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A plant-based diet for the prevention and treatment of type 2 diabetes

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Abstract

The prevalence of type 2 diabetes is rising worldwide, especially in older adults. Diet and lifestyle, particularly plant-based diets, are effective tools for type 2 diabetes prevention and management. Plant-based diets are eating patterns that emphasize legumes, whole grains, vegetables, fruits, nuts, and seeds and discourage most or all animal products. Cohort studies strongly support the role of plant-based diets, and food and nutrient components of plant-based diets, in reducing the risk of type 2 diabetes. Evidence from observational and interventional studies demonstrates the benefits of plant-based diets in treating type 2 diabetes and reducing key diabetes-related macrovascular and microvascular complications. Optimal macronutrient ratios for preventing and treating type 2 diabetes are controversial; the focus should instead be on eating patterns and actual foods. However, the evidence does suggest that the type and source of carbohydrate (unrefined versus refined), fats (monounsaturated and polyunsaturated versus saturated and trans), and protein (plant versus animal) play a major role in the prevention and management of type 2 diabetes. Multiple potential mechanisms underlie the benefits of a plant-based diet in ameliorating insulin resistance, including promotion of a healthy body weight, increases in fiber and phytonutrients, food-microbiome interactions, and decreases in saturated fat, advanced glycation endproducts, nitrosamines, and heme iron.

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1 Introduction

Type 2 diabetes is a global epidemic, with approximately 422 million cases worldwide and a rapidly rising prevalence in middle- and low-income countries.[1] In the United States in 2011–2012, 12%–14% of adults had type 2 diabetes and 38% had prediabetes.[2] Prediabetes is even more common among those aged ≥ 65 in the United States, with a prevalence of 50%.[3] Diabetes accounts for $176 billion of direct medical costs in the US, including annual per capita costs of $7900, a number 2.3 times higher than costs for adults without diabetes.[4] In 2015, type 2 diabetes was the 7th leading cause of death in the United States.[5] Diabetes in older patients is associated with an increased risk of mortality, reduced functional status, and increased risk of institutionalization.[6] Older patients also have the highest rates of macro- and micro-vascular complications from diabetes, including myocardial infarction, major lower extremity amputations, end stage renal disease, and visual impairment.[3] Moreover, geriatric patients are at increased risk of medication-related complications, particularly hypoglycemia; the elderly have twice the number of emergency room visits for hypoglycemia than the general population with diabetes.[6]

Dietary choices are a key driver of insulin resistance, especially in an aging, more sedentary population. Increases in consumption of calorie-dense foods, including fast foods, meats and other animal fats, highly refined grains, and sugar-sweetened beverages, are thought to play a critical role in the rising rates of type 2 diabetes worldwide.[7] Lifestyle changes, particularly diet, can be highly effective in preventing, treating, and even reversing type 2 diabetes.[8–11] Among the 20% of participants in the landmark Diabetes Prevention Program who were ages 60 and over, lifestyle changes conferred a 71% reduction in risk of type 2 diabetes, demonstrating that older adults reaped the greatest benefit from lifestyle interventions compared to other age groups.[8] Lifestyle changes address the root causes of type 2 diabetes and can ameliorate comorbidities while reducing the risk of polypharmacy, particularly in the elderly. Plant-based diets—i.e., eating patterns that emphasize legumes, whole grains, vegetables, fruits, nuts, and seeds and discourage most or all animal products—are especially potent in pre-

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venting type 2 diabetes and have been associated with much lower rates of obesity, hypertension, hyperlipidemia, cardiovascular mortality, and cancer.[12] We will review the evidence supporting the use of plant-based diets for the prevention and treatment of type 2 diabetes and its complications, and explore mechanisms by which plant-based diets reduce insulin resistance.

2 Plant-based diets for the prevention of type 2 diabetes

Observational studies strongly support the role of plant-based diets, and components of plant-based diets, in reducing the risk of type 2 diabetes.

2.1 Plant-based diets in cohort studies

Large cohort studies demonstrate that the prevalence and incidence of type 2 diabetes are significantly lower among those following plant-based eating patterns compared with omnivores and even semi-vegetarians. Those following plant-based diets tend to have lower body mass indices,[13] which protects against type 2 diabetes. Nevertheless, differences in diabetes risk persist despite adjustments for adiposity.

The Adventist Health Study 2 examined disease prevalence by different eating patterns in an overall health-conscious cohort. Among nearly 61,000 individuals, the prevalence of type 2 diabetes decreased in a stepwise fashion with each reduction in animal products in the diet: from 7.6% in non-vegetarians, 6.1% in semi-vegetarians, 4.8% in pesco-vegetarians, 3.2% in lacto-ovo vegetarians, to 2.9% in vegans.[13] The apparent protection of the vegan dietary pattern remained after adjustment for body mass index and other variables, with vegans having half the rate of type 2 diabetes compared with non-vegetarians (OR: 0.51; 95% CI: 0.40–0.66). Semi-vegetarians experienced intermediate benefit (OR: 0.76; 95% CI: 0.65–0.90). It is worth noting that the non-vegans in this cohort ate meat and poultry relatively infrequently (once a week or more for non-vegetarians; less than once a week for semi-vegetarians), suggesting that even small increases in red meat and poultry consumption disproportionately increase the risk of type 2 diabetes.

Prospective studies of the same Adventist cohort demonstrate similar findings. Among 41,387 individuals followed for two years, multiple logistic regression analysis controlling for body mass index and other variables demonstrated that vegans had a dramatically lower risk of developing type 2 diabetes compared with non-vegetarians (OR: 0.381; 95% CI: 0.236–0.617).[14] In another study of 8401 members of the Adventist Mortality Study and Adventist Health Study, long-term (17-year) adherence to a diet that included at least weekly meat intake was associated with a 74% increase (OR: 1.74; 95% CI: 1.36–2.22) in odds of developing diabetes compared with long-term adherence to a vegetarian diet (zero meat intake); this association was attenuated but persisted after statistical adjustment for weight and weight change (OR: 1.38; 95% CI: 1.06–1.68).[15]

In a cohort of 4384 Taiwanese Buddhists, vegetarian men had approximately half of the rate of diabetes (OR: 0.49, 95% CI: 0.28–0.89), and vegetarian post-menopausal women had one-quarter the rate of diabetes (OR: 0.25, 95% CI: 0.15–0.42), compared with their omnivorous counterparts, despite statistical adjustment for body mass index and other factors. Interestingly, the omnivores in this study consumed a predominantly plant-based diet with little meat or fish, again implying that small amounts of meat contribute significantly to the development of insulin resistance.[16]

In the largest prospective study of plant-based eating patterns to date, Satija, *et al*.,[17] evaluated dietary choices and type 2 diabetes incidence in the Nurses' Health Study, Nurses' Health Study 2, and the Health Professionals Follow-up Study. Eating patterns were stratified by an overall plant-based diet index, in which plant foods received positive scores while animal foods (including animal fats, dairy, eggs, fish/seafood, poultry, and red meat) received reverse scores. In the "healthful" version of this plant-based index, fruit juices, refined grains, and added sugars also received reverse scores. Analysis of data from 4.1 million person-years of follow up revealed that those most adherent to the healthful plant-based dietary index had a 34% lower risk of developing diabetes compared with those least adherent. These associations were independent of body mass index and other diabetes risk factors.

2.2 Food and nutrient components of plant-based diets

A whole-foods, plant-based eating pattern generally includes legumes, whole grains, fruits, vegetables, and nuts, and is high in fiber. All of these elements have been found to be protective against diabetes. Whole grains, including whole-grain bread, whole-grain cereals, and brown rice, have been associated with reduced risk of developing diabetes;[18,19] a recent systematic review and meta-analysis of 16 cohort studies found a summary relative risk of 0.68 for three daily servings of whole grains.[20] Specific fruits and vegetables, including root vegetables, green leafy vegetables, blueberries, grapes, and apples, have been linked to lower diabetes rates.[21,22] Legumes have also been shown to ameliorate insulin resistance and protect against metabolic syndrome,[23–26] and greater nut consumption has been associated with lower diabetes risk.[7] Cereal fiber appears to be especially protective against type 2 diabetes.[27–29]

Diets based on whole plant foods not only maximize protective foods, but they also exclude key animal-based foods that tend to promote insulin resistance, particularly processed and unprocessed red meat.[7,30–38] Risk estimates from recent meta-analyses on meat consumption and type 2 diabetes range from 1.13 to 1.19 per 100 g of total red meat per day and from 1.19 to 1.51 per 50 g of processed meat per day.[39] Animal protein and animal fats have also been linked in both metabolic as well as large cohort studies to worsening insulin resistance and increased incidence of type 2 diabetes.[17,39–48] In the EPIC-interact cohort, for example, van Nielen *et al*.,[40] observed a 22% higher type 2 diabetes incidence over 12 years in the highest versus lowest quintile of animal protein consumption, as well as a 5% higher incidence per 10 g increment of animal protein intake (multivariate-adjusted model, including body mass index).

Similarly, during 4.1 million person-years of follow up of participants in the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study, Malik *et al*.,[47] found that individuals in the highest quintile of animal protein consumption had a 13% increased risk of type 2 diabetes (95% CI: 6–21) compared with those in the lowest quintiles (pooled multivariate model including body mass index). These authors also found that substituting 5% of energy intake from animal protein with vegetable protein was associated with a 23% reduced risk of type 2 diabetes (95% CI: 16–30). In a geriatric population (ages 65 to 100 years) in Greece, a 5% increase in protein intake from meat and meat products was associated with a 34% greater likelihood of type 2 diabetes even after adjustments for age, gender, obesity, history of hypertension, hyperlipidemia, and other dietary habits.[49] In contrast, protein intake from plant sources offered protection against diabetes.

3 Plant-based diets for the treatment of type 2 diabetes

As far back as the 1950s, studies have been published on treating hyperglycemia with a high-carbohydrate, low-fat diet,[50–52] documenting the effectiveness of employing a predominantly vegetarian diet to treat diabetes. Barnard *et al*.,[53] performed the first major randomized clinical trial on diabetic patients treated purely with a plant-based (vegan) diet, comparing it to a conventional diet based on the 2003 American Diabetes Association (ADA) guidelines. A total of 99 individuals, ages 27–82 years, were randomized to counseling on a low-fat vegan diet or the ADA diet and followed for 22 weeks. The recommended vegan diet comprised approximately 10% of energy from fat, 15% from protein, and 75% from carbohydrates and consisted of vegetables, fruits, grains, and legumes. Participants in the vegan group were asked to avoid animal products and added fats and to favor low-glycemic index foods, such as beans and green vegetables. By the end of the trial, 43% (21 of 49) of the vegan group and 26% (13 of 50) of the ADA group participants reduced their diabetes medications. Excluding those who changed medications, hemoglobin A1c fell 1.23 points in the vegan group compared with 0.38 points in the ADA group (P = 0.01). Body weight decreased 6.5 kg in the vegan group and 3.1 kg in the ADA group (P < 0.001). Among those who did not change lipid-lowering medications, LDL cholesterol fell 21.2% in the vegan group and 10.7% in the ADA group (P = 0.02). After adjustment for baseline values, even the reduction in urinary albumin was significantly greater in the vegan group (15.9 mg/24 h) than in the ADA group (10.9 mg/24 h).

When these individuals were followed for a total of 74 weeks, a sustained and equivalent weight loss was noted in both groups, but there was a significant absolute reduction in hemoglobin A1c of −0.40 points in the vegan group versus +0.01 in the ADA group (using the last available hemoglobin A1c value prior to any medication changes).[54] In addition, there was a significant reduction in total cholesterol (−20.4 mg/dL *vs*. −6.8 mg/dL) and LDL cholesterol (−13.5 mg/dL *vs*. −3.4 mg/dL) in the vegan versus ADA diet, respectively. Dietary modification is an integral part of the lifestyle recommendations for persons with diabetes; it is worth noting that while the vegan diet required greater changes in macronutrient intake than the ADA-guided diet, there was no difference in acceptability or adherence to the diets,[55] a finding that has also been demonstrated in other trials.[56,57] While this may be surprising given the potential degree of change required to adopt a vegan diet, the authors hypothesized that not limiting portion sizes, not counting calories or carbohydrates, and experiencing of a variety of new flavors in the vegan diet likely offset any hardship imposed by restricting animal products or added oils.[55]

High-carbohydrate, low-fat, predominantly vegetarian diets are often associated with weight loss, making it difficult to ascertain what proportion of the improvement in glycemic control is due to weight loss versus dietary changes. To evaluate this question, Anderson *et al*.,[52] performed a study on a metabolic ward enrolling lean men with type 2 diabetes who were taking insulin, and placing them on high-carbohydrate, high-fiber (HCF) diet (< 10% calories from fat, 70% from carbohydrates, and 65 g of fiber/day). Body weights were kept stable by simply having participants eat more if they lost weight on the HCF diet. Half of the participants were able to discontinue insulin, and the remainder were able to significantly reduce their insulin; overall, the average insulin dose decreased from 26 units on the baseline (control) diet to 11 units on the HCF diet. Fasting and 3 h postprandial plasma glucose values were lower in most patients on the HCF diets than on the control diets despite lower insulin doses. These results argue for the efficacy of low-fat, plant-based diets (which are naturally high in carbohydrates and fiber) in reversing the insulin resistance that is at the root of type 2 diabetes—though it remains unclear what component of a plant-based diet is most effective: the high carbohydrate and fiber content, the low fat and low-animal protein content, or both.

A 2014 review and meta-analysis of controlled clinical trials of vegetarian diets in the treatment of type 2 diabetes found a significant reduction in hemoglobin A1c of −0.39 points compared to control diets.[58] This effect is approximately half of that seen with the addition of the first-line oral hypoglycemic agent, metformin, which in a recent meta-analysis was reported to reduce hemoglobin A1c by 0.9 points.[59] A more recent randomized controlled trial conducted in Korea compared a brown-rice-based vegan diet with a conventional diabetic diet in patients ages 30−70 years with type 2 diabetes.[60] Participants assigned to the vegan diet were asked to eat brown rice, favor low-glycemic index foods (e.g., legumes, legumes-based foods, green vegetables, and seaweed), and avoid polished/white rice, processed food made of rice flour or wheat flour, and all animal food products. Portions, calories, and frequency of meals were not restricted. Hemoglobin A1c levels decreased by 0.5 points in the vegan group compared with 0.2 points in the conventional group, a significant difference that was even more pronounced when the analysis was restricted to participants who were highly adherent to their respective diets (−0.9 *vs.* −0.3). The inclusion of individuals older than age of 60 in this trial, and in the majority of vegetarian trials mentioned in the meta-analysis above, supports recommending plant-based diets to all age groups with type 2 diabetes, including older adults.

4 Reduction of diabetes-related complications

The benefits of tight glycemic control with pharmacotherapy have been called into question, based on a lack of evidence for it preventing major clinical endpoints, including all-cause mortality, cardiovascular mortality, dialysis, renal death, blindness, and neuropathy.[61] In contrast, plant-based diets have demonstrated improvements in glycemic control while also reducing macro- and micro-vascular risks of type 2 diabetes.

4.1 Cardiovascular disease and risk factors

Cardiovascular disease is the major cause of premature mortality in the diabetic population and many trials have demonstrated the benefits of plant-based diets in preventing and treating cardiovascular disease. In large cohort studies, vegetarian diets have been associated with 24%–32% reductions in ischemic heart disease incidence and mortality relative to omnivorous diets.[62–64] Intervention trials of plant-based diets have also documented angiographic and clinical reversal of coronary artery disease. Ornish, *et al.*,[56] randomized individuals with cardiovascular disease to usual care or lifestyle treatment that included a low-fat vegetarian diet in combination with moderate exercise, stress management, and smoking cessation. After 5 years, LDL levels in the lifestyle intervention group decreased 20% from baseline without lipid-lowering medications—levels similar to that of the usual care group, 60% of whom were on lipid-lowering medications. In the lifestyle group, the average degree of coronary artery stenosis decreased over five years with a 7.9% relative improvement by year 5, compared to a 27.7% worsening in the usual care group. There was a 60% reduction in cardiac events in the lifestyle group compared with the usual care group. Other studies have demonstrated the significant cardiovascular benefits of using this plant-based lifestyle approach,[65] and as a result, in 2010 Medicare began to reimburse the Ornish lifestyle intervention as part of an intensive cardiac rehabilitation program.[66]

Esselstyn, *et al.*,[67] examined the effects of making dietary changes alone, without other lifestyle interventions, on patients with established cardiovascular disease. The authors reported that in 11 patients with severe coronary artery disease who were compliant with a low-fat plant-based diet, 8 (73%) had documented regression of coronary artery disease on repeat angiogram after five years on the diet. In a subsequent review, outcomes were reported on 198 consecutive patients with cardiovascular disease who voluntarily came to the Esselstyn program.[68] A total of 89% were adherent to the diet, consuming a whole-foods, plant-based diet without any meat (including poultry and fish), dairy, eggs, or added oils. The cardiovascular event rate was extraordinarily low: 0.6% among the adherent patients versus 62% among the non-adherent group.

A large body of evidence also supports the use of plant-based diets for the reduction of cardiovascular risk factors. It is well known that the prevalence and incidence of hypertension are significantly lower in those following plant-based diets compared with omnivores.[69–72] In the Adventist Health Study 2 cohort, vegans had approximately half the odds of having hypertension as omnivores, even after adjustment for body mass index.[69] Animal protein has been shown in several prospective studies to increase the risk of hypertension,[73–75] while plant protein tends to lower blood pressure, even in elderly patients.[76,77] Interventional trials of vegetarian diets have been shown to lower blood pressure when compared to omnivorous control diets.[78]

A literature review of plasma lipids and plant-based diets found that among different plant-based diets (i.e., lacto-ovo vegetarian, lactovegetarian, and vegan), populations following vegan diets had the lowest cholesterol concentrations.[79] This review also found that plant-based diets are associated with up to a 35% reduction in serum LDL cholesterol, whereas interventions allowing small amounts of lean meat demonstrated less dramatic reductions in total cholesterol and LDL levels. In the EPIC-Oxford cohort, those following vegan diets had lower levels of apolipoprotein B, reflecting lower levels of circulating atherogenic particles.[80]

Chronic inflammation, as measured by serum biomarkers such as C-reactive protein, has been linked to risk of cardiovascular events,[81] and is closely tied to dietary choices; those following Western, or 'meat-based' diets, tend to have higher levels of biomarkers of inflammation, whereas those following 'vegetable-and-fruit' based patterns tend to have lower levels of these biomarkers.[82] Among intervention trials of plant-based diets, a recent systematic review and meta-analysis found that those adopting a fully or mostly plant-based diet had significant reductions in C-reactive protein and other obesity-related inflammatory biomarkers compared to those following control, non-plant-based diets.[83]

4.2 Renal disease

Chronic kidney disease rates increase with age, and among those older than 60 years, renal impairment is more common in diabetic versus nondiabetic patients (60% *vs.* 41%).[3] Using NHANES 3 data, Chen, *et al*.,[84] found that in individuals with chronic kidney disease, defined as a glomerular filtration rate < 60 mL/min, every 33% increase in plant to total protein consumption was associated with a significant 23% lower mortality risk. To evaluate which foods may be associated with worsening renal disease in diabetic patients, Almeida, *et al*.,[85] obtained a detailed diet history in diabetic patients with and without micro-albuminuria. High intake of protein from animal sources and low intake of polyunsaturated fatty acids, particularly from plant oils, was associated with the presence of micro-albuminuria.

In a crossover trial testing whether albuminuria can be improved in diabetic patients with advanced kidney disease simply by replacing the source of protein, red meat in the usual diet was replaced by either chicken as the major source of protein or a low-protein lacto-ovo vegetarian diet. At the end of four weeks, albuminuria on the vegetarian and chicken diets (330 mg/day and 387 mg/day, respectively) was significantly less than after four weeks on the red meat diet (449 mg/day), strongly suggesting that the protein source impacts the degree of albuminuria.[86] Similarly, Azadbakht, *et al*.,[87] performed a randomized controlled trial in diabetic adults with macro-albuminuria (300−1000 mg total protein excretion/day), substituting half of the animal protein for soy protein in the intervention group and following them for four years. They found that the soy protein intervention group had a significant improvement in proteinuria (−150 mg/day *vs*. +502 mg/day), along with significant decreases in total cholesterol (−23 mg/dL *vs*. +10 mg/dL, P = 0.01), LDL cholesterol (−20 mg/dL *vs*. +6 mg/dL, P = 0.01) and fasting glucose (−18 mg/dL *vs*. +11 mg/dL, P = 0.03).

A recent review outlined how a Western-style diet, characterized by high intake of red meat, animal fat, highly processed food and low intake of fruits and vegetables, is associated with kidney disease.[88] A variety of mechanisms were proposed for this association, including increased animal protein leading to decreased renal blood flow and glomerular filtration rate, an increased acid load from animal protein that must be excreted by the kidneys, and lower fruit and vegetable ingestion leading to lower alkali levels and a net high endogenous acid load, which increases nephron workload. Taken together, these observational and interventional studies support the use of a plant-based diet in treating diabetic nephropathy by both reducing animal-based foods and increasing plant foods.

4.3 Diabetic neuropathy

Diabetic neuropathy is a microvascular complication of diabetes that can be debilitating. At least two small studies have shown that a plant-based diet can ameliorate diabetic neuropathic pain. One study demonstrated a remarkable resolution of burning neuropathy in 81% of participants during a 25-day residential lifestyle program in which plant-based meals were provided, including a sustained response in the participants who adhered to the diet after returning home.[89] A recent randomized controlled pilot study also demonstrated how a plant-based diet can effectively treat diabetic neuropathy: among community-dwelling patients with painful diabetic neuropathy, pain scores were significantly improved at 20 weeks on a plant-based diet compared with a control diet.[90]

5 Current guidelines and macronutrients

In their 2017 "Standards of Medical Care in Diabetes," the

ADA states that a variety of eating patterns are acceptable for the management of type 2 diabetes and pre-diabetes, including Mediterranean, DASH, and plant-based diets.[91] These guidelines recommend carbohydrate intake from legumes, whole grains, fruits, vegetables, and dairy products, with an emphasis on nutrient-dense, high-fiber, low-glycemic load foods. They also include a recommendation that people with diabetes follow the guidelines for the general population for intakes of saturated fat, dietary cholesterol, and trans fat. Plant-based diets are consistent with these guidelines. The Academy of Nutrition and Dietetics states that vegetarian and vegan diets are appropriate for all stages of life, from infancy to adulthood, and may provide benefits for the prevention and treatment of diabetes, obesity and ischemic heart disease.[92]

There has been a wealth of research on macronutrient ratios and subtypes in relation to insulin resistance. Current ADA guidelines state that the optimal mix of macronutrients in type 2 diabetes has not been established.[91] In general, sources of foods (e.g., animal *vs*. plant, refined versus unrefined) are equally important as, if not more important than, specific ratios of carbohydrate, protein, and fats when it comes to glycemic control and the prevention of type 2 diabetes. Moreover, in the most practical terms, people eat foods and combinations of foods, not individual macronutrients or macronutrient ratios. However, it is worth highlighting research on macronutrients and food sources that supports the use of plant-based foods in treating insulin resistance, improving overall health, and reducing mortality.

5.1 Protein

While the 2015 United States Dietary Guidelines emphasize "lean" sources of protein,[93] the evidence does not support turning to animal sources for protein, particularly for individuals with diabetes. Plant sources of protein have the benefit of being truly low fat in many cases (e.g., most legumes). In addition, they supply fiber and many beneficial phytonutrients, all of which are lacking in animal foods and are deficient in the average American diet.[94] In terms of treating type 2 diabetes, a recent systematic review and meta-analysis of 13 randomized controlled trials evaluated the effect of replacing animal protein with plant protein on glycemic control.[45] Among participants, whose average age was 62 years, there was a significant decrease in hemoglobin A1c (−0.15%), fasting glucose (−0.53 mmol/L) and fasting insulin (−10 pmol/L) in diets that replaced animal protein with plant sources of protein at a median level of about 35% of total protein/day, compared with control diets. Another study carried out among 6107 diabetes patients from 15 European cohorts demonstrated that replacing 10 g of dietary carbohydrate with total and animal protein was associated with a mean 5-year weight gain, whereas replacement with plant protein was not significantly associated with weight change.[95] Moreover, substitution with plant protein conferred a significant 21% decrease in all-cause mortality risk. Similarly, a recent large cohort study of 131,342 adults found that in participants with at least one unhealthy lifestyle factor, substitution of 3% of energy from plant protein in lieu of animal protein was associated with a 10% decrease in all-cause mortality and a 12% decrease in cardiovascular mortality.[96] The mortality benefit of plant protein over animal protein was evident across the board, for all major types of animal protein sources (processed meat, red meat, eggs, dairy, poultry, and fish). These studies point to the importance of specifying the type of protein recommended for the management of diabetes and for overall mortality reduction.

5.2 Fats

In relation to insulin resistance, the weight of metabolic studies and epidemiologic evidence suggests that the type of fat in the diet (e.g., saturated, polyunsaturated, or monounsaturated) is highly relevant. Saturated and trans fats increase the risk of developing diabetes;[43] moreover, in diabetic patients, saturated fats are actually associated with increased mortality when they replace carbohydrates in the diet.[97] A recent systematic review of randomized controlled feeding trials evaluated the effects of saturated, monounsaturated, and polyunsaturated fats, as well as carbohydrates on metrics of glucose insulin homeostasis.[98] Replacing carbohydrates (mainly refined starches and simple sugars) and saturated fats with monounsaturated and polyunsaturated fats lowered hemoglobin A1c and improved insulin resistance; polyunsaturated fats were also noted to improve insulin secretion. The authors concluded that in comparison to carbohydrates and saturated fats, monounsaturated and polyunsaturated fats had the most favorable effect on glycemia, insulin resistance, and secretion. In terms of foods, these findings support consumption of vegetable fats (e.g., nuts, avocados, olives) in place of animal fats and refined grains.

Furthermore, there may be a threshold beyond which total fat also affects insulin resistance. In an observational study of 1785 European adults aged 50−75 years with type 2 diabetes, increasing total fat intake from < 25% to ≥ 35% was associated with a significant increase in LDL cholesterol, triglycerides, hemoglobin A1c, and C-reactive protein ($P < 0.05$), whereas increasing carbohydrate intake from < 45 to ≥ 60% was associated with significantly lower triglycerides, hemoglobin A1c, and C-reactive protein ($P < 0.05$).[99] Similarly, Vessby, *et al.*,[100] found that the beneficial impact of monounsaturated fats over saturated fats on insulin sensitivity was absent in individuals with a high total fat intake (> 37% of energy). It is important to note that in key randomized trials of plant-based diets for type 2 diabetes, recommended total fat intake has been low (approximately 10% of energy) for intervention groups.[53,55]

5.3 Carbohydrates

It is a common perception that carbohydrate-rich foods should be avoided in people who have, or are at risk for, type 2 diabetes. As with protein and fat, it is essential to distinguish between the types and sources of carbohydrates. Meta-analyses of cohort studies demonstrated that carbohydrates from whole grains and cereal fibers reduce the risk of developing diabetes while refined,[20,101] low-fiber carbohydrates can increase the risk of diabetes.[29] Metabolic studies also confirm benefits of carbohydrates in comparison to animal protein. Sargrad, *et al*.,[102] compared high-protein versus high-carbohydrate diets, while keeping fat intake constant at 30%, for a period of eight weeks in patients with type 2 diabetes. The high-carbohydrate group was instructed to eat more bread, cereal, pasta, and starchy vegetables while the high-protein group was instructed to have more fish, chicken, eggs, low fat milk, cheese, and nuts. Although weight loss was equivalent in both groups, the high-carbohydrate group had a decrease in hemoglobin A1c (from 8.2% to 6.9%, $P < 0.03$) and fasting plasma glucose (from 8.8 to 7.2 mmol/L, $P < 0.02$), and an increase in insulin sensitivity (from 12.8 to 17.2 mmol/kg per minute, $P < 0.03$). No significant changes in these parameters occurred in the high-protein group.

Moreover, low-carbohydrate diets have been found in several studies to actually increase the risk of type 2 diabetes. Among more than 40,000 men in the Health Professionals Follow-Up Study, the highest quintile of a low-carbohydrate eating pattern, when based on animal sources, conferred a 37% increased risk of diabetes; interestingly, when the low-carbohydrate diet was based on vegetable sources, it was protective, decreasing risk by 22%.[103] Halton, *et al*.,[104] found a similar protective effect of plant-based low-carbohydrate diets among women in the Nurses' Health Study, although, in this population, the overall low-carbohydrate score did not increase risk. In the Nurses' Health Study II cohort, among 4502 women with a history of gestational diabetes, there was a 36% increased risk of diabetes among women with the highest overall low-carbohydrate diet score, and a 40% increased risk when the low-carbohydrate diet favored animal products.[105] In the EPIC-Potsdam cohort, Schulze *et al*.,[106] noted that a higher carbohydrate intake at the expense of protein might decrease diabetes risk. In the general and geriatric populations, low-carbohydrate diets have been associated with increased all-cause, cardiovascular, and cancer mortality.[107–110]

6 Mechanisms of plant-based diets in treating insulin resistance

Diets based in whole and minimally processed plant foods reduce insulin resistance and improve glycemic control by a variety of proposed mechanisms. Plant-based diets are high in fiber, antioxidants, and magnesium, all of which have been shown to promote insulin sensitivity.[7,17] Antioxidants such as polyphenols may inhibit glucose absorption, stimulate insulin secretion, reduce hepatic glucose output, and enhance glucose uptake.[111] Fiber, which is found only in plant foods, modulates postprandial glucose response, and is fermented by intestinal bacteria to produce short-chain fatty acids, which also improve the glucose response, insulin signaling, and insulin sensitivity.[112–115] Furthermore, fiber reduces the energy density of foods, promotes satiety, and has been associated with weight loss, which in turn reduces insulin resistance.[113] Dietary fiber has been linked to decreased markers of inflammation, which may also ameliorate insulin resistance.[17] Finally, a diet high in plant-based foods and low in meat is likely to exert beneficial metabolic effects by promoting shifts in the gut microbial profile, decreasing the production of trimethylamine N-oxide, a compound that has been tied to insulin resistance.[17,39,115]

Plant-based diets also tend to be low in saturated fat, advanced glycation endproducts, nitrosamines, and heme iron dietary elements that have been associated with insulin resistance in epidemiologic and metabolic studies. Saturated fat, which is found primarily in animal-based foods, contributes to lipotoxicity, a phenomenon in which toxic fat metabolites (e.g., species of diacylglycerol and ceramide) accumulate in hepatic and skeletal muscle cells, impairing insulin signaling and thus decreasing glucose uptake.[116–119] Saturated fat has been associated with oxidative stress, mitochondrial dysfunction, and insulin resistance in numerous metabolic and epidemiologic studies as well.[42–44,98,100,120] In addition, diets high in saturated fat are associated with a predominantly gram-negative, lipopolysaccharide-rich gut microbial pattern, which also leads to insulin resistance and inflammation.[118] A plant-based diet has been shown to reduce visceral fat and improve markers of oxidative stress more than a conventional diet in individuals with type 2 diabetes.[121]

Advanced glycation endproducts are oxidant compounds that are high in meat (especially when grilled, broiled, roasted, seared, or fried), and low in plant-based foods such as fruits, vegetables, legumes, and whole grains.[122] Advanced glycation endproducts have been implicated in the pathogenesis of type 2 diabetes,[39] and a diet low in these compounds has been shown to improve insulin resistance in people with type 2 diabetes.[123] Nitrosamines, which are created when nitrite and nitrate preservatives in processed meat bind to amino compounds in those foods, have been shown to accelerate DNA damage and generation of reactive oxygen species and pro-inflammatory cytokines, leading to oxidative stress and insulin resistance.[39] Iron from heme (animal) sources is a pro-oxidant molecule that promotes insulin resistance through various likely mechanisms: increased oxidative stress leading to impaired insulin signaling, direct pancreatic beta cell toxicity, decreased translocation of glucose transporter type 4 channels to the cell membrane, and increased hepatic glucose output.[39] Several meta-analyses have demonstrated a strong link between serum ferritin or dietary heme iron and the risk of type 2 diabetes.[124–127]

Finally, plant-based diets tend to promote weight loss and lower adiposity,[13,128–131] factors that are highly protective against insulin resistance. In contrast, meat consumption (including poultry) is highly predictive of obesity and weight gain over time.[15,132–137] Thus, meat increases type 2 diabetes risk not only by promoting weight gain, but also by mechanisms independent of body mass index, as aforementioned. Furthermore, when a hypocaloric high-protein diet is used for weight loss, the high protein content itself may negate key metabolic benefits of weight loss. Smith *et al*.,[138] found that in obese postmenopausal women, a low-calorie, high-protein diet prevented the therapeutic effect of weight loss on skeletal muscle insulin sensitivity—likely due to worsening oxidative stress, as well as alterations in muscle cell structure and organization, induced by the high-protein diet.

Refined grains and added sugars have also been implicated in weight gain and insulin resistance.[29,139,140] A whole-foods, plant-based dietary approach excludes animal products, refined grains, and added sugars, thus encouraging insulin sensitivity through loss of excess weight and maintenance of a healthier body weight. However, as noted previously, metabolic and epidemiologic studies confirm that plant-based diets improve insulin resistance even when there is no weight loss, and/or with statistical adjustment for body weight.

7 Implementation in clinical practice

Several reviews have presented practical strategies for using plant-based diets in clinical scenarios, including type 2 diabetes management.[141–143] The key elements of the eating pattern include avoidance of animal products, highly refined grains, added sugars, and oils, and consumption of an abundance of legumes, leafy greens, cruciferous vegetables, starchy vegetables, whole grains, and fruits. In key randomized clinical trials of plant-based diets, low-glycemic index foods have been encouraged.[53,54]

Some clinicians may assume that their patients will not be open to adopting a plant-based diet. However, a plant-based diet has been shown to be similarly acceptable to an ADA diet among people with diabetes;[55] plant-based diets have also been found to be highly acceptable in other medical contexts.[144–146] Common questions about specific macro- and micronutrients in plant-based diets have been addressed elsewhere.[141,143,147,148] Patients who adopt a plant-based diet can experience decreases in blood sugar and blood pressure relatively quickly after changing their diet, especially if they are taking medications for these conditions. Close monitoring and anticipation of hypoglycemia is critical; medications may require adjustment.[141] Ongoing support, education, and follow-up can help patients achieve and maintain dietary changes.

8 Conclusions

There is a general consensus that the elements of a whole-foods plant-based diet—legumes, whole grains, fruits, vegetables, and nuts, with limited or no intake of refined foods and animal products—are highly beneficial for preventing and treating type 2 diabetes. Equally important, plant-based diets address the bigger picture for patients with diabetes by simultaneously treating cardiovascular disease, the leading cause of death in the United States, and its risk factors such as obesity, hypertension, hyper-lipidemia, and inflammation. The advantages of a plant-based diet also extend to reduction in risk of cancer, the second leading cause of death in the United States; the World Cancer Research Fund and the American Institute for Cancer Research recommend eating mostly foods of plant origin, avoiding all processed meats and sugary drinks, and limiting intake of red meats, energy dense foods, salt, and alcohol for cancer prevention.[149] Large healthcare organizations such as Kaiser Permanente are promoting plant-based diets for all of their patients because it is a cost effective, low-risk intervention that treats numerous chronic illnesses simultaneously and is seen as an important tool to address the rising cost of health care.[147] Plant-based eating patterns also carry significant environmental benefits. The World Health Organization and the United Nations have promoted diets higher in plant foods as not only effective for preventing chronic diseases and obesity, but also more environmentally sustainable than diets rich in animal products,[150] a position also supported in the scientific report of the 2015 United States Dietary Guidelines Advisory Committee.[151] While larger interventional studies on plant-based diets carried out for longer periods of time would add even more weight to the already mounting evidence, the case for using a plant-based diet to reduce the burden of diabetes and improve overall health has never been stronger.

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