2017

The effects of a plant-based diet on diabetes mellitus

https://hdl.handle.net/2144/23788

Boston University
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

THE EFFECTS OF A PLANT-BASED DIET
ON DIABETES MELLITUS

by

CAITLIN DESCOVICH O’HARE
B.S., University of Massachusetts Amherst, 2013

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science
2017
Approved by

First Reader

Caroline M. Apovian, M.D., FACP, FACN
Professor of Medicine and Pediatrics
Director of Nutrition and Weight Management Center at BMC
Director of Nutrition and Support Service at BMC

Second Reader

C. James McKnight, Ph.D.
Associate Professor of Physiology and Biophysics
ACKNOWLEDGMENTS

I would like to thank Drs. Caroline Apovian and James McKnight for their wonderful help; this thesis would never have been possible without them. Additionally, thank you to my amazing family and friends for always supporting me on this journey, especially Haejin for being right there next to me every day through MAMS.
THE EFFECTS OF A PLANT BASED DIET ON DIABETES MELLITUS

CAITLIN DESCOVICH O’HARE

ABSTRACT

Diabetes is a global epidemic that has unfortunately been significantly increasing in number of cases annually. It is currently the 7th leading cause of death in the United States and leads to many further complications including cardiovascular disease, neuropathy, retinopathy, and kidney failure. With the increase in Western dietary patterns there has been a subsequent rise in both obesity and diabetes. In fact, type 2 diabetes makes up 90% of diabetes cases and is, in most cases, preventable with lifestyle changes and weight loss. The aim of this review is to look at the option of a plant-based diet as a means of prevention and treatment for type 2 diabetes. In order to understand type 2 diabetes the basics of pathophysiology, risk factors, statistic, complications and current treatments is discussed. Based on an analysis of a low-fat, plant-based diet compared to current conventional type 2 diabetes treatments there is evidence that a vegan diet increases insulin sensitivity, decreases body weight, lowers cardiovascular risk factors, and decreases need for oral antidiabetic treatments. A review of the efficacy of a plant-based diet for treatment and prevention of type 2 diabetes is also discussed in-depth. Further studies may be helpful to validate adopting a low-fat, plant-based diet in treatment of type 2 diabetes. Overall, it is important for physicians to address the individual needs of their patients and allow for the option of lifestyle changes with adequate guidance and support.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td>i</td>
</tr>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>iv</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>x</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes Overview</td>
<td>2</td>
</tr>
<tr>
<td>Type 2 Diabetes Pathophysiology</td>
<td>3</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>7</td>
</tr>
<tr>
<td>Effects of Obesity</td>
<td>8</td>
</tr>
<tr>
<td>Diabetes Statistics</td>
<td>11</td>
</tr>
<tr>
<td>Complications</td>
<td>14</td>
</tr>
<tr>
<td>Vasculature Complications</td>
<td>14</td>
</tr>
<tr>
<td>Diabetic Neuropathy</td>
<td>18</td>
</tr>
</tbody>
</table>

vi
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Common Treatments for T2D</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>Components of low-fat, plant-based diet</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>Nutritional Concerns and Sources for a Plant-Based</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Diet</td>
<td></td>
</tr>
</tbody>
</table>
# List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pathways involved in insulin secretion from β-cells</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Pathway from Obesity &amp; Insulin Resistance to T2D</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>The Randle Cycle</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Rate of Diagnosed Diabetes by Race/Ethnicity</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>Stages of Development of Atherosclerosis</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>Risk of MI for Diabetic vs Non-diabetic Individuals</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>Summary of Pathologic Mechanisms of DN</td>
<td>19</td>
</tr>
<tr>
<td>8</td>
<td>Normal versus Diabetic Glomerulus</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>HbA1c Levels for Participants in 74 Wk Study</td>
<td>34</td>
</tr>
<tr>
<td>10</td>
<td>Prevalence of Type 2 Diabetes for different diets</td>
<td>36</td>
</tr>
<tr>
<td>11</td>
<td>Factors Influencing Successful Treatment of T2D</td>
<td>43</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

AACE ................................................... American Association of Clinical Endocrinologists
ADA .......................................................... American Diabetes Association
AMPK ............................................................................................... AMP-activated Kinase
ATP ................................................................................................ Adenosine Triphosphate
β-Cell ...................................................................................................................... Beta Cell
BMC ........................................................................................................ Boston Medical Center
CAD ............................................................................................... Coronary Artery Disease
CDC .......................................................................................... Centers for Disease Control
CHF ............................................................................................... Congestive Heart Failure
CVD ............................................................................................... Cardiovascular Disease
DN ........................................................................................................ Diabetic Neuropathy
DPN ........................................................................................................ Diabetic Peripheral Neuropathy
DPP-4 ................................................................................................. Dipeptidil Peptidase-4
ESRD ............................................................................................ End Stage Renal Disease
FDA .......................................................................................... Food & Drug Administration
FFA ............................................................................................................. Free Fatty Acids
GLP-1 ............................................................................................. Glucagon-like Peptide-1
GLUT4 ................................................................................................ Glucose-transporter 4
HbA1c ........................................................................................................ Hemoglobin A1c
HDL ............................................................................................ High Density Lipoproteins
LDL ........................................................................................................ Low density Lipoproteins
MetS ................................................................. Metabolic Syndrome
MI ................................................................................................. Myocardial Infarction
NO .................................................................................................. Nitric Oxide
PAD .............................................................................................. Peripheral Artery Disease
PVD .......................................................................................... Peripheral Vascular Disease
SGLT2 ................................................................................ Sodium Glucose Co-Transporter-2
T1D ............................................................................................. Type 1 Diabetes
T2D ............................................................................................. Type 2 Diabetes
VLDL ........................................................................................ Very Low Density Lipoproteins
INTRODUCTION

Metabolism includes all of the chemical reactions that maintain life and convert food into energy. Any disorders that occur when the body is incapable of metabolizing nucleic acids, fats, proteins, or carbohydrates are termed metabolic disorders and can be life threatening.\(^6\) A common metabolic disorder is diabetes mellitus, which includes both type 1 diabetes (T1D) and type 2 diabetes (T2D). Diabetes is currently the 7\(^{th}\) leading cause of mortality in the United States and there are an estimated 1.4 million new cases each year.\(^{15}\) Since 1990 the occurrence and frequency of diabetes has continued to dramatically increase in the United States \(^{48}\). Associated with the escalation in diabetes is a rise in obesity in the United States, with greater than a third of adults over the age of twenty falling into the category of obese and 70\% of adults over the age of twenty categorized as overweight.\(^{17}\)

Diabetes is currently a global health concern and until effective interventions are implemented it will continue to be a serious health problem. Globally the number of diabetes cases was estimated to be around 422 million in 2014, which is significantly increased from the estimated 150 million cases in 2001.\(^{74, 81}\) Many of the changes in environment, human behaviors, and lifestyle of the 21\(^{st}\) century are implicated in the diabetes epidemic.

One of the leading underlying causes of T2D and obesity is the Western diet which places an emphasis on animal-sourced foods.\(^{45}\) This paper focuses on the treatment and prevention of T2D with a plant-based diet. The focus on T2D versus T1D is due to the increasing prevalence of T2D as well as the preventable nature of the
disease. This paper will review the basics of T2D including the pathophysiology, risk factors, current statistics, and major complications, as well as current treatments for T2D, a plant-based diet as a treatment option, and research on the efficacy of a plant-based diet versus the current treatments. The conclusion will explore whether this type of diet would be a beneficial approach to treat T2D and if there should be more focus on a plant-based diet for prevention in high risk patients.

**Diabetes Overview**

T2D is, on the basic level, the result of defects in insulin secretion or insulin function. It is a disease with both genetic and environmental causes and is often linked to a combination of both in individuals. Normal blood glucose levels are in the range of 70 to 120 mg/dL. T2D is diagnosed based on average blood glucose, fasting plasma glucose, or an oral glucose intolerance test, indicated by results of 6.5% or higher, 126 mg/dL or higher, and 200 mg/dL or higher, respectively. Average blood glucose is measured by checking hemoglobin A1c (HbA1c), also known as glycated hemoglobin; normal ranges are less than 6%. Prediabetes is classified as impaired glucose tolerance and leads to greater risk of developing both T2D and cardiovascular disease. A fasting glucose of greater than 110 mg/dL, but less than 126 mg/dL or oral glucose tolerance test values of greater than 140 mg/dL, but less than 200 mg/dL are considered indicators of prediabetes.

T1D is classified by deficiency of insulin due to the destruction of beta cells (β-cells) in the pancreas, while T2D is a decrease in insulin production secondary to
development of resistance to insulin.\textsuperscript{(34)} Although T1D is typically the result of an autoimmune attack and is not preventable, T2D can be prevented in many cases by weight loss and exercise.\textsuperscript{(2, 34)} With T2D making up 90\% of diabetes cases it becomes increasingly important to research prevention of this disease.\textsuperscript{(70)} Complications increasing the severity of T2D include hypoglycemia, hypertension, cardiovascular disease (CVD), heart attack, renal failure, stroke, neuropathy, blindness and psychological stress.\textsuperscript{(5, 70)}

**Type 2 Diabetes Pathophysiology**

In order to understand ways to treat and prevent T2D it is imperative to understand the physiology behind the disease. On the pathophysiological level T2D is related to insulin resistance, impaired insulin secretion, increased hepatic glucose production, and eventual \( \beta \)-cell dysfunction. It is a very complex disease and this section will provide a basic review.

Insulin is a hormone produced by \( \beta \)-cells in the pancreatic islets of Langerhans.\textsuperscript{(63)} The secretion of insulin is stimulated by the presence of glucose, which increases after an individual eats.\textsuperscript{(34)} Glucose enters \( \beta \)-cells, accelerating metabolism to yield adenosine triphosphate (ATP) and close ATP-sensitive potassium channels.\textsuperscript{(24)} The closing of these channels depolarizes the \( \beta \)-cell membrane and establishes oscillating influxes of calcium by voltage-dependent calcium channels. These channels, in turn, activate oscillating releases of insulin from the cell (outlined in Figure 1 below).\textsuperscript{(39)} Insulin secretion is biphasic, meaning it has two phases.\textsuperscript{(14, 26)} During the first phase insulin is released
rapidly from stored vesicles in the β-cells in response to food consumption. The second phase involves a slower release of newly synthesized insulin from the β-cells. (26, 63)

Figure 1. Pathways involved in insulin secretion from β-cells.

Taken from Castiello, Heileman, & Tabrizian (2016).

Once released, insulin decreases plasma glucose concentrations. (35) This is achieved by promoting the uptake and storage of glucose in skeletal muscle and adipocytes. In these tissues, insulin increases mobilization of glucose-transporter 4
GLUT4) from intracellular storage vesicles to the cell membrane. This mobilization enhances glucose uptake into the cells. In addition, insulin suppresses hepatic production of glucose, which also decreases plasma glucose concentrations. When glucose levels fall (hypoglycemia), counter-regulatory hormones, including glucagon and adrenaline, are released to promote the production of glucose. When the body is fasting, levels of glucagon increase, while levels of insulin decrease to prevent hypoglycemia. After a meal, glucagon levels decrease, while levels of insulin increase to prevent hyperglycemia. These processes are critical in maintaining homeostasis, which is why normal insulin secretion and function is imperative.

Although glucose regulation is one of the more significant effects of insulin, it also has several other functions, including promotion of lipogenesis, amino acid uptake, protein synthesis, initiation of DNA synthesis, and growth and differentiation of certain cells. Additionally, there is evidence that insulin effects neuropeptides involved in regulation of food intake, similarly to the hormone leptin.

When target tissues fail to normally respond to insulin it is called insulin resistance. This results in decreased uptake of glucose, decreased glycolysis, decreased fatty acid oxidation in liver, and an inability to suppress hepatic gluconeogenesis, which all lead to hyperglycemia. Insulin resistance is caused by a combination of genetics, obesity, tissue inflammation, high fat diet, and sedentary lifestyle. It is commonly the earliest manifestation in the development of T2D, often developing 5-10 years before postprandial (after meal) glucose levels are in diabetic range. It can be present even with obesity unaccompanied by hyperglycemia and increases in severity with age and
obesity. Although often linked to T2D, insulin resistance does not necessarily mean T2D will develop.\textsuperscript{(34)} This is due to the compensation of β-cells, meaning as insulin resistance increases, insulin secretion increases with rising glucose levels. As long as β-cells can compensate, with increased insulin secretion, the body can maintain homeostasis for many years. Unfortunately, with increased long term demands, β-cell compensation can become inadequate.\textsuperscript{(18)} Cell exhaustion combined with chronically elevated levels of glucose and free fatty acids (FFA) that are associated with hyperglycemia and obesity, respectively, leads to β-cell dysfunction and progression to T2D (outlined in Figure 2 below).\textsuperscript{(34, 39)} Once developed T2D is a progressive disease because of increased β-cell dysfunction and destruction over time.

\textbf{Figure 2. Pathway from Obesity & Insulin Resistance to T2D}

![Figure 2: Pathway from Obesity & Insulin Resistance to T2D](Taken from Beller. (2001).)
Risk Factors

As mentioned earlier, T2D is an extremely complex disease that has numerous factors involved, including behavioral, environmental, and genetic. In order to develop preventive measures it is essential to identify these risk factors. This section will focus on the various risk factors throughout an individual’s life, including both non-modifiable and modifiable factors with an in-depth look at the specific effects of obesity.

Determinants of health and development of T2D can begin as early as before birth or during infancy. It has been shown that mothers with gestational diabetes increase the likelihood of their babies developing T2D in their lifetime by a factor of 32. Low and high birth weight extremes have both been associated with increased risk of T2D. This is most likely due to the increased risk of developing visceral fat. Furthermore, breast-feeding has been associated with 13-22% less risk of developing obesity and subsequent T2D later in life.

Non-modifiable risk factors for T2D are those that cannot be changed and include family history, genetics, and age. Research has shown genetics increase susceptibility of β-cells to the pathogenesis of T2D, but they do not solely cause the dysfunction of β-cells. Therefore, having these genes does not make the development of T2D inevitable. For this reason genetics is only one factor in T2D development and is not solely correlated with T2D. It is insulin resistance, caused by many factors, which increases environmental stresses on β-cells leading to their dysfunction.

Modifiable risk factors of T2D include behaviors such as lack of physical activity, lack of sleep, smoking, and western dietary patterns. Furthermore, metabolic syndrome
(MetS) is a preventable syndrome, which includes a compilation of risk factors that predisposes individuals to T2D. It includes central obesity, hyperglycemia, dyslipidemia, and hypertension. MetS increases the risk factor of T2D by a factor of 7 and accounts for nearly 50% of T2D cases. (31)

Effects of Obesity

One of the leading modifiable risk factors of T2D is obesity. Excess body fat, specifically visceral fat has been linked with increased risk of T2D. Visceral fat, or intra-abdominal fat, is the fat found packed around the organs in the abdominal cavity. Adipose tissue is an endocrine organ and has a very large role in metabolism. It releases many hormones, including leptin and adiponectin, as well as pro-inflammatory cytokines, and FFAs. (31)

Leptin is a hormone involved in satiety. Obesity is linked to leptin resistance or dysfunction of leptin receptors. Therefore, in obese individuals, as adipose tissue increases, leptin levels increase, but the body continues to crave energy intake in the form of food. (28) Leptin is also involved in lipid metabolism and decreased sensitivity of leptin has been shown to lead to increased levels of triglycerides in adipose tissue, skeletal muscle, the liver and pancreas, which attributes to insulin resistance. (35) Lastly, leptin has pro-inflammatory actions, the effects of which will be discussed below.

Adiponectin is a protein hormone that increases insulin secretion, ameliorates insulin resistance by increasing insulin sensitivity, increases oxidation of muscle fat and exhibits anti-inflammatory properties. (35, 49) It has an extremely important role in glucose
and lipid metabolism. Adiponectin receptors have been found on pancreatic β-cells and are shown to increase glucose related insulin secretion by increasing calcium influx. (42) It is also related to insulin sensitivity of target tissues and as levels of adiponectin decrease, insulin resistance increases. This increase in insulin sensitivity is caused by an increase in phosphorylation of AMP-activated kinase (AMPK) in liver and muscle tissue. AMPK is an enzyme that increases glucose uptake and FFA oxidation in addition to upregulating insulin receptor substrate-1. With more insulin receptors on the cell surface, insulin sensitivity increases. (41, 42)

Adiponectin secretion is shown to decrease in obese patients, especially those with visceral fat. (41) This is partially because as adipocytes increase in size, adiponectin secretion decreases, although the exact mechanisms are still being researched. (49) Decreased levels of adiponectin have been associated with the development of both MetS and T2D. (41) In individuals with an already increased risk of developing T2D, those with low levels of adiponectin are more likely to develop T2D. (35)

Pro-inflammatory cytokines (including tumor necrosis factor, TNF-α; c-reactive protein, CRP; and interleukin-6, IL-6) increase as adipose tissue increases and contribute to insulin resistance. This may be due to inducing insulin resistance in adipocytes leading to increased lipolysis and elevating levels of FFAs, which are key in insulin sensitivity. (31, 48) Pro-inflammatory cytokines also lead to upregulation of mediators in inflammation that can lead to insulin resistance. (31)

Lastly, increased FFAs are associated with increased insulin resistance and β-cell dysfunction. This is due to a few mechanisms, including accumulation of intracellular
fatty acid metabolites, inflammatory signaling, oxidative stress, mitochondrial dysfunction, and the Randle cycle. With an increase in FFAs the ability of adipose tissue to store fatty acids can be exceeded, which leads to FFA accumulation in the liver and skeletal muscle. (35) This accumulation of intracellular content of fatty acid metabolites subsequently diminishes insulin-receptor signaling, decreasing translocation of GLUT4 and subsequent glucose uptake. (31, 35) FFAs also increase inflammatory signaling via Toll-like receptors (TLR) and increased secretion of cytokines. TLR detect microbes and transmit inflammatory signaling and FFAs can signal through TLR-2 and -4 to induce pro-inflammatory gene expression. A loss of TLR-2 and -4 has been shown to resolve high fat induced insulin resistance in mice. (35)

With increased fat accumulation, decreased adiponectin, and increased cytokines, reactive oxygen species (ROS) increase and oxidative stress increases. An increase in ROS leads to delayed insulin signaling by impairing GLUT4 translocation. (35) It is also shown that an increase in FFAs mediates mitochondrial dysfunction. This dysfunction has been connected with insulin resistance in skeletal muscle. (35)

Finally, as demonstrated in the Randle Cycle, also known as the glucose-fatty acid cycle, (shown in Figure 3 below) glucose and FFAs compete as the source of fuel for tissues. (29, 35) Normally after a meal glucose and insulin inhibit fat breakdown, and glucose is used as the major metabolic fuel in muscle and adipose tissue. During starvation there is increased oxidation of fatty acids and ketones to preserve glucose stores. (29) When an individual has a diet very high in fat, FFAs become the dominate source of fuel, similar to the fasted state, and with chronically elevated FFAs there is
increased intracellular glucose and decreased glucose uptake. (35) On the other hand, with a diet very high in carbohydrates, which break down into glucose, there is an increase in plasma triglycerides (an ester derived from glycerol and fatty acids), partially because of reduced clearance to fatty acids. (51) For these reasons it is extremely important to have a balanced diet in order to avoid the consequences of one too high in fat or glucose.

**Figure 3. The Randle Cycle**

![Diagram of the Randle Cycle](image)

Diagram of the Randle Cycle, where LCFA stands for long chain fatty acids and TAG stand for triacylglycerol or triglyceride. Taken from Hue, L., & Taegtmeyer, H. (2009).

**Diabetes Statistics**

There have been a few T2D statistics already mentioned in this paper, but in order to gain a better perspective of the severity of this disease this section will focus solely on additional statistics. At this moment there are over 29 million Americans living with diabetes and 86 million Americans with prediabetes, greatly increasing their risk of developing T2D. (5, 17) Of the 29 million with diabetes, 1.25 million have T1D while 27.75 million have T2D. Moreover, 8.1 million cases of the 29 million are currently
undiagnosed. It is predicted by year 2050 the number of Americans with diabetes will have increased to 48.3 million.\(^{(48)}\)

Diabetes is the leading cause of adult onset blindness, lower limb amputations and kidney failure.\(^{(17)}\) In addition, the average cost of medical care is two times higher in those with diabetes and greater than 20% of health care spending is for diabetes.\(^{(5, 17)}\) Zhuo et al. found in 2013 that the average lifetime cost of diabetes is around $85,000.\(^{(79)}\) One in every five health care dollars is spent for people with diabetes.\(^{(3)}\) One in every three Americans will develop T2D in their lifetime and the risk of death is 50% greater than for those without diabetes.\(^{(5, 17)}\)

Race/ethnicity plays a role in percentage of those with T2D, the highest being in Alaskan Native and American Indian populations, who are two to five times more likely to develop T2D than non-Hispanic white Americans (see Figure 4 below).\(^{(48)}\) Having a lower socioeconomic status also increases incidence of T2D, although it is uncertain whether it is due to stresses, environmental factors, or lack of public health and medical care in this group.\(^{(48)}\)
Each day 3,835 Americans will be diagnosed with diabetes, 200 will undergo amputations related to diabetes, 1,795 will develop severe diabetic retinopathy, and 136 will enter end stage renal failure due to diabetes.\(^{(3,16)}\)

With the increases predicted in the above statistics it becomes increasingly imperative to focus on changes in the current preventions and treatments in the health care system for T2D, as it makes up a majority of diabetes cases and is preventable.
Complications

T2D leads to many serious complications and has effects on nearly all of the body systems. The most substantial complications include peripheral vascular disease (PVD), cardiovascular disease (CVD), myocardial infarction (MI), stroke, diabetic neuropathy (DN), diabetic nephropathy, and diabetic retinopathy. Each of these complications is incredibly complex and multifactorial. The onset and severity depends on the duration of T2D as well as the degree of metabolic control of the individual. For the purpose of this thesis, this section will go into a very brief review of these complications including the basic pathophysiology. There is still a great amount of research being done to understand each complication in order to provide better prevention and treatment options.

Vascular Complications

Although, as mentioned above, all T2D complications are multifactorial, a leading underlying factor is persistent hyperglycemia, which has a great effect on the vascular system. Hyperglycemia leads to alteration of arterial structure and function through several biochemical changes.\(^{(25, 60)}\) These changes in vasculature have severe impact on many organs, especially the heart. As previously discussed, hyperglycemia results in release of pro-inflammatory cytokines. An increase in CRP leads to increased binding to endothelial cell receptors in vasculature and has several molecular effects (such as increased production of anti-fibrinolytic factors, stimulation of tissue factor production, and inhibition of endothelial nitric oxide (NO) synthase), all of which lead to endothelial dysfunction.\(^{(27, 60)}\) Alteration of NO metabolism seen in T2D plays a role in
atherosclerosis, a disorder of the arterial wall with plaque formations. Hyperglycemia and endothelial dysfunction also lead to generation of ROS, platelet hyperactivity, hypercoagulability, enhanced proliferation of vascular smooth muscle cells, and synthesis of extracellular matrix. All of these effects potentiate atherosclerosis. (34)

Pathogenesis of diabetic atherosclerosis involves not only hyperglycemia, but also insulin resistance, FFAs, and dyslipidemia. Diabetic atherosclerosis follows the same histologic course as non-diabetic atherosclerosis. Endothelial cell injury leads to increased permeability as well as leukocyte adhesion, which causes retention of low density lipoproteins (LDL). LDL interacts with the extracellular matrix and can undergo oxidation by ROS leading to the eventual development of foam cells in vasculature walls seen in atherosclerotic plaques. This occurs with LDL particles inducing further leukocyte adhesion and eventual migration of monocytes into the tunica intima (the innermost layer of blood vessels). Monocytes then mature into macrophages, which engulf oxidized LDL to form foam cells. (39) At this time there is also smooth muscle proliferation and recruitment due to activated platelets and inflammation. Smooth muscle cells gives rise to a fibrous cap, making vasculature susceptible to occlusion. (60) The pathological course of atherosclerosis is shown in Figure 5 below.
In addition to atherosclerosis, T2D also leads to hyaline thickening of the wall of arterioles and diffuse basement membrane thickening. Even with this thickening of the basement membrane the capillaries are leakier. (34) Hyperinsulinemia causes increased LDL and very low density lipoproteins (VLDL) as well as a decrease in high density lipoproteins (HDL). This change in lipoproteins causes a rise in plasma triglycerides. Also, hyperinsulinemia is associated with hypertension, which may be due to hyaline thickening of arteriolar walls, an increase in sodium reabsorption from proximal renal tubules, or increased sympathetic nervous stimulation, all of which are seen with T2D. (11)
These changes in the vasculature system are important factors in the many complications seen with T2D.

With the increased risk of atherosclerosis and the vascular changes with T2D, there is an increased cardiovascular risk, including increased risk of PVD, also known as peripheral artery disease (PAD), CVD, MI, and stroke. In fact, a patient with diabetes who has never had a vascular event is at the same risk of having an event as a patient without diabetes who has had a previous MI (demonstrated in Figure 6 below). (11)

Once a patient with diabetes has had a cardiovascular event they are at an even greater risk for congestive heart failure (CHF) or MI compared to non-diabetic MI survivors. (11, 12) Outcomes for patients with diabetes hospitalized for angina or MI are significantly lower than patients without diabetes who have been hospitalized. Also, mortality rates after primary angioplasty are twice as high in patients with diabetes compared to patients without diabetes. (12) Additionally, of patients with diabetes the risk of MI is the same in men and women. Typically MI is uncommon in women without diabetes of reproductive age, but this protection seems to be lost with diabetes. (34) MI is currently the most common cause of death in diabetes, which is why prevention and treatment of T2D focuses not only on the aspects of T2D, but also of CVD. (34)
PAD/PVD seen with endothelial dysfunction, atherosclerosis, platelet hyperactivity, and hypercoagulability, is associated with critical limb ischemia and subsequent gangrene and need for lower limb amputations. (60) Gangrene of lower extremities is one hundred times more likely in patients with diabetes than those without diabetes. (34) Diabetic foot ulceration is multifactorial and may result from acute or chronic injury along with advanced vascular disease and DN. (60)

**Diabetic Neuropathy**

DN affects between 30-50% of patients with diabetes and is defined as the progressive loss of somatic and automatic nerve fibers. (60) It is the leading long term complication associated with T2D. (64) A summary of the pathologic mechanisms is

Taken from Beller (2001).
shown in Figure 7 below and a brief look at effects of glucose will be discussed. The nervous system is dependent on supplies of glucose and oxygen and the uptake of glucose depends on extracellular concentrations. With chronic hyperglycemia there is chronic intraneuronal hyperglycemia and secondary neurotoxicity. This leads to neuronal damage and disruption of the nerve-axon reflux. There are many neuropathies involved with T2D, but the most common is diabetic peripheral neuropathy (DPN). DPN is a key factor in the pathogenesis of diabetic foot ulcers and impairment of wound healing, leading to eventual need for lower limb amputations. Costs associated with foot ulcers, wound healing, and amputations are extremely high and unfortunately the pathophysiology is very complex and not well understood, making treatments difficult to develop.

**Figure 7. Summary of Pathologic Mechanisms of DN**

Taken from Yagihashi, Mizukami, & Sugimoto. (2010).
Patient’s with DN may be unaware or experience numbness, tingling, contact pain, shooting pain, persistent aches, or hot and cold sensations. Autonomic neuropathies can have cardiovascular symptoms (dizziness, postural hypertension, and exercise intolerance), upper gastrointestinal symptoms (nausea, vomiting, and bloating), lower gastrointestinal symptoms (diarrhea and constipation), erectile dysfunction, and bladder problems. \(^{64}\)

**Diabetic Nephropathy**

Diabetic nephropathy occurs in nearly 40% of patients with diabetes and is the single leading cause of end stage renal disease (ESRD). \(^{25}\) Renal failure is second only to MI as a cause of death of patients with diabetes. \(^{34}\) Diabetic nephropathy is characterized by persistent albuminuria, the presence of albumin in urine, with an albumin excretion rate of >300 mg/24 hours. \(^{66}\) Hyperglycemia leads to hemodynamic and renal changes as well as mesangial lesions in the kidney. \(^{1}\) Major changes in early kidney disease include glomerular hyper-filtration, epithelial hypertrophy, increased renal blood flow, and development of microalbuminuria (albumin excretion rate of 20-200 mg/24 hours). \(^{1,66}\) Subsequent development of thickened glomerular basement membrane, accumulation of mesangial matrix, and overt proteinuria lead to glomerular sclerosis and ESRD.\(^{1}\) Figure 8, below, shows a normal versus a diabetic glomerulus. Without intervention early kidney disease can develop into clinical albuminuria in 10-15 years and is associated with retinopathy, hypertension, PVD, and DN. \(^{66}\)
Figure 8. Normal versus Diabetic Glomerulus

Diabetic Retinopathy

Diabetic retinopathy is the leading cause of blindness in developed countries and is primarily caused by microvascular changes in the retina due to hyperglycemia. (20) Hyperglycemia causes progressive vessel loss, increased vascular permeability, and neuronal damage. An increase in blood flow in the capillaries stimulates production of vasoactive substances from capillary walls and increases endothelial cell proliferation, resulting in the closure of capillary circulation and retinal ischemia. (11) Also involved is tissue edema and bleeding, both of which contribute to vision loss as well. Patients with diabetes are at increased risk for cataracts, retinal vein or artery inclusion, glaucoma, and macular degeneration.
Other Complications of Diabetes

A recent study by Yang et. al. showed an increased risk of Parkinson’s with diabetes, with a 23% greater risk of developing Parkinson’s for older patients with diabetes. (76) Additionally, many patients with diabetes are more susceptible to gum diseases, including gingivitis and periodontitis. (5, 22)

Furthermore, many patients with diabetes suffer from depression, anxiety and eating disorders, which can all lead to poor prognosis. In fact, depression is twice as likely in patients with diabetes, compared to those without diabetes. (54) Due to poor psychological wellbeing it can be very difficult for patients to change daily habits and keep up with doctor appointments. It has been shown that only 39% of T2D patients are able to have complete success of 2/3 of their self-care. (52)

With inability to maintain healthcare needed for T2D and the psychological stress related to T2D and obesity it becomes increasingly important for physicians to establish a good relationship with patients and help them work on preventive care. The following sections will review the various preventions and treatments for T2D as well as a look into plant based options.
SPECIFIC AIMS

The specific aims of this paper are to:

1. Discuss the basics of current T2D treatments, including lifestyle changes, oral diabetic medications, and injectable insulin.
2. Evaluate a plant-based diet and the use of treatment for T2D and its major complications.
3. Discuss the efficacy of a plant-based diet versus the conventional treatments.
4. Review the findings from this assessment and whether further research should be implicated for plant-based diets and T2D treatment.
CURRENT TYPE 2 DIABETES TREATMENTS

T2D management includes diet modifications, increased physical activity, oral medications, possible insulin injections, and blood glucose monitoring. The goal of any treatment is to achieve effective glycemic control (HbA1c reduction) in order to reduce microvascular complications. (54) Although, for maximum clinical benefit, all underlying pathophysologies need to be addressed with treatment. (57) A study by Poulos et al. showed that when US physicians consider treatment options they are most concerned by glucose control, followed by reducing the five-year risk of a fatal MI and changes in body weight. (54) Liver monitoring and reduction of depression were the least important factors of medication choice, but overall physicians valued treatments that went further than simple glycemic control. Physicians also like to avoid any amount of weight gain with patients as this can further complicate T2D. (54)

One of the biggest challenges when treating patients is that almost a third of patients with T2D do not adhere to their treatment regimen. (54) Nonadherence is commonly seen in patients with chronic diseases and leads to poor treatment outcomes. With T2D this leads to poor glycemic control and increased risk of complications. Nonadherence is often correlated with the major lifestyle changes required to manage this disease, such as continuous blood glucose monitoring and costs of medications. Additionally, less than 50% of T2D patients achieve their glycemic treatment goal even with medications. (58) Another challenge is that many patients are required to take additional medications in order to treat comorbidities and complications associated with
T2D. When physicians treat these patients, interactions between medications has to be considered.

Table 1, below, highlights the major diabetic medications available for T2D, including their mechanism of action, major side effects, and any additionally important notes. Of note, newer agents tend to cost more than older ones and some therapies are only approved as adjunctive therapies.

Treatment often begins with lifestyle modifications and metformin, unless metformin is contraindicated or not tolerated. These first line therapies are recommended by the American Diabetes Association (ADA) as well as the American Association of Clinical Endocrinologists (AACE). The goal of these therapies is to reach blood glycemic targets based on measured HbA1c levels.

Metformin is the most common first line oral diabetic treatment because it is widely available, inexpensive, has been shown to decrease HbA1c levels by around 1.5%, and has a low risk of hypoglycemia. Additionally, it is not associated with weight gain as some other medications have been. This makes it particularly ideal for obese T2D patients.

Changes in diet are often of interest for patients with T2D, although there is not currently one specific diet in place. Diets used for treatment have the same goals as medications; to regulate blood glucose levels. In addition, the focus of diet as treatment is popular due to the high incidence of obesity related to development of T2D. With the high risk factors and complications associated with high FFAs it is imperative to work on lowering volume of fat, especially visceral fat. Many of the current diets related to
treatment of T2D focus on low-carbohydrate and higher protein intake. \(^{(21)}\) It has been shown that low-carbohydrate diets are successful in regulating glucose levels, reducing the amount of medications needed, reducing LDL levels, and promoting weight loss short term. \(^{(21)}\) The downside is that, similarly to many diets that exclude certain foods, there is an increased risk of mineral deficiencies. Also, a diet high in animal proteins can lead to kidney dysfunction, disturbances in fluids and electrolytes, and changes in bone remodeling. \(^{(21)}\)

Due to the progressive nature of T2D, most patients will require a combination therapy at some point in their treatment course and may even progress to a triple therapy. Lifestyle changes and metformin can become inadequate in maintaining glycemic control. \(^{(67)}\) Due to the many other oral diabetic medications available, there is not one universal standard for adding agents to a patient’s plan. There are many factors to take into account, but often physicians try to use drugs with complimentary actions that do not have contraindications for the patient. For instance, metformin increases insulin sensitivity and may be used with an agent that increases insulin secretion. \(^{(67)}\) Often, when patients are no longer maintaining glycemic control with two or three oral diabetic medications, injectable insulin is initiated. \(^{(67)}\)

Both insulin and sulfonylureas can cause significant hypoglycemia (blood glucose levels less than 70 mg/dL) if taken incorrectly. \(^{(4, 72)}\) This risk can be up to 4-5 days with insulin and anywhere from hours to days with sulfonylureas. There is also a moderate risk of hypoglycemia with meglitinides and SGLT2 inhibitors. \(^{(72)}\) Profound hypoglycemia can lead to neurological deficits including cognitive impairment, altered
behavior, slurred speech, tachycardia, seizures, and unconsciousness. Hypoglycemia can be reversed with use of intravenous glucose.

**Table 1. Common Treatments for T2D.**

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Action</th>
<th>Side Effects</th>
<th>Special Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metformin</strong></td>
<td>Increases sensitivity of body tissues to insulin and suppresses gluconeogenesis from lactate and pyruvate</td>
<td>Nausea, vomiting, diarrhea, upset stomach, lactic acidosis</td>
<td>Typically first medication prescribed, particularly effective for patients with T2D and obesity, approved by US Food &amp; Drug Administration (FDA) in 1995</td>
</tr>
<tr>
<td>(Glucophage, Glumetza, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td>Stimulates pancreas to secrete more insulin by blocking ATP-sensitive potassium channels, depolarizing the cell and allowing calcium entry therefore increasing insulin secretion. They are only effective when there is still β-cell function</td>
<td>Hypoglycemia, weight gain, hunger, upset stomach</td>
<td></td>
</tr>
<tr>
<td>(glyburide [DiaBeta, Glynase], glipizide [Glucotrol] and glimepiride [Amaryl])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meglitinides</strong></td>
<td>Stimulates pancreas to secrete more insulin by blocking ATP-sensitive potassium channels, depolarizing the cell and allowing calcium entry therefore increasing insulin secretion.</td>
<td>Hypoglycemia, weight gain</td>
<td>Faster acting than sulfonylureas, but shorter duration of action</td>
</tr>
<tr>
<td>(repaglinide [Prandin] and nateglinide [Starlix])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class</td>
<td>Mechanism</td>
<td>Side Effects</td>
<td>Summary</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td>Increases sensitivity of body tissues to insulin by stimulating peroxisomal proliferator-activated receptor gamma</td>
<td>Hypoglycemia, weight gain, macular edema, increased risk of heart failure, bone fractures, and risk of hepatitis and liver failure</td>
<td>Riskier medication, most have been removed from the US market (only rosiglitazone and pioglitazone remain)</td>
</tr>
<tr>
<td>Thiazolidinediones (rosiglitazone [Avandia] and pioglitazone [Actos])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dipeptidil peptidase-4 (DPP-4) inhibitors</strong></td>
<td>Inhibit the enzyme DPP-4 to prevent degradation of GLP-1; stimulates insulin production, inhibits glucagon production, and preserves β-cell mass by stimulating cell proliferation and inhibiting apoptosis</td>
<td>Nausea, diarrhea, upset stomach</td>
<td></td>
</tr>
<tr>
<td>Dipeptidil peptidase-4 (DPP-4) inhibitors (sitagliptin [Januvia], saxagliptin [Onglyza] and linagliptin [Tradjenta])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glucagon-like-peptide-1 (GLP-1) receptor agonists</strong></td>
<td>Slow digestion and increases insulin secretion</td>
<td>Nausea, increased risk of pancreatitis</td>
<td>Associated with some weight loss</td>
</tr>
<tr>
<td>Glucagon-like-peptide-1 (GLP-1) receptor agonists (exenatide [Byetta] and liraglutide [Victoza])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sodium glucose co-transporter-2 (SGLT2) inhibitors</strong></td>
<td>Inhibit SGLT2, an active transport mechanism for renal tubular glucose reabsorption in the proximal tubule, thereby preventing the kidneys from reabsorbing sugar into the blood; the</td>
<td>Yeast infections, urinary tract infections, increased urination, hypotension</td>
<td>Effects are diminished in patients with renal failure; newer class of oral antidiabetic drugs: Invokana was approved by FDA in 2014 and Farxigal was approved in 2013.</td>
</tr>
<tr>
<td>Sodium glucose co-transporter-2 (SGLT2) inhibitors (canagliflozin [Invokana] and dapagliflozin [Farxiga])</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sugar is instead, excreted in the urine.

**Insulin Injections**

(Insulin glulisine [Apidra], Insulin lispro [Humalog], Insulin aspart [Novolog], Insulin glargine [Lantus], Insulin detemir [Levemir], Insulin isophane [Humulin N, Novolin N])

- Modifies glucose transporter function via its tyrosine kinase-linked receptor
- Severe hypoglycemia

Adapted from Mayo Clinic Staff Print (2016), Stumvoll, Häring, & Matthaei (2007), Zimmerman (1997), Ruscica et al. (2017), and Waring (2016).

For all patients treatment plans need to be chosen based on the individual. Physicians need to take into account any major complications the patient has, as well as the impact treatment will have on their quality of life and the cost of the treatments. Other factors that should be considered include age of the patient, duration of T2D, life expectancy, risk of hypoglycemia, etc. It is extremely important to always closely monitor patients’ blood glucose levels throughout to ensure proper treatment. If glycemic control is maintained it can reduce the risks of microvascular and macrovascular complications as well as reducing costs in the long term. \(^{(57)}\)
PLANT-BASED DIET

Poor diet is one of the largest contributors to early death. (47) The aim of our diet should be to improve our health, not make us vulnerable to disease. This section will consider the benefits of a plant-based diet and its option for treatment of T2D as well as CVD and obesity. In 2006 2.3% of the American population followed a vegetarian diet while around 1.4% followed a vegan diet. (53) Additionally, many consumers expressed interest in vegetarian diets with 22% reporting consumption of meat substitutes regularly. Much of this increase in interest is due to emergence of college courses on vegetarian nutrition, more web sites promoting the diets, and more cookbooks and restaurants with a vegetarian theme. (53)

A vegan diet is defined as one that does not include any animal-based products. Variations include a lacto-ovo vegetarian diet which excludes meat, but includes dairy, dairy products, and eggs, a pesco-vegetarian diet which includes dairy, dairy products, eggs and fish, and a semi-vegetarian diet which is cutting back on meat products, but still includes them. An omnivore diet includes animal products: the Western diet typically has animal products in two or three meals and is high in fat and animal protein while a non-Western diet has less processed food and minimal animal products. (70) Meat is often a central aspect of the Western diet, whereas in other cultures it is treated more as a side dish or condiment. Of note, although plant-based diets have been shown to be beneficial to health, there are vegetarian foods that are unhealthy. (59) These include juices, other sweetened drinks, desserts, processed snacks, etc. Diets reviewed for this paper were those that were low-fat, plant based diets (outlined in Table 2 below).
Those who eat plant-based diets tend to consume fewer calories, less total and saturated fat, less cholesterol, and foods with lower glycemic index. They also typically have a lower body mass index (BMI) than non-vegetarians and consume more potassium, fiber, and vitamin C. Vegetables and fruits reduce oxidative stress and chronic inflammation, both of which are risk factors in development of insulin resistance. Previous research has shown that a low-fat, plant-based diet results in a significant decrease in cholesterol, weight, blood pressure, blood glucose, and cardiovascular risk. Those who follow a plant-based diet have lower prevalence of T2D, CVD, hypertension, and obesity and tend to spend less on medical care. Interestingly, Denmark achieved its lowest mortality rate in its history when restrictions on dairy, fats, and meat were imposed during World War I; similar findings were observed in Wales and England during war time when restrictions were also imposed.

Intake of saturated fats that is seen with those who eat high meat diets is associated with insulin sensitivity. This might be due to the accumulation of lipids, particularly in skeletal muscle, which negatively affect the insulin signaling pathway and leads to chronic inflammation.
Table 2. Components of low-fat, plant-based diet.

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad libitum foods from four food groups: whole grains, legumes (beans, peas, and lentils), vegetables, and fruits</td>
<td>Limit or avoid added vegetable oils and other high-fat foods for weight and glycemic control. Use nuts and seeds sparingly (to top a salad or oatmeal; not as a snack)</td>
</tr>
<tr>
<td>Unprocessed and minimally processed foods are best</td>
<td>Choosing low glycemic index foods (e.g., old-fashioned oatmeal, sweet potatoes, pasta, grains, most fruits and vegetables) may have an additional benefit</td>
</tr>
<tr>
<td>≥40 g of fiber from whole foods per day is recommended</td>
<td>Avoid all animal products</td>
</tr>
<tr>
<td>B12 supplementation of 5 μg/d (e.g., a common multivitamin) is recommended for anyone avoiding animal products and all people over 50 years of age</td>
<td>A macronutrient profile of ~75% to 80% of energy from carbohydrate, 10% to 15% from protein, and 10% from fat is recommended</td>
</tr>
</tbody>
</table>

Table taken from Trapp & Barnard, 2010

Role of Diet in Type 2 Diabetes Treatment

Despite the availability of a range of treatments and efforts of physicians, the number of patients with T2D as well as the number with complications due to T2D is still on the rise. This is why considering different types of treatments and preventive measures is important. There is a great amount of controversy over the best diet to address glycemic control, CVD risk factors, and weight control. This section will review current research on low-fat, plant-based diets as a means to address prevention and treatment of the many factors of T2D.
T2D has followed Western dietary habits and there is a prevalence of T2D in population groups with higher fat intake and animal-based diets.\(^{(69)}\) A low-fat plant-based diet is linked with a decrease in body weight, an increase in insulin sensitivity, and reduction in CVD risk factors, all of which are critical to T2D patients.\(^{(9,44)}\) Recently both the ADA and the American Academy of Nutrition and Dietetics incorporated an option for a well-balanced, plant-based diet in recommendations for diabetes nutrition.\(^{(70)}\) Plant-based diets are beneficial for glycemic control in part because they contain less total and saturated fats, reducing FFA levels and lipid accumulation and thereby reducing risks associated with FFAs that were discussed in the T2D risk factor section.

A 22 week study conducted by Barnard et al. examined the effects of a low-fat, low-glycemic index, vegan diet compared to a control group following individualized diet plans based on the ADA’s 2002 guidelines. In both groups there were improvements, but the vegan group showed better improvements in weight loss and decreased HbA1c. Additionally, the vegan group reduced LDL levels by an average of 21.2\%, compared to 9.3\% in the conventional group. Both groups were able to lower medication requirements, but in the vegan group 43\% were able to reduce medications compared to 26\% in the conventional group.\(^{(8)}\) It should be mentioned that both groups were able to decrease calorie intake, total and trans fat, and cholesterol, but they both had difficulty meeting recommended intake of calcium, potassium, and vitamins D and E.\(^{(70)}\)

Following the same patients for 74 weeks showed significant weight loss in both groups, while improvements in glycemic control and lipid concentrations remained greater in the vegan diet group.\(^{(69)}\) The principal change in the conventional diet group
was a decrease in energy intake due to smaller portion sizes as opposed to changes in macronutrient balance. It should be noted that due to the medication changes needed for patient safety in long term T2D studies, such as this one, there is a confounding variable in the analysis of glycemic control. Nonetheless there was an overall decrease in HbA1c values, as shown in Figure 9 below.

**Figure 9. HbA1c Levels for Participants in 74 Wk Study**

![Figure 9](image)

Fig. Glycated hemoglobin (Hb A1c) values for all participants ($n = 49$ vegan diet; $n = 50$ conventional diet). The mean ($\pm SD$) data shown are last values before any change to diabetes medications carried forward. $t$ Test for between-group comparison of changes from baseline to final values, $P = 0.03$. Taken from Barnard et al. (2009).

Two major cohort studies have been conducted on Seventh day Adventists to review diet and risk of T2D. Seventh day Adventists are encouraged by the church to avoid consumption of meat, fish, eggs, coffee, tobacco, and alcohol.\(^{(36)}\) A large number follow vegetarian or vegan diets making them an ideal population to study for diet
relationships for T2D. The first Adventist study showed a positive correlation between meat consumption and self-reported T2D.  \(^{(61)}\) The second study showed increasing prevalence of T2D among vegans, lacto-ovo vegetarians, pesco-vegetarians, semi-vegetarians, and non-vegetarians. Figure 10 shows the prevalence of T2D in these five different diet groups. They also found that even consumption of meat or fish on less than a weekly basis limited the protection associated with vegan and vegetarian diets.  \(^{(55, 68)}\) Also, fruits and vegetables were associated with around a 40% reduction in T2D. Although they saw that lower T2D incidence in vegan diets was partially due to lower BMI, there were still effects of the diet independent of weight factors.
Cardiovascular Risk and Plant-Based Diets

The possible cardiovascular benefits of a plant-based diet is significant to T2D patients, for whom CVD is a leading cause of premature mortality. (9) Low-fat, plant-based diets sufficiently reduce LDL concentrations, resulting in a decreased CVD risk. In fact, a review by Ferdowsian et al. found that a plant-based diet that included nuts, soy, and/or soluble fiber can significantly reduce LDL cholesterol levels, decreasing levels by up to 25-30%, which is comparable to the decrease achieved with statin drugs. (24)
Plants reduce cholesterol by several mechanisms. Many of the compounds such as dietary fiber, phytosterols, flavonoids, carotenoids, and phenolics that are derived from whole grains, vegetables, and fruits attribute to these mechanisms. (24) A diet low in total and saturated fat as well as cholesterol leads to decreased absorption and conversion to plasma cholesterol. A vegan diet also is typically high in complex carbohydrates and fiber which decreases serum cholesterol concentration. (6) Soluble fiber increases cholesterol removal by binding to bile acids and cholesterol. (24) Populations that follow plant-based diets have an overall decreased risk of ischemic heart disease mortality and lower blood pressure.

**Weight loss and Plant-Based Diet**

Typically vegans and vegetarians are slimmer than non-vegetarians and these diets produce significant weight loss. The European Prospective Investigation found that BMI was lowest in vegans and highest in meat eaters. (68) This weight loss occurs without the need for calorie restriction or changes in exercise, which is important when considering adherence to diet plans. (70) Similarly Barnard et al. demonstrated that weight loss in postmenopausal women was significantly greater in low-fat vegan diets, without the need for calorie or portion restrictions. (10) Also, weight loss is maintained long term versus the short term weight loss seen in low-carbohydrate diets. In a five year analysis between various diets conducted by Rosell et al., vegans had the lowest weight gain in the five year period while meat eaters had the highest weight gain. (56) Additionally, they
also found that vegans had the lowest BMI to start, although it is hard to be sure if this is
due to the diet food content or vegans being more health conscious.

In summary, based on the selected studies reviewed in this section, along with
many more that were not discussed, there is evidence that a low-fat plant-based diet,
when properly planned, is sufficient to prevent and treat T2D as well as cardiovascular
risk factors and obesity. Further clinical studies would be able to provide even better
support for using low-fat, plant-based diets as treatment in the medical field.
EFFICACY OF PLANT-BASED DIET VERSUS CURRENT TREATMENTS

As discussed in the previous section, many studies have proven that plant-based diets are effective for treatment and management of T2D, specifically through increased insulin sensitivity, decreased body weight, and lowered cardiovascular risk factors. With the comparison studies conducted by Barnard et al. it has been proven that plant-based diets are as effective, if not more effective, than the conventional ADA recommended diets in treatment of T2D, specifically in reduction of medications, lower HbA1c levels, and decreased plasma LDL. Also, recent research has shown that 58% of T2D cases can be prevented or delayed via increased physical activity, weight loss, and healthy eating. (38)

Although there is a great amount of research on the beneficial effects of a plant-based diet for treatment and prevention of T2D, and many physicians agree that it is beneficial, it is often seen as too difficult for patients to comply with. Currently in America meat and other animal products are often consumed at each meal of the day. There is a perception that plant-based diets are extreme, difficult to follow, or lacking in nutrients. A major factor involved in the efficacy of this treatment compared to the current standard treatments is patient compliance. Due to the already low adherence to therapy in T2D patients it is imperative to look at whether or not a plant-based diet is a treatment patients can comply with. At this time most physicians do not emphasize a plant-based diet as a first line treatment for T2D. (77)

A study by Lee et al. showed that at a diabetes education center in Canada, although 72% of staff were aware of benefits of a plant-based diet, only 32%
recommended it to patients. When patients were asked 89% had no knowledge of using plant-based diets to treat or manage T2D and less than half were aware of any benefits to improve T2D, weight, CVD, hypertension, or hyperlipidemia. Although, 66% of non-vegetarian patients were willing to try given appropriate support and guidance. (38) This shows that while staff perceived plant-based diets as too difficult to comply with or thought patients were unlikely to accept it, there were in fact 2/3 of patients who were willing to try. Additionally, Lea et al. found that the largest perceived barrier to changing to a plant-based diet on a consumer survey was a lack of information, although there appeared to be awareness of the benefits the diet provided. (37)

In several studies using a plant-based diet some participants even found it easier to follow due to the lack of limitations on caloric intake. Many participants followed the diets longer than calorie-restricted diets. (70) A workplace study conducted by Katcher et al. that compared a low-fat vegan and control groups, showed there was 95% adherence rate in the low-fat vegan diet group. When compared to the control group, the low-fat vegan diet group noted improvements in general health, mental health, and overall diet satisfaction. They reported decreased food costs, but an increase in difficulty eating out. There was also a decrease in health-related productivity impairments at work and on a daily basis in the vegan diet group. (33)

Overall lifestyle intervention has been shown to be similar, if not more effective than metformin at preventing and treating T2D. The Diabetes Prevention Program looked at lifestyle intervention with a low calorie, low fat diet and increased physical activity versus metformin in the prevention of T2D in adults at high risk for developing the
disease.\(^{(23)}\) They found 39% lower incidence of T2D in the lifestyle intervention group compared to metformin although both groups had similar rates of hospitalizations and mortality. Both lifestyle intervention and metformin were effective in restoring normal glucose levels.\(^{(23,32)}\) There was also weight loss seen in the lifestyle intervention group, although only 50% achieved the goal of 7% weight loss. The Diabetes Prevention Program showed the importance of lifestyle intervention, but did not research the use of a plant-based diet. Similar results of lifestyle intervention versus metformin were shown in a meta-analysis conducted by Yokoyama et al. who found similar reduction in HbA1c with a vegetarian diet versus treatment with metformin.\(^{(77)}\) There has been little research to assess a plant-based diet compared to metformin to lower the risk of T2D and further studies would need to be conducted on the efficacy compared specifically with this common first line drug treatment.

There have been several other long term studies based on use of intensive lifestyle interventions for T2D treatments, but unfortunately not many include plant-based diets, with the exception of the 5 year study conducted by Rosell et al. The Look AHEAD study compared use of intensive weight loss intervention and diabetes support education. The lifestyle intervention group was provided instruction for a low calorie, low fat diet based on the Diabetes Prevention Program study. They were also provided with nutrition counseling during the course of the study. They found an average of 8.6% weight loss in the first year, but only a modest weight loss was sustained after 8 years with an average of 4.7%.\(^{(65)}\) With the previous study showing calorie restrictive diets can be harder to follow, it would be important to assess a plant-based diet over a similar long term period
in order to see if the initial weight loss could be sustained. The Look AHEAD study, although proving greater weight loss in the intensive lifestyle intervention group, found no decrease in CVD events compared with the diabetes support education group. (65)

Both the Diabetes Prevention Program and the Look AHEAD studies showed that with intensive lifestyle modifications, including diet, increased physical activity, and nutritional counseling, it is possible to lose more weight than compared to no intervention. This shows that whether lifestyle changes include plant-based diet or not, it is still possible to live a healthier lifestyle and reduce risk of T2D. One very important factor in these two studies was the inclusion of nutritional counseling during the course of the lifestyle intervention, which is helpful to keep patients healthy and focused on their goal of healthy living. Although research has shown better improvements with plant-based diets having any healthy lifestyle changes should be encouraged in patients with T2D, especially if they find a plant-based diet too difficult to comply with.

Patients with T2D often have anxiety with therapy options due to feelings of failure because of poor glycemic control, anxiety about hypoglycemia or weight gain, fear of injections, complexity of disease management, and poor education about T2D treatments. (57) Many of these fears are related to oral diabetic medications and the use of injectable insulin. For this reason a focus on lifestyle changes that patients can comply with may be beneficial. Influences that factor into successful treatment of T2D are outlined in Figure 11 below.
Cost is also a concern for many when they consider changing to healthy diet. Many of the inexpensive foods available in America are those that are unhealthy and poor in nutrients. Nansel et al. showed that although price does influence consumer purchase, it is feasible to switch to a healthier diet without increased spending. There may be initially a greater effort required to make cost-effective healthy food decisions. Overall,
in the long run focusing on lifestyle changes and healthier diet decrease costs through decreased needs for medications and other interventions.

There are also concerns with nutritional intake with vegetarian and vegan diets. In 2009 the American Dietetic Association published a position on these diets. They stated that both vegetarian and vegan diets, when appropriately planned, are healthy, nutritionally adequate, and can provide health benefits for many diseases. Also, these diets are suitable for all stages of life including pregnancy, infancy, and adolescence. Often, vegetarian and vegan diets implemented in childhood establish lifelong healthy eating patterns and there are no adverse effects on growth or BMI. In their position they also mentioned that vegetarians and vegans appear to have lower LDL levels, lower blood pressure, lower rates of hypertension, and lower rates of T2D compared with non-vegetarians.\(^{(53)}\)

Plant protein can meet protein requirements when an assortment of vegetables are eaten throughout the day. Research also shows that a variety of plant foods can provide all of the essential amino acids and ensure sufficient nitrogen retention. It is recommended that dietary adjustments are made to include more beans and soy products for adequate lysine intake.\(^{(53)}\) Recommendations are also made to soak and sprout beans, grains, and seeds to ensure adequate iron and zinc intake. Vegans need to be mindful to eat leafy greens for calcium intake as well as fruits and vegetables rich in magnesium and potassium, which slow bone reabsorption and decrease calcium losses.\(^{(53)}\) Additionally, foods fortified with vitamin B-12 should be added to the diet or vegetarians and vegans
can add in supplements. Table 3 below outlines the common nutritional concerns, some considerations for diet and examples of sources for a plant-based diet.

Table 3. Nutritional Concerns and Sources for a Plant-Based Diet

<table>
<thead>
<tr>
<th>Nutrition Concern</th>
<th>Nutrition Considerations</th>
<th>Examples of Sources for A Plant-Based Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protein</strong></td>
<td>Essential amino acids are those that cannot be synthesized by the body and must be obtained from diet</td>
<td>Quinoa, brown rice, beans, and soybeans</td>
</tr>
<tr>
<td><strong>Iron</strong></td>
<td>Iron from plants has lower bioavailability than iron from meat</td>
<td>Kidney beans, soybeans, spinach, cashews, raisins, cabbage, oatmeal; certain food preparation such as soaking and sprouting grains, beans and seeds as well as fermenting tofu and miso, can enhance absorption</td>
</tr>
<tr>
<td><strong>Calcium</strong></td>
<td>Low intake of calcium can run risk of bone fractures, vegetables and fruits high in potassium and magnesium can slow calcium loss</td>
<td>Bok choy, broccoli, kale, collard greens, and foods fortified with calcium such as tofu and soy milk</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td>Plays a role in bone health, obtained through sun exposure or fortified foods. Common in the general population, especially in winter</td>
<td>Fortified soy milk and cereal grains</td>
</tr>
<tr>
<td><strong>Essential Fatty Acids</strong></td>
<td>Only obtained through diet and include omega-6 and omega-3 fatty acids; plant based diets tend to be low in omega-3</td>
<td>Walnuts, flax oil, flax seeds, soy and canola oil</td>
</tr>
</tbody>
</table>
Given that patients are counseled on balanced meals and adequate nutrient intake, a low-fat, plant-based diet is an effective treatment in order to enhance compliance, calm anxieties with current treatment, and lower costs for patients with diabetes. In order to properly imply a plant-based diet as treatment a registered dietician or nutritionist should be involved in the health care team and the diet should be catered to the individual. Further research and clinical studies on oral diabetic medications and insulin vs low-fat, plant-based diet would be needed in order to replace conventional medications as treatment.
DISCUSSION

Based on the past and current research on a plant-based diet for treatment and prevention of T2D, it is proven that this diet is sufficient to decrease insulin sensitivity, lower HbA1c, decrease cardiovascular risks, and lower weight. There is some evidence that a vegan diet is as efficient, if not more, as metformin in the treatment of T2D. At this time, further clinical studies should be implemented to address specific efficacy of replacing prescription treatment with plant-based diet. Treatment may also vary based on individual patient care, the extent of T2D, and patient compliance.

A large factor in implementing a low-fat, plant-based diet is physician guidance. As the Lee et al. study showed, there is higher patient interest in treatment with plant-based diet than perceived by physicians. It may be helpful to patient care to address plant-based diet treatment during office visits with patients with T2D. Physicians can ask the patient if they are interested and inform them of the current findings from clinical studies. If the patient shows interest, the physician can then provide information on having a balanced plant-based diet or refer patients to follow-up with a nutritionist or dietician. Additionally, if possible, it may be helpful for physicians to complete a nutrition course in order to better implement diet changes. Hospitals and other health care facilities can also work on having suitable plant-based options for patients.

With any treatment for chronic diseases, there is a need for close monitoring. For T2D, even with a plant-based diet, patients need to be monitored to ensure they are maintaining effective glycemic control. It may still be necessary for patients to be on oral
diabetic medications or insulin while initiating a change in diet. Any changes in medication must be closely supervised by a physician.

The best takeaway from this review is that a low-fat, plant-based diet may be beneficial for prevention of T2D. For patients with family history, genetic susceptibility, or other risk factors such as obesity a preventive diet may be helpful. It is indicated that a plant-based diet can lower risk of T2D. Due to the ever increasing rise in T2D, prevention becomes especially important. If low-fat, plant-based diets were addressed more in public health and during patient check-ups there may be a rise in those who adapt the diets, or even reduce their overall intake of animal products. With these measures it is possible that T2D could see a plateau or even decline in subsequent years.
REFERENCES


35. Lam DW, LeRoith D. Metabolic Syndrome. [Updated 2015 May 19]. In: De Groot
LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth
(MA): MDText.com, Inc.; 2000-. Available from: https://www-ncbi-nlm-nih-
gov.ezproxy.bu.edu/books/NBK278936/


44. McCarty, Mark F. (September 2014). “GCN2 and FGF21 Are Likely Mediators of the Protection from Cancer, Autoimmunity, Obesity, and Diabetes Afforded by


