The Prevention and Treatment of Type 2 Diabetes Mellitus with a Plant-Based Diet

1. Introduction

Today's physicians are only too aware of the prevalence of Type 2 Diabetes Mellitus (T2DM) currently in America, and of its complications such as [diabetic peripheral neuropathy](#) and diabetic nephropathy. The increased risk of coronary artery disease that type 2 diabetics face is on every physician's mind. Administrators and policy makers grapple with the dollar cost to the health care system from type 2 diabetes, and perhaps most worrisome of all, the rise in obesity and metabolic syndrome tells public health officials that the problem will likely get worse if nothing changes.

This article presents evidence of the safety and efficacy of plant-based diets for prophylaxis and treatment of type 2 diabetes mellitus. We have used "plant-based" to be synonymous with the term "vegan". The term "vegetarian" is used to define a plant-based diet that also may include dairy or eggs or both.

It has long been known and documented by a wide range or researchers that vegetarians in general, and vegans in particular, have much lower rates of type 2 diabetes. This fact has led researchers to investigate why those following a plant-based diet have a much lower risk of the disease. It has also led to the study of the efficacy of plant-based diets as a treatment for type 2 diabetes. The results of research are compelling. Plant-based diets both very substantially lower the risk of type 2 diabetes, and are quite efficacious in treating the disease.

Several reasons for this have emerged. Vegetarians have a much lower prevalence of type 2 diabetes mellitus risk factors such as obesity and metabolic syndrome. Those following a plant-based diet tend to consume more polyunsaturated fats and whole grain fibers, which have both been shown to reduce the risk of type 2 diabetes. They have less skeletal intramyocellular lipids, and better myocellular glucose disposal and mitochondrial function, and therefore have less peripheral insulin resistance. Vegetarians and vegans also have a much better inflammatory status, indicated by lower levels of inflammatory markers such as cardio-reactive protein and inflammatory adipocytokines such as IL-6, leptin, and higher levels of anti-inflammatory adipocytokines such as adiponectin. Since inflammation is now a known pathogenic factor, and since the adipocytokines have been shown to mediate insulin resistance and type 2 diabetes, vegetarians and vegans have a reduced risk of T2DM from these factors as well. Because persistent organic pollutants (POPs) strongly bio-concentrate in animal fats, those following a plant-based diet consume much lower levels of POPs which have been shown to cause beta-cell mitochondrial dysfunction. Finally, the gut microbiome of vegetarians has also been shown to play a role in reducing insulin resistance and the level of inflammation in the body and consequently the risk of T2DM.

Vegetarians and vegan diets have been shown to be safe and efficacious treatments for type 2 diabetes, and their effects rival drugs such as Metformin. It should be noted that a full response usually takes a couple of months, but some initial effects may be noted after only two weeks. Patient compliance is good and the treatment is practically devoid of contraindications and adverse effects. Clinical chemistry should be monitored frequently at first and medications should be titrated accordingly until the full effect of the dietary therapy is evident.

2. Epidemiology

Vegetarian and vegans have a substantially lower risk of Type 2 Diabetes. The consumption of meat and the increase in risk of T2DM in a dose dependent manner has been established since at least 1985. (1) More recently, a large, well-regarded study showed that semi-vegetarians reduced their risk by 38%, pesco vegetarians by 51%, vegetarians by 61% and vegans by 78%. This indicates a dose response relationship between risk reduction and amount of plant foods in the diet. (2)

Many studies have been made of different demographic groups, showing substantial reductions in risk in those consuming a plant-based diet. Here are just a couple of examples. One study of the Taiwanese showed that vegetarian men had a decreased risk of T2DM of 51%, while pre-menopausal women had a decreased risk of 74%, and post-menopausal women a decreased risk of 75%. (3) These were considered notable findings, due to the increased genetic vulnerability to T2DM of this population, and that the average Taiwanese diet is already a relatively low-meat diet in the first place.

Among Blacks in the United States, those following a vegetarian diet reduced their risk of type 2 diabetes mellitus by 53% and those following a vegan diet by 70%. (4) This finding is notable, due to the increased prevalence of T2DM in this group.

2.1   Risk Factors

High body mass index (BMI) is a well-established risk factor for T2DM. Vegetarians and vegans have significantly lower BMI's on average. A study of American vegetarians and vegans found that that vegetarians had a mean BMI of 25.7 and vegans a mean BMI of 23.6. (5) A European study found the average BMI of vegetarians and vegans to be 23.3 and 22.4 respectively for men and 22.8 and 21.8 for women. (6) A study of German vegans found an average BMI of 22.3. (7) A study of vegetarian children found that they too had lower BMI's than their meat- eating counterparts with an average BMI of 17.3 in ages 6 to 11 and average of 20.0 ages 12-18. (8) One study found the risk of being overweight or obese is 65% less for vegans and 46% less for vegetarians. (9)

Another key risk factor is metabolic syndrome. Vegetarians have a reduced risk of metabolic syndrome. One study showed a 56% risk reduction with a vegetarian diet. (10) This study also showed that vegetarians have fewer risk factors for metabolic syndrome.

2.2   Dietary Components

When considering the different components in the diet, the consumption of n-6 (Omega 6) fats and whole grain foods stand out in the epidemiological research.

The evidence from research suggests that consuming polyunsaturated and or monounsaturated fats in preference to saturated fats and trans fatty acids, has beneficial effects on insulin sensitivity, and reduces the risk of T2DM. (11)

Among those consuming polyunsaturated fats, those who prefer linoleic acid from the n-6 series (Omega 6 fatty acids) show the best insulin sensitivity. (11) On the other hand, long-chain n-3 (Omega 3) fatty acids do not appear to improve insulin sensitivity or glucose metabolism. (11) Moreover, the research shows that high consumption of n-3 fatty acids may even impair insulin action in subjects with type 2 diabetes. (11, 12, 13, 14, 15, 16, 17, 18) While some believed that n-6 FAs are pro-inflammatory compared with n-3 fatty acids, this hypothesis is not supported by clinical or epidemiologic data in humans. (11) Rather, some data show that consumption of linoleic acid is inversely related to plasma C-reactive protein concentrations, and therefore is anti-inflammatory. (19, 20)

People who consume approximately 3 servings per day of whole grain foods are less likely to develop type 2 diabetes than low consumers (<3 servings per week) with a risk reduction in the order of 20-30%. (21)

3. Pathogenesis

3.1   Skeletal muscle insulin resistance

Skeletal muscle is the major site for disposal of ingested glucose in lean, healthy, normal-glucose-tolerant people. (22, 23, 24, 25, 26) Following a meal, approximately one third of ingested glucose is taken up by the liver and the rest by peripheral tissues, primarily skeletal muscle, via an insulin dependent mechanism. (22, 23, 24, 25, 26) The postprandial hyperglycemia stimulates insulin secretion from the pancreas and the rise in plasma insulin concentration stimulates glucose uptake in skeletal muscle leading to the disposal of ingested glucose. (22, 23, 24, 25, 26)

In insulin resistant states, such as type 2 diabetes and obesity, insulin stimulated glucose disposal in skeletal muscle is markedly impaired. (22, 23, 24, 25, 26, 27, 28) The decreased insulin-stimulated glucose uptake is due to impaired insulin signaling, and multiple post receptor intracellular defects, including impaired glucose transport and glucose phosphorylation, and reduced glucose oxidation and glycogen synthesis. (29, 30, 31, 32)

There is growing evidence that mitochondrial dysfunction contributes to insulin resistance. (33, 34) Mitochondrial DNA content is frequently used as a marker for mitochondrial density in skeletal muscles. It has been shown to be lower in T2DM patients in comparison to lean controls. (35) Metabolic stresses imposed by obesity and hyperglycemia are often accompanied by increased rates of mitochondrial Reactive Oxygen Species (ROS) production. ROS affect mitochondrial structure and function and lead to Beta-cell failure. (36)

It can be concluded that both decreased mitochondrial fat oxidation and increased free fatty acid influx into skeletal muscle take place while in an insulin resistant state. Increased intramyocellular fat content and fatty acid metabolites, for example, FACoA and DAG, are likely to play a pivotal role in the development of insulin resistance in skeletal muscle.

Through activation of serine/threonine kinases and serine phosphorylate, fatty acid metabolites impair IRS-1 phosphorylation by the insulin receptor and lead to the defect in insulin signaling in insulin resistant individuals. (22)

An increased intramyocellular fat content and fatty acid metabolites have been shown to play a pivotal role in the development of insulin resistance in skeletal muscle. Since the majority of fat oxidation take place in the mitochondria, impaired fat oxidation in insulin resistant individuals suggests the presence of a mitochondrial defect, that contributes to the impaired muscle fat oxidation and increased intramyocellular fat content. Studies in humans, using molecular, biochemical, and MR spectroscopic techniques, have documented a defect in mitochondrial oxidative phosphorylation in a variety of insulin resistant states. While it is not usually possible to carry out these kinds of studies on humans, this study was able to use human skeletal muscle due to the accessibility of the tissue. (22)

The adiocytokine adiponectin, discussed in more detail in the next section, is found in lower levels in type 2 diabetic patients and the insulin resistant. Human studies show that low levels of adiponectin are also strongly correlated with high levels of intramyocellular lipids. (37) This is especially the case with the high molecular weight isoform. (38) As reported below, those following a plant-based, or vegan diet have higher levels of adiponectin. This adds to the lowered risk of insulin resistance that vegans experience.

Ex vivo human studies showed vegans to have an advantage with regard to skeletal muscle insulin sensitivity. One study showed that those following a plant based, or vegan diet, were shown to have lower intramyocellular lipid levels in their skeletal muscles. (39) Another study of those on a plant-based diet documented a lower intramyocellular lipid levels, a higher glucose disposal value and a higher mitochondrial DNA content. (40)

These studies help explain the better skeletal muscle insulin sensitivity and much lower risk and prevalence of type 2 diabetes mellitus among vegans. The lower intramyocellular lipid levels, higher levels of adiponectin, better glucose disposal and increased mitochondrial DNA combine, in addition to the other factors addressed elsewhere in this report, to give those following a plant-based diet the advantages they experience with respect to type 2 diabetes.

3.2   Adipocytokines

Until recently, the adipose tissue was merely considered to support thermoregulation and provide the storage and release for free fatty acids. Within the last decade, it has become increasingly clear that adipose tissue is much more complex than was initially considered. The adipose tissue is an important endocrine organ that plays a key role in the integration of endocrine, metabolic, and inflammatory signals for the control of energy homeostasis (41).   In addition to the dysregulation of its free fatty acid buffering capacity, (42) the adipocyte has been shown to secrete a variety of bioactive proteins into the circulation. These secretory proteins have been collectively named adipocytokines. (41)

Examples of adipocytokines include leptin, (43) tumor necrosis factor (TNF)-α, (44) plasminogen-activator inhibitor type 1 (PAI-1), (45) adipsin, (46) resistin, (47) adiponectin, (48) and interleukin (IL6) (48).

These interact with central as well as peripheral organs such as the brain, liver, pancreas, and skeletal muscle to control diverse processes, such as food intake, energy expenditure, carbohydrate and lipid metabolism, blood pressure, blood coagulation, and inflammation.

While many of these substances are adipocyte-derived and have a variety of endocrine functions, others are produced by resident macrophages and interact in a paracrine fashion to control adipocyte metabolism.

It is also abundantly clear that the dysregulation of adipocytokine secretion and action that occurs in obesity, plays a fundamental role in the development of a variety of cardiometabolic disorders, including the metabolic syndrome, type 2 diabetes, inflammatory disorders, and vascular disorders, that ultimately lead to coronary heart disease. (49, 50)

Adipocytokines can have pro- or anti-inflammatory properties according to their effects on inflammatory responses in adipose tissues. Most adipocytokines show pro-inflammatory activity with the noted exceptions of adiponectin, secreted frizzled-related protein 5 (SFRP5), visceral adipose tissue-derived serine protease inhibitor (Vaspin), and omentin-1. The pro-inflammatory adipocytokines are increased whereas the anti-inflammatory adipocytokines are decreased in obese rodents and humans that are associated with insulin resistance. (51)

The levels of some adipocytokines correlate with specific metabolic states and have the potential to impact directly upon the metabolic homeostasis of the system. Several of these

adipocytokines mediate insulin resistance and diabetes (51, 52) While many adipocytokines have been discovered, this report will cover three with respect to insulin sensitivity and type 2 diabetes mellitus: leptin, adiponectin and IL 6. We refer you to other articles in the field that offer more extensive overviews of the entire secretome of adipocytes. (53, 54, 55)

3.2.1 Leptin

Leptin is an adipocyte-derived hormone and cytokine that regulates energy balance through a wide range of functions, including several that are important to cardiovascular health. Increased circulating leptin, a marker of leptin resistance, is common in obesity, and independently associated with insulin resistance and cardiovascular disease in humans. (56)

Evidence suggests that central leptin resistance causes obesity, and that obesity-induced leptin resistance injures numerous peripheral tissues, including liver, pancreas, platelets, vasculature, and myocardium. This metabolic and inflammatory mediated injury may result from either resistance to leptin's action in selective tissues, or excess leptin action from adiposity associated hyperleptinemia or both. (56)

In this sense, the term "leptin resistance" encompasses a complex pathophysiological phenomenon. The leptin axis has functional interactions with elements of metabolism, such as insulin, and inflammation, including mediators of innate immunity, such as interleukin 6. Leptin is even purported to physically interact with C-reactive protein, resulting in leptin resistance, which is particularly intriguing, given C-reactive protein's well-studied relationship to cardiovascular disease. (56)

Leptin plays a major role in the regulation of body weight. It circulates in both free and bound form. One of the leptin receptor isoforms exists in a circulating soluble form that can bind leptin. (57) Obesity in humans is associated with decreasing levels of the circulating soluble leptin receptor. The relationship of soluble leptin receptors with the degree of adiposity suggests that high soluble leptin receptor levels may enhance leptin action in lean subjects more than in obese subjects. (57)

Vegetarian diets reduce leptin levels in T2DM patients, as discussed in the Intervention section below.

3.2.2 Adiponectin

Adiponectin is the gene product of the adipose tissue's most abundant gene transcript 1 (apM1). (48) It is a collagen-like protein that is exclusively synthesized in white adipose tissue.

It is induced during adipocyte differentiation, and circulates at relatively high (microgram/milliliter) concentrations in the serum. Adiponectin is highly expressed by adipocytes with potent anti-inflammatory properties. (51) Although adiponectin is secreted only from adipose tissue, its levels are paradoxically lower in obese than in lean humans. (52, 58)

A strong correlation between adiponectin and systemic insulin sensitivity has been well established both in vivo and in vitro in mice, other laboratory animals, and, most importantly, humans. (59, 41) In humans, plasma levels of adiponectin are significantly lower in insulin-resistant states including T2DM. (52, 58) Higher adiponectin levels are associated with a lower risk of T2DM across diverse populations, consistent with a dose-response relationship. (52, 60) As reported below, those placed or following a plant-based diet have higher levels of adiponectin.

3.2.3 Interleukin 6 and CRP

IL-6 is one of the major pro-inflammatory adipocytokines. Its expression level increases in the adipose tissue of obese patients. IL-6 secretion is increased in the adipocytes of obese subjects and may be important either as a circulating hormone or as a local regulator of insulin action. (61, 62) IL-6's mechanism of action is still not yet fully understood but is under active investigation. (63)

The primary source of circulating IL-6 is macrophages that have infiltrated white adipose tissue. It thus exerts its effect in a paracrine manner. (63) IL-6 has an important role in the regulation of whole body energy homeostasis and inflammation. Both in vitro and in vivo studies have confirmed that IL-6 is capable of suppressing lipoprotein lipase activity. IL-6 receptor is also expressed in several regions of the brain, such as the hypothalamus, which has a role in controlling appetite and energy intake. (64)

C-reactive protein (CRP) is an annular, pentameric protein found in blood plasma, the levels of which rise in response to inflammation. It is an acute phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells.

Studies suggests that IL-6 may also be secreted in an endocrine manner in proportion to the expansion of fat mass particularly in the abdominal region, with a corresponding increase in hepatic production of CRP. (65)

Elevated CRP levels have been linked to an increased risk of later development of diabetes. (66, 67) Furthermore, CRP levels are higher in people with diabetes compared with those without diabetes, (68, 69, 70, 71) and the likelihood of elevated CRP concentrations were found to increase with increasing HbA1c levels. These findings suggest an association between glycemic control and systemic inflammation in people with established diabetes.

In patient studies, increased serum IL-6 correlates with obesity and insulin resistance. (72, 73, 74) Elevated levels of IL-6 and CRP resulted in a much higher risk of type 2 diabetes in a large cohort study P(<.001). The risk was 7.5 times higher for IL-6 and 15.7 times greater for CRP for highest versus lowest quartile in both. (66) Plasma IL-6 is also strongly correlated with obesity and insulin resistance. (61)

As reported below, intervention with a plant-based diet lowers the level of both IL-6 and CRP.

3.3   Persistent Organic Pollutants

Persistent organic pollutants (POPs) are synthetic organic chemicals that have an intrinsic resistance to natural degradation processes, and are therefore environmentally persistent and bio-accumulate through the food chain, increasing greatly in concentration at each subsequent trophic level. Examples of POPs include dioxins, furans, polychlorinated biphenyls (PCBs), and organochlorine pesticides - chemicals mainly created by industrial activities either intentionally or as by-products. (75) The introduction of POPs into the environment from anthropogenic activities resulted in their widespread dispersal and accumulation in soils and bodies of water, as well as in human and ecological food chains, where they are known to induce toxic effects.

Despite international agreements intended to limit the release of POPs such as organochlorine pesticides, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs), these POPs still persist in the environment and food chains. Regulations are often either not enforced or subscribed to. (76, 77, 78, 79, 80, 81)

There is evidence of long range transport of these substances to regions where they have never been used or produced, resulting in exposure of most human populations to POPs through consumption of fat-containing food such as fish, dairy products, and meat, (82, 83, 78) with the highest POP concentrations being commonly found in fatty fish. (75, 77, 82, 83, 84, 85, 86) Humans bioaccumulate these lipophilic pollutants in their adipose tissues for many years because POPs are highly resistant to metabolic degradation. (78, 87)

Persistent Organic Pollutants are widespread amongst the American public. A considerable number of POPs have been detected in the tissues of those studied. (88)

3.3.1 The Impact of POP exposure on laboratory animals

While human studies are always to be preferred, controlled experimentation of the impact of POPs must be limited to lab animals for ethical reasons. In the following study, the levels of POPs the rats were exposed to resulted in adipose concentrations typical of the average northern European adult, making the results obtained more realistic and therefore more relevant for human medical practice.

Adult male rats exposed to unrefined salmon oil, with its ordinarily occurring levels of POPs, developed insulin resistance, abdominal obesity, and hepatosteatosis. (89) The contribution of POPs to insulin resistance was also confirmed in cultured adipocytes where POPs, especially organochlorine pesticides, led to robust inhibition of insulin action. (89)

The rats exhibited profound dysregulation in hepatic lipid homeostasis accompanied by elevated levels of triacylglycerol, diacylglycerol, and total cholesterol. Altogether, these results demonstrate that POP exposure significantly affects the expression of critical genes involved in the regulation of lipid homeostasis. (89) Moreover, the POPs induced down-regulation of insulin-induced gene-1 (Insig-1) and Lpin1, (89) which are two master regulators of lipid homeostasis (and synthesis of triglyceride and cholesterol). (90, 91, 92, 93)

The effect of POPs on whole body insulin action was hyperinsulinemia and a greatly increased HOMA-IR. Moreover, intake of unrefined salmon oil led to impaired insulin-mediated glucose disposal in peripheral tissues, which mainly include skeletal muscles and adipose tissue.

As explained in the Skeletal Muscle Insulin Resistance section above, mitochondrial dysfunction contributes to insulin resistance, (33, 34) and mitochondria in type 2 diabetes Beta-cells exhibit both morphologic and functional abnormalities that are not observed in normal Beta-cells. (94) Mitochondria in type 2 diabetes Beta-cells exhibit both morphologic and functional abnormalities that are not observed in normal Beta-cells. (94) Together, these findings indicate that human Beta-cells exhibit abnormalities in glucose metabolism, and in mitochondrial structure and function, impairing both ATP production and glucose-stimulated insulin secretion. (95) Metabolic stresses imposed by obesity and hyperglycemia are often accompanied by increased rates of mitochondrial Reactive Oxygen Species (ROS) production. ROS affect mitochondrial structure and function and lead to Beta-cell failure. (36)

In this animal study, there was also significantly reduced expression of several genes related to mitochondrial function, such as *PGC1α* (peroxisome proliferator- activated receptor gamma-coactivator-1 alpha), citrate synthase, medium-chain acyl CoA dehydrogenase, and *SDHA* (succinate dehydrogenase), indicating the presence of alterations in mitochondrial function and oxidative capacities in the liver of the rats exposed to POPs. (89)

In vivo, chronic exposure to low doses of POPs commonly found in food chains induced severe impairment of whole body insulin action and contributed to the development of abdominal obesity and hepatosteatosis. Treatment in vitro of differentiated adipocytes with nanomolar concentrations of POP mixtures at levels found in many foods induced a significant inhibition of insulin dependent glucose uptake. (89)

These data taken together provide compelling evidence that exposure to POPs increases the risk of developing insulin resistance and metabolic disorders.

3.3.2 Epidemiological studies of POPs

Several epidemiological studies have reported an association between persistent organic pollutants and diabetes risk. Since 2005, at least 20 cross-sectional studies, conducted in about 12 countries, have been published documenting the association of POPs with diabetes risk. In addition, at least 7 longitudinal studies have been published from about 3 countries, showing the association of POPs with diabetes risk. (96) These findings have been supported by experimental studies both in humans and animals. Pathophysiological derangements, through which these pollutants exercise their harmful effect on diabetes risk, were studied. (97)

Several studies show a very strong association with several classes of POPs such organochlorine pesticides, PCBs (especially those with more than seven chlorines) and probably dioxins. Some specific congeners were associated with an increase in risk of over 30 times for those most exposed. Compared with subjects with serum concentrations below the limit of detection, after adjusting for age, sex, race and ethnicity, poverty income ratio, BMI, and waist circumference, diabetes prevalence was strongly positively associated with lipid-adjusted serum concentrations of all six POPs tested. (98)

When study participants were classified according to the sum of category numbers of the six POPs, adjusted odds ratios were 1.0, 14.0, 14.7, 38.3, and 37.7 (P for trend < 0.001). Surprisingly, in people with the lowest levels of POPs, being obese or overweight was not associated with an increased risk of diabetes. (98, 99) In an editorial published in The Lancet on the subject of Dr. Lee's findings, Dr. M. Porta writes, "This finding would imply that virtually all the risk of diabetes conferred by obesity is attributable to persistent organic pollutants, and that obesity is only a vehicle for such chemicals. This possibility is shocking." (100) Even low dose exposure to POPs conferred a very significant rise in the risk of type 2 diabetes. (101)

There is also a strong association between POPs and insulin resistance, often considered a pathogenic precursor of type 2 diabetes. The relationship strengthened with increasing HOMA-IR percentile: adjusted odds ratios comparing the highest versus lowest POPs quartile were 1.8 for being > or = 50th percentile of HOMA-IR, 4.4 for being > or = 75th percentile, and 7.5 for being > or = 90th percentile. (102) Other longitudinal studies have confirmed a significant association between POPs and insulin resistance. (103)

The role of POPs with endocrine disrupting activity, in the etiology of obesity and other metabolic dysfunctions, has been recently highlighted. Adipose tissue is a common site of POPs accumulation where they can induce adverse effects on human health. (104) Research strongly implicates Beta-cell mitochondrial dysfunction in the pathogenies of type 2 diabetes. (105, 106) Research shows an association between POPs and mitochondrial dysfunction in the Beta cells. (104, 107) One study showed a strong association, with a dose-response relationship with organochlorine POPs and diabetic peripheral neuropathy. Among five subclasses of POPs, organochlorine pesticides showed a strong dose-response relation with prevalence of peripheral neuropathy, adjusted odds ratios were 1.0, 3.6, and 7.3 (P for trend <0.01),

respectively, across three categories of serum concentrations of organochlorine pesticides. (108) Studies show that diabetics with higher levels of POPs have several times the risk of diabetic nephropathy. (109, 110, 111, 112)

3.4   Microbiome Epidemiology

The gut microbiome has been suggested to play a role in type 2 diabetes. A small study in men, with and without type 2 diabetes, showed a lower abundance of Firmicutes and the class Clostridia, as well as a nonsignificant increase in Bacteroidetes and Proteobacteria in those with type 2 diabetes. (113) Furthermore, the ratio of Bacteroidetes to Firmicutes was positively associated with plasma glucose concentrations. A larger metagenome-wide association study in Chinese patients with T2DM reported differences in the gut microbiota relative to controls, with a decrease in the number of butyrate-producing bacteria, and an increase in the number of opportunistic pathogens. (114) Similarly, this shift in the gut microbiota was also observed in a European cohort with type 2 diabetes. (115)

Plant-based dietary patterns may promote a more favorable gut microbial profile. Such diets are high in dietary fiber and fermentable substrate (i.e. non digestible or undigested carbohydrates), which are sources of metabolic fuel for gut microbial fermentation and, in turn, result in end products that may be used by the host (i.e. short chain fatty acids such as butyrate). These end products may have direct or indirect effects on modulating the health of their host. (116)

Over the past 10 years or so, data from different sources have established, to some degree, a causal link between the intestinal microbiota and obesity and insulin resistance. The lipopolysaccharide from intestinal flora bacteria can induce a chronic subclinical inflammatory process and obesity, leading to insulin resistance through activation of toll-like receptor 4. The reduction in circulating short-chain fatty acids may also have an essential role in the installation of reduced insulin sensitivity and obesity. Other mechanisms include the effects of bile acids, branched chain amino acids, and some other lesser known factors. (117) It is important to emphasize that diet-induced obesity promotes insulin resistance by mechanisms both independent and dependent on gut microbiota.

4. Interventional Studies

A number of studies have demonstrated that plant-based diets are safe and efficacious treatments of T2DM. These studies have demonstrated improvements across a broad range of clinical variables. We focus here mostly on those specifically related to type II diabetes. However, given the increased risk that type II diabetics have of coronary artery disease,

concomitant improvement in cardiovascular parameters are very important and have been achieved by the studies noted below.

In one particularly successful study, which emphasized employing a plant-based diet and eliminating highly refined foods, good results were obtained in diabetic patients. After a median length on the diet of 7 months, the mean HbA1C dropped from 8.2% to 5.8% (p = 0.002), with sixty-two percent of participants reaching normoglycemic levels (HbA1C < 6.0%). (118)

A 3-month study of diabetic Koreans showed that a plant-based diet lowered their HbA1c levels by 0.9%, nearly triple the amount achieved with the Korean Diabetes Association diet. (119)

An Italian study using a vegan diet with Macrobiotic type menu items showed reductions in fasting glucose and insulin resistance (HOMA) along with improvements in BMI and cardiovascular measurements. (120)

Here in the US, a 22-week study showed a drop of 1.23 Hba1c points on a vegan diet, while the standard American Diabetes Association diet resulted in only a 0.38 point drop. This study also showed a plant-based diet was about three times more effective. As in other studies, those on the plant-based diet had better reductions in BMI and cholesterol levels. (121)

Compare these results to the average effects of the most commonly prescribed drug for treatment of T2DM, Metformin. In a meta-analysis study of Metformin, the average change of glycosylated hemoglobin was 0.9% (95% CI -1.1 to -0.7), (122) so the effects of a plant-based diet rival, and in some cases, exceed the average effects of Metformin.

Looking more broadly at other variables, a 24-week study of diabetics placed on a vegetarian diet showed a wide range of effects including changes in adipocytokines and inflammatory markers, BMI, fasting glucose, Hb1Ac as they have in other studies. However, this study also looked at additional variables. Highly Sensitive Cardio Reactive Protein (hsCRP) and homocysteine levels fell, a very desirable effect, indicating reduced inflammation and insulin resistance. In addition, adiponectin levels rose, which is also a desirable effect indicating improved insulin sensitivity. Resistin and leptin both were reduced, again indicating less insulin resistance. (123)

Linoleic acid is the most abundant polyunsaturated fat in the diet. One of the insulin-sensitizing components of a plant-based diet may be its n-6 polyunsaturated acid content. In a randomized trial by Summers et al., a diet rich in polyunsaturated n-6 (i.e. linoleic acid) improved insulin sensitivity when compared with a saturated-fat-rich diet after only 5 weeks. (124) A 24-week study of subjects placed on a n-6 strong plant-based diet showed that the insulin sensitizing effect experienced was related to the increased proportion of linoleic acid (n-6) in serum phospholipids. (125)

While the recommendation for most patients to increase exercise is sound, many are not compliant. It is therefore important to determine the benefit of dietary intervention

independent of exercise. In a small 12-week pilot study, the use of a low fat, vegetarian diet in patients with non-insulin dependent diabetes was associated with significant reductions in fasting serum glucose concentration and body weight, in the absence of increased exercise. The mean fasting serum glucose of the experimental group, from 10.7 to 7.75 mmol/L (195 to 141 mg/dl) and the mean weight loss was 7.2 Kg and was significantly better than the control group (P<0.05). (126)

In a 7-month study by Jenkins et. al, a high-protein vegetarian diet, utilizing meat and dairy analogues, such as veggie burgers, veggie sausages (containing soy and wheat gluten proteins) and soy milk, along with tree nuts, was compared with a high carbohydrate vegetarian diet as a control. The experimental diet achieved the same significant reductions in HOMA-IR and fasting glucose as the control group. However, the experimental group achieved significantly greater weight loss, reduction in BMI, total cholesterol, LDL-C, TC:HDLC, and APOB and APOB:APOA1 and CHD 10-year risk on the experimental diet. There was also trend for lower hsCRP, though this was not quite significant. Given the popularity of meat and dairy analogues and tree nuts, patients preferring these foods may be able to achieve the same glycemic control while achieving even greater reduction in CHD risk. (127)

Generally, most patients require several weeks to several months to achieve a full therapeutic response. However, one study showed some results after only a week on a plant-based diet. Those with a fasting glucose above 126 mg/dL showed an average drop of 17mg/dL. (128)

Low grade inflammation of the intestine results in metabolic dysfunction, in which dysbiosis of the gut microbiota is intimately involved. Soluble dietary fiber induces prebiotic effects that may restore imbalances in the gut microbiota. In one study, obese subjects with type 2 diabetes were assigned to a vegetarian diet for 1 month, and blood biomarkers and fecal microbiota were monitored. The vegetarian diet reduced the Firmicutes to Bacteroidetes ratio in the gut microbiota. There was also notably a decrease in the pathobionts such as the Enterobacteriaceae and an increase in commensal microbes such as Bacteroides fragilis and Clostridium species belonging to clusters XIVa and IV, resulting in reduced intestinal lipocalin-2 levels. (129)

Reduced Lipocalin-2 levels are associated with increased insulin sensitivity. (130) Lipocalin-2 is also an inflammatory marker. (130) This study underscores the benefits of soluble dietary fiber in the treatment of metabolic diseases, and shows that increased soluble fiber intake reduces gut inflammation by altering the gut microbiota. (129) The study also showed reduced body weight and concentrations of triglycerides, total cholesterol, low-density lipoprotein cholesterol and hemoglobin A1c, and improved fasting glucose and postprandial glucose levels.

5. Clinical Considerations

Patient compliance on plant-based diets has been good in almost all studies. The degree of compliance has often been very high. For instance, one study obtained a 99% compliance. (131) In a 22-week study 94% of subjects on a vegan diet were compliant. (121) In a somewhat longer study, 84% of the participants in each group completed all 24 weeks. (125) In studies of patients placed on plant- based diets for coronary artery disease, high compliance has been noted even over several years. For instance, one study of patients placed on a plant-based diet showed 89% compliance for 3.7 years**.** (132)

Compliance may be enhanced when the rationale for the treatment, and that the treatment is backed by research, is explained to the patient. (133) The doctor should prescribe the treatment by writing it down on a prescription form or other stationary with the physician's name on it. This written prescription is not only valuable to the patient, but can also be valuable in enlisting the support of family, friends and social contacts.

The effect of diet can be considerable. Treatment with a plant-based diet can be more effective than an anti-diabetic medication such as Metformin, combined with the recommended diet by the American Diabetes Association. While a patient using Metformin is transitioning to a plant-based diet, it is very important to reduce the risk of hypoglycemia, by monitoring clinical variables frequently in the early phase of treatment, until the full effect of a plant-based diet is evident. Medications should be titrated as the patient shows improvements. Severe cases will likely need continued medication albeit at reduced dosage.

As most clinicians are aware, several pathologies often cluster together. The same patient that presents with T2DM will often have one or more of the following diseases: obesity, hypertension, hypercholestolemia/dyslipidemia and coronary artery disease. As plant-based diets are also effective treatments for those diseases as well, the physician will need to monitor clinical variables for those diseases and titrate the dosages of any medications prescribed for those conditions as well.

For patients with complications of type 2 diabetes such as diabetic peripheral neuropathy, a plant-based diet is also an efficacious treatment. Therefore, the symptoms associated diabetic peripheral should be monitored for improvement and any medications prescribed adjusted accordingly.

When starting the patient on a plant-based diet, foods with high levels of dietary fiber should be introduced slowly to avoid flatulence. From the point of view of treatment, soluble fiber is prebiotic for a therapeutic microbiome in type 2 diabetic patients. However, from the point of view of prevention, the insoluble fiber of whole grain cereals is the most effective.

6. Discussion

The type 2 diabetic patient faces an increased risk of coronary artery disease and complications such diabetic peripheral neuropathy, diabetic nephropathy and diabetic retinopathy. The patient may already have comorbid conditions such as coronary artery disease, hypertension and obesity along with diabetic complications such as diabetic peripheral neuropathy. T2DM is a chronic disease that usually requires treatment for the rest of the patient's life.

The plant-based diet is not only a safe and efficacious treatment for T2DM, rivaling Metformin in effectiveness in many patients, but is also a safe and efficacious treatment for its most common comorbidities and complications. This treatment has no known contraindications or adverse effects. It obeys well the first rule of medicine: first do no harm. It is also much more cost effective. Plant- based nutritional medicine relies on evidence-based medicine and should form the standard of care.

Prevention and treatment of T2DM with a plant-based diet operates on several levels at once. It reduces insulin resistance in the skeletal muscles. It reduces exposure to persistent organic pollutants, which cause mitochondrial cell dysfunction in the Beta cells and increased peripheral insulin resistance. It improves the profile of adipocytokines secreted. It also fosters a microbiome that helps prevent inflammation associated with type 2 diabetes. This multidimensional aspect of the treatment may account for its effectiveness. While some patients will still need medication, many others may no longer need medication. Even for those patients who still require medication to maintain a normoglycemic status, a substantial reduction in dosage may be possible.

While much research has been done on the prevention and treatment of T2DM with a plant-based diet, more research is needed to elucidate the relative benefits of the different foods that are included in the diet, beyond dietary fiber and polyunsaturated fats which have already been studied. While the therapeutic effect of a plant-based diet on complications, such as diabetic peripheral neuropathy, have been studied, there have been no studies on the risk reduction of diabetic retinopathy.

We live in an age of advanced medical technology. These advances have alleviated much suffering and saved countless lives. They have an unquestioned place in modern medicine. However, this can sometimes lead towards a kind of technological tunnel vision. Little notice is taken of treatments that, while lacking in technological sophistication, are nevertheless safe and quite efficacious. This indeed seems to be the case with treating T2DM with a plant-based diet.

Type 2 Diabetes Mellitus has a major impact on a patient's life, causing suffering and dollar costs to the patient as well. It is in the patient's interest to have this treatment presented to

them. Many physicians are surprised to see how many patients would like to give it a try and patient compliance is usually quite good when the treatment is properly presented.

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