humans show that increased SFA intake significantly decreases insulin sensitivity.^{71,72} Also, SFA was associated with diabetes risk in the 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study⁷³ and the Melbourne Collaborative Cohort Study.⁷⁴ However, these associations did not exist in other investigations after adjusting for multiple confounders.^{75,76} In the US National Health Service (NHS) observational study, there was an approximately 40% increase in risk of diabetes associated with a 2% increase in energy from TFA intakes in multivariate analyses.⁷⁶ However, this increase in diabetes risk was not seen in the Iowa Women's Health Study.⁷⁷

Intake of PUFA is more consistently related to improved glycemic control and/or a reduced risk of diabetes in observational studies.^{42,76,78,79} Furthermore, substituting PUFA for SFA is inversely related to the diabetes risk.⁷⁷ Riserus et al⁷⁸ found that among the PUFAs, linoleic acid (*n*-6) improved insulin sensitivity, whereas, α -linolenic acid (*n*-3) did not affect insulin sensitivity. Data on the intake of MUFA has been shown to be neutral regarding diabetes risk in prospective studies.^{75,76} However, in a randomized 4-week clinical trial, the investigators found that feeding MUFA to overweight adults resulted in an improvement in insulin sensitivity when compared with those consuming SFA.⁷²

Physical Inactivity

A protective effect of physical activity or exercise (used interchangeably) on the risk of developing T2D is biologically plausible.⁸⁰ Skeletal muscle represents the predominant site of insulin resistance in diabetes, and exercising has been shown to improve insulin sensitivity in this tissue.^{81,82} The current joint position stand statement from the American College of Sports Medicine and ADA recommends ≥ 150 min/wk of moderate-to vigorous-intensity physical activity as part of lifestyle changes to prevent T2D in a high-risk population.⁸³

Exercising can improve glycemic control and prevent or delay the onset of T2D.^{4,6,84} Lifestyle modification interventions in high-risk individuals that included groups with exercise only and the combination of exercise and dietary modification reduced the risk of T2D by 42% to 58%.⁴⁻⁶ Weight loss is the dominant predictor of a reduced risk of T2D, but increased physical activity reduced the risk of T2D even when weight loss goals were not achieved or adjusted for in the model.^{38,85} Also, physical activity has been shown to improve insulin sensitivity independent of weight loss.^{86,87}

Long-term prospective studies showed that increasing physical activity reduced the risk of diabetes. In the British Regional Heart Study Cohort,⁸⁸ a substantial fall in risk of diabetes was observed in men engaged in moderate levels of physical activity relative to physically inactive men (after adjusting for age and BMI). In the US NHS Cohort,⁸⁹ the risk of developing T2D was lower (33% reduction) among the women engaging in vigorous exercise at least once weekly compared with women not engaging in exercise weekly (still apparent after adjusting for BMI). Both moderate walking and vigorous activity have been associated with a decreased risk, and greater volumes of physical activity may provide the most prevention.⁹⁰ Numerous epidemiological studies that focused on sedentary behavior indicated that increased physical activity reduced the risk of diabetes, whereas sedentary behaviors

(such as watching television) increased the risk.⁹¹⁻⁹³ Similar to low levels of physical activity, a low level of cardiorespiratory fitness (determined by a maximal exercise test on a treadmill) is also a risk factor for T2D, and increasing levels of cardiorespiratory fitness can lower the incidence rates of T2D.⁹⁴⁻⁹⁸

Smoking and Alcohol Consumption

Apart from obesity, unhealthy eating habits, and physical inactivity, there are other modifiable risk factors for T2D such as cigarette smoking and heavy alcohol consumption. Smoking and alcohol consumption represent a potentially important risk factor for T2D, especially because 52% (alcohol users) and 18% (smokers) of US adults are currently engaging in these unhealthy behaviors (National Health Interview Survey, 2012).⁹⁹ Although cigarette smoking is well documented as a risk factor for cardiovascular disease, its association with T2D is less clear. Also, the association between alcohol use and T2D has been inconsistent in the literature.

There is evidence that suggests smoking is associated with an increase in the risk of T2D¹⁰⁰⁻¹⁰⁵ and also linked to insulin resistance.^{106,107} Smoking cessation is often accompanied by substantial weight gain,¹⁰⁴ and obesity is an important risk factor for the development of diabetes.¹⁰⁸ In the British Regional Heart Study,¹⁰⁴ men who stopped smoking during the first 5 years of follow-up showed significant weight gains, which resulted in a higher risk of diabetes than continuing smokers. However, the benefits of smoking cessation were apparent in those who stopped smoking over 5 years ago; also, it took 20 years for the risk of diabetes to revert to that of never smokers. In the same study, when the current cigarette smokers were compared with the never smokers, the smokers had a higher risk of diabetes (even after adjustments for age, BMI, and other potential confounders). Data from the US NHS¹⁰³ and Health Professionals' Follow-up Study,¹⁰² showed at the follow-up period

a relative risk of 1.42 in women and 1.94 in men who smoked ≥ 25 cigarettes/d compared with nonsmokers. More recent investigations, for example, the Coronary Artery Risk Development in Young Adults (CARDIA) Study¹⁰¹ indicated that 16.7% of individuals with normal glucose tolerance at baseline developed glucose intolerance at the 15-year follow-up. Consequently, the incidence of glucose intolerance was the highest among smokers (21.8%) and lowest in the never smokers without any exposure to secondhand smoke (11.5%).

Although evidence suggests that light to moderate alcohol consumption is associated with reduced risk of diabetes, heavy alcohol intake increases diabetes risk. There was a 30% to 40% reduced risk of T2D among those individuals consuming 1 to 4 drinks/d, and this reduction in risk was less or no longer existed in individuals consuming >4 drinks/d.^{102,109} Also, in the Atherosclerosis Risk in Communities (ARIC) Study,¹¹⁰ women and men consuming a moderate amount of alcohol (7.1-14 drinks/wk) were not at higher risk of developing T2D compared with their counterparts consuming little alcohol (≤ 1 drink/wk). However, men consuming >21 drinks/wk were about 50% more likely to develop T2D when compared with their counterparts consuming less alcohol (≤ 1 drink/wk). These findings were consistent with earlier results reported by Holbrook et al,¹¹¹ which found that alcohol intake was a risk factor for the development of T2D in men, but not in women.

Alternative Strategies for Managing Glucose Intolerance

Lifestyle interventions are well-established strategies that reduce the risk of T2D. Although lifestyle changes can provide many benefits for the management of glucose metabolism, sometimes these changes are difficult to implement and maintain. When lifestyle modifications are insufficient or inappropriate, pharmacological or

botanical interventions should be considered.

Pharmaceutical Treatments

Pharmacological treatments targeted at improving insulin sensitivity and glucose homeostasis in vivo have represented the conventional approach by most physicians. Several studies have measured the effects of various drug interventions on the development of T2D in people with IGT. Specifically, oral diabetes drugs such as metformin (a biguanide), troglitazone (a thiazolidinedione), acarbose (an α -glucosidase inhibitor), and orlistat (an intestinal lipase inhibitor) have reduced the incidence of T2D in individuals with IGT.

The ADA recommends that metformin therapy for prevention of T2D may be considered in those with IGT, IFG, or a hemoglobin A1C between 5.7% and 6.4%.⁹ To date, metformin is the most extensively used and researched pharmacological treatment for people with prediabetes, and its long-term safety has been demonstrated. The DPP and DPPOS clinical lifestyle modification intervention trials found that metformin reduced the incidence of diabetes by 31% at the 2.8-year follow-up and by 18% at the 10-year follow-up when compared with the placebo group.^{6,14} Metformin was most effective in more obese (BMI ≥ 35 kg/m²) and younger (<45 years old) participants, and they experienced reductions in diabetes incidence of 53% and 44%, respectively. In contrast, metformin was less effective in those >60 years old, with a BMI <35 kg/m², and a fasting plasma glucose ≤ 6.1 mmol/L.⁶ Gastrointestinal symptoms, including diarrhea, flatulence, nausea, and vomiting, occurred in 77 of every 100 persons on metformin in the study.⁶ In addition, studies in China and India reported similar reductions in diabetes risk, with the use of metformin as an intervention, as well as improvements in glucose metabolism, such as fasting glucose, glucose tolerance, and insulin sensitivity.^{15,112}

The drug troglitazone has been shown to improve insulin sensitivity and glucose tolerance in obese individuals with IGT

or normal glucose tolerance.¹¹³ Troglitazone was used as a drug intervention in the DPP trial, and it reduced the development of T2D by 75% when compared with the placebo.¹¹⁴ However, this drug was discontinued in the DPP trial and withdrawn from the market because of an increased incidence of drug-induced hepatotoxicity. The drug's action did not persist long-term after it was discontinued, and the diabetes incidence rate was eventually similar to that in the placebo group.

The drug acarbose was studied in a meta-analyses that included people with IGT and IFG, and it was found that the use of acarbose reduced the incidence of T2D.¹¹⁵ In the Study to Prevent Non-Insulin-Dependent Diabetes (STOP-NIDDM) trial,¹¹⁶ 1429 participants with IGT were randomized to receive either the α -glucosidase inhibitor acarbose or a placebo. After a mean follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes was observed in the acarbose-treated group compared with the placebo group. However, almost one-third of the acarbose group was unable to complete the study because of gastrointestinal side effects (eg, flatulence and diarrhea).

Orlistat, a weight-loss drug, has been studied in individuals with IGT. Clinical trials showed improved glucose tolerance and reduced risk of progression from IGT to diabetes among individuals randomized to the orlistat group compared with the placebo group.^{117,118} The beneficial health effects of this drug on glucose intolerance may be attributable to the weight loss.

Botanicals

Current pharmacological approaches marketed to control hyperglycemia tend to have untoward side effects,¹¹⁹⁻¹²⁴ thus shifting Americans' interest to complementary and alternative medicine (CAM). Currently, it is estimated that approximately 38% of adults use CAM in pursuit of achieving good health and well-being.¹²⁵ Specifically, the most commonly used CAM therapies are nonvitamin, nonmineral, and natural

products (especially derived from botanicals) because they are perceived to be less toxic with fewer side effects than synthetic products. Botanicals, such as blueberries, have demonstrated many beneficial antidiabetic properties in rodent and cell culture models.¹²⁶⁻¹³² In a clinical trial conducted by Stull and Colleagues,¹³³ daily supplementation of blueberries for 6 weeks improved insulin sensitivity in obese adults with prediabetes. These health benefits may be attributable to the blueberry phenolic bioactive compounds, such as anthocyanins, which are natural dark pigment colors in fruits and vegetables that also have antioxidant properties.¹³⁴⁻¹³⁶

Likewise, other commonly used botanicals such as fenugreek, bitter melon, and cinnamon have been reviewed by Deng¹³⁷ and Graf et al.¹³⁸ The hypoglycemic effects of these botanicals were inconsistent in the literature. However, there were clinical studies that found these botanicals reduced hyperglycemia and improved insulin sensitivity in individuals with glucose intolerance. In a meta-analysis using 15 different Chinese herbal medicines, Grant et al¹³⁹ found that several Chinese herbal medicines could be considered as potential treatments in people with prediabetes. Specifically, 8 of the 16 clinical trials reviewed showed that individuals consuming Chinese herbal medicines combined with lifestyle modification were more than 2-fold as likely to have their fasting plasma glucose levels reverted to normal levels when compared with lifestyle modification alone. Additionally, individuals receiving Chinese herbs were less likely to progress to diabetes over the duration of the trial.

Caution must be taken when reviewing the data from botanical clinical studies because certain limitations exist, such as small sample sizes and poor experimental designs. Also, there are variations in the participant population, botanical preparation, dose, and treatment duration. Therefore, before recommending botanicals as beneficial for the delay or prevention of diabetes,

more botanical research is warranted to better understand their safety efficacy, and mechanisms of action with more well-designed, randomized, and controlled clinical trials.

Summary

The worldwide problem of T2D underscores the urgent need for efforts to improve awareness of prediabetes, increase promotion of healthy behaviors, and improve availability of evidence-based lifestyle programs to slow the progression to T2D. Clinical trials have convincingly shown that lifestyle modification in high-risk individuals is the most effective tool in delaying or preventing T2D, with the reduction in the incidence of diabetes being mediated primarily through weight loss. The lifestyle modification interventions have a similar or greater effect than the pharmacological interventions, which can exhibit adverse effects. Although there is evidence that lifestyle modification interventions translate well in community-based programs and also have beneficial long-term effects, the challenge of increasing or maintaining compliance among individuals in the long-term still exists. To achieve successful interventions, physicians and health care professionals must be willing to incorporate lifestyle changes as part of their medical practice and encourage their patients to adapt these lifestyle changes to postpone or prevent T2D.

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