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RESEARCH ARTICLE

# Dietary Treatments to Reduce Insulin Resistance and Inflammation in Type-2 Diabetic Patients

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ABSTRACT

**Abstract**

Type 2 diabetes (T2D) has increased dramatically in the last 20 years afflicting more than 425 million people all over the world with 34 million located in the US, emphasizing the need for strategic therapies including dietary prescriptions or other lifestyle changes to reduce these numbers. In addition to abnormally high plasma glucose levels, high concentrations of glycosylated hemoglobin and insulin resistance, T2D is also characterized by dyslipidemias, oxidative stress, and low-grade systemic inflammation. Insulin resistance and inflammation in T2D can lead to cardiac problems, non-alcoholic fatty liver disease and kidney failure. T2D can be controlled by modifying current unhealthy practices by focusing on wholesome diets, exercise regimes and maintenance of a healthy body weight. In this review, we aim to demonstrate how specific dietary prescriptions including carbohydrate restriction, the Mediterranean diet, plant-based diets and the dietary approaches to treat hypertension (DASH) can improve not just the inflammatory response and reduce the biomarkers of inflammation but also have additional benefits on insulin resistance, weight loss, plasma lipids and blood pressure. In addition, the mechanistic evaluation of specific nutrients including antioxidants (polyphenols and carotenoids), certain fatty acids and vitamins and their exclusive role in decreasing inflammation will be discussed.

**Keywords:** type 2 diabetes, inflammation, insulin resistance, dyslipidemia, dietary treatments, antioxidants

**Abbreviations used**

| | | |
|---|---|---|
| ADA | - | American Diabetics Association |
| CVD | - | Cardiovascular disease |
| CRP | - | C reactive protein |
| DASH | - | Dietary approaches to stop hypertension |
| DHA | - | Docosahexaenoic acid |
| EPA | - | Eicosapentaenoic acid |
| HbA1c | - | Glycosylated hemoglobin |
| HDL-C | - | HDL cholesterol |
| IL | - | Interleukin |
| LC | - | low carbohydrate |
| MD | - | Mediterranean diet |
| NAFLD | - | non-alcoholic fatty liver disease |
| PBD | - | plant-based diets |
| T2D | - | Type 2 Diabetes |
| TG | - | Triglycerides |
| TNF-α | - | Tumor necrosis Alpha |
| VLDL | - | Very low-density lipoprotein |
| W-3 | - | Omega 3 |

## 1. Introduction

Diabetes Mellitus (DM), characterized by abnormally high levels of glucose, insulin resistance and elevated concentrations of glycosylated hemoglobin, is a world-wide problem affecting more than 425 million people, a number corresponding to 8.5% of the adult population.[1] Diabetes has also been associated with dyslipidemias [low HDL cholesterol (HDL-C) and high plasma triglycerides (TG)], oxidative stress and systemic inflammation.[2] Diabetes can lead to microvascular and macrovascular complications. Microvascular complications include retinopathy, which is the leading cause of blindness in working aged adults, neuropathy, that can cause damage to the nerves located outside the brain and spinal cord causing numbness and weakness and nephropathy that leads to deterioration of kidney function.[3] Macrovascular complications include cardiovascular disease, peripheral vascular disease and cerebrovascular disease, all severe complications that lead to either myocardial infarction or stroke.[3] Type-1 diabetes is an autoimmune genetic disorder that leads to the destruction of pancreatic β-cells that produce insulin and needs to be controlled by insulin injections through the lifetime of the patient.[4] In contrast, type-2 diabetes (T2D) is a more prevalent form and is characterized by defects in insulin secretion and the outfcomes on target tissues. This type can be controlled by modifications in lifestyle practices including diet, exercise, and weight loss.[5] The focus of this review will be on T2D patients.

There are several conditions that can be associated with T2D and its consequences. Obesity, for example has been related to T2D and has been recognized as a key player in the development of both insulin resistance and inflammation in diabetic individuals.[6] Cardiovascular disease (CVD) remains a high burden in diabetes and is the first cause of death in individuals with T2D.[7] Dyslipidemias observed in these patients also contribute to CVD. Elevated plasma TG consistently observed in T2D are associated with high production of TG-rich lipoproteins including chylomicrons produced by the intestine and very low-density lipoprotein (VLDL) secreted by the liver. These lipoproteins can be removed from circulation by adipose tissue via specific macrophage receptors.[8] The increased concentration of cholesterol derived from these lipoproteins promotes an inflammatory cascade[9] that is characteristic of diabetic patients. Small dense LDL are also prominent in diabetic patients. These particles can easily penetrate the arterial wall where they become oxidized and initiate the

atherosclerosis process as has been demonstrated in cohort studies[10] and consequently contribute to systemic inflammation. Another dyslipidemia present in T2D is low levels of HDL-C and in the number of HDL particles.[10] HDL has a number of functions that protect against diabetes including, being a carrier of numerous antioxidants, protecting endothelial function, decreasing inflammation and effluxing cholesterol from macrophages in the reverse cholesterol transport process.[11] One of the drawbacks of diabetes is its association with a dysfunctional HDL.[12] The main protective roles of HDL are depicted in **Figure 1** to illustrate the importance of raising HDL cholesterol and HDL functionality through diet to reduce inflammation in T2D patients.

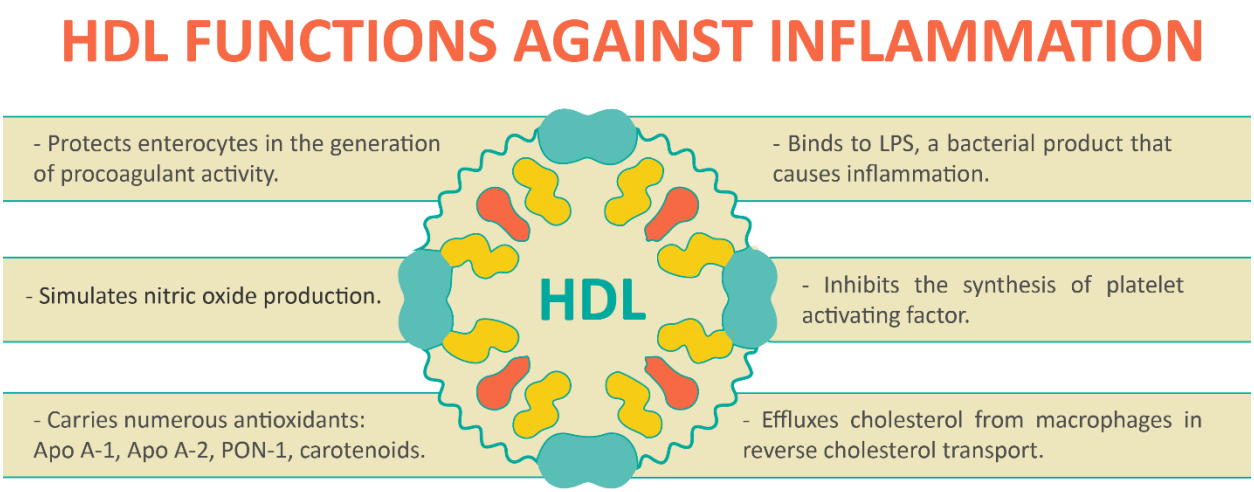


**Figure 1**. Roles of HDL in protecting against inflammation highlighting the importance of functional HDL particles in T2D patients

Other diseases associated with T2D, insulin resistance and inflammation are non-alcoholic fatty liver disease (NAFLD)[13], kidney failure[14] and cancer.[15] Overall, individuals with T2D have a shortened life expectancy.[16]

## 2.0 Diet and Inflammation in T2D

Low-grade inflammation has been associated with inflammatory processes, which may trigger various diseases over time including T2D.[17] Healthy dietary habits have been consistently shown as a means to control the incidence and the progression of chronic disease and T2D is not an exception.[18] Although certain diets have been postulated to increase the inflammatory response in diabetes, the focus of this review will be on those dietary regimes that have been demonstrated to improve the biomarkers of diabetes correlated with increases in insulin resistance and in the inflammatory response. There are several dietary treatments both conventional and unconventional that have been prescribed for individuals with T2D. In this review, we will discuss four dietary patterns that have been successfully used in protecting against inflammation and other metabolic disturbances associated with T2D, mainly Carbohydrate Restricted Diets, the Mediterranean Diet, Plant-Based Diets, and the Dietary Approaches to Stop Hypertension (DASH).

### 2.1 Carbohydrate Restricted Diets

Dietary carbohydrates play a central role in the management of T2D[19] in that blood glucose levels are affected by carbohydrate intake although other nutrients present may affect the postprandial glucose profile.[20] It is important to distinguish among the types of carbohydrates. Those that are rapidly digestible with a high glycemic index are associated with poor glycemic control while dietary fiber has been shown the opposite effect.[21]

The definition of carbohydrate-restricted diets is very broad. It goes from low carbohydrate (LC) diets (about 130 g per day) to those that have a more rigorous carbohydrate intake, the ketogenic diets, characterized by 10% of energy derived

from carbohydrates (between 30- 50 g) per day.[22] While an excess of carbohydrate intake can lead to insulin resistance, obesity, and higher risk for CVD and ultimately T2D[23], carbohydrate restriction has been shown numerous metabolic improvements that decrease chronic disease risk.[24]

A recent study was conducted to assess the effectiveness of carbohydrate restriction for the prevention of T2D with a two-year follow up in 96 patients with prediabetes.[25] At the end of this period, a normalization of glycemia as measured by glycosylated hemoglobin as well as decrease in hepatic steatosis and type 2 diabetes were observed indicating the success of these diets to control T2D.[25]

A recent review on the documented effects of low carbohydrate (LC) on T2D demonstrated the efficacy of these dies in reducing several metabolic drawbacks caused by the disease including obesity[26], hunger reduction[27], improved glucose control[28], reduced blood pressure[29] and reduction of hepatic fat and therefore protections against NAFLD[30] highlighting the usefulness of these diets in ameliorating all the metabolic deranges associated with T2D.

Although clinical trials have not been specifically focused on inflammation, they have demonstrated the usefulness of LC diets when used with T2D patients. A study by Tay et al[31] compared the effectiveness of LC versus a high carbohydrate diet in 115 obese patients with T2D in a parallel study. LC proved to be more effective in reducing plasma TG, improving glycemic control, and HbAc1 levels as well as increasing HDL-C. In another study where a low fat was compared to a LC diet, more positive outcomes were found with the LC diet (20% energy from carbohydrate) with significant reductions in plasma insulin and increases in HDL-C.[32] Daly et al.[33] reported a decrease in body weight and increases in HDL-C and weight reductions in a LC diet versus a low-fat diet in 102 patients with T2D. Similarly, another trial that compared low fat (n =18) versus low carbohydrate diet (n =16), improvements in HbA1c, better weight reductions and greater percentage of T2D patients who discontinued medications were observed in the LC diet group after 3 months of the intervention.[34] Westman et al[35] also reported that a LC diet was more effective in reducing plasma insulin, HbA1C and weight when compared to a low glycemic index dietary intervention. Yamada et al[36] also reported more effectiveness in a LC versus a conventional weight loss diet in diabetic patients. The effectiveness of LC compared to other dietary interventions is presented in **Table 1**.

Although the use of low carbohydrate diets is still controversial, there are groups of physicians who advocate their use and benefits.[37] The presented meta-analysis and clinical outcomes support their use and the associated advantages.

### 2.2 Mediterranean Diets

A recent review regarding the Mediterranean diet (MD) and people at risk or having developed T2D, concluded that the components of the MD improve insulin sensitivity and the gut microbiome by their anti-inflammatory and antioxidant actions.[38] Meta analysis of the effects of MD on T2D have also demonstrated positive effects.[39] The MD has been highlighted for its uniqueness in having major effects in maintaining glucose homeostasis by sustaining optimal levels of HbA1c and body weight and by positively affecting the dyslipidemias associated with T2D.[40]

In a meta-analysis of 17 original research studies, Koloverou et al[39] concluded that the MD produced a 23% decreased risk in reducing risk of T2D. Torres Peña et al[41] demonstrated a significant improvement in endothelial function in 805 subjects who were pre-diabetic or had T2D after being treated with the MD. Significant decreases in inflammatory markers were also observed in a group of 89 women with metabolic syndrome, a condition that puts them at risk for T2D, who followed a Mediterranean-like diet for 3 months.[42] Ceriello et al[43] reported an improvement in endothelial function in a group of 24 T2D patients who followed a MD for 3 months. Compared to a low-fat diet, the MD had a better prognosis in the subclinical parameters of CVD in 215 newly diagnosed T2D patients who were followed for 4 years.[44] A summary of the effects of the MD on inflammation and endothelial health is presented in **Table 1**.

### 2.3 Plant-based diets

Food choices play a key role in the development or prevention of non-transmittable diseases such as T2D. A typical western diet, characterized by calorie-dense, ultra-processed foods, red and processed meats, animal fats, refined grains, and sugary beverages, is recognized to be one of the reasons why the morbidity of T2D is rising worldwide.[45,46] .

Plant-based diets (PBD) are dietary patterns that focus on higher intakes of plant derived foods such

as fruits, vegetables, legumes, mushrooms, whole grain, seeds, nuts and vegetable oils while limiting certain foods of animal origin.[47,48,49,50] Although all PBD exclude meats such as beef, poultry and pork, some include dairy products and eggs (lacto-ovo vegetarian), fish (pesco vegetarian) and some others exclude all animal products, including honey (vegan.).[51] While PBD have been associated with a lower risk of cardiovascular risk factors, such as obesity, hypertension, T2D, and ischemic heart disease[47], we will focus on inflammation and T2D.

Using the data from 41,387 non-diabetic participants from the Adventist Health Study-2, Tonstad et al.[51] divided the subjects into 5 groups according to the dietary pattern they followed: vegan, lacto ovo vegetarian, pesco-vegetarian, semi-vegetarian or non-vegetarian (used as control group). After two years, a follow-up questionnaire was given to the participants to assess if any of them developed T2D. Once correcting for cofounder variables such as BMI, age, physical activity, alcohol use and smoking, the data showed that vegans, lacto-ovo vegetarians and semi vegetarians had lower risk of developing T2D than non-vegetarians.[51]

In a 16-week randomized clinical trial with overweight adults, Kahleova et al.[52] found that a PBD improves insulin sensitivity. Eligible participants (n=75) were randomly allocated to follow a low fat PBD (n=38) or to make no changes to their dietary pattern (n=37) for 16 weeks. Insulin resistance (IR), BMI, visceral fat mass and β cell function were measured at baseline and at the end of the intervention. After 16 weeks, individuals who followed the PBD had an improved meal-stimulated insulin secretion when compared with controls, similarly HOMA-IR index fell significantly ($p < 0.001$) in the intervention group.[52] These results suggest that following a PBD can improve β cell function and insulin sensitivity in overweight adults, thus could be used as a preventive strategy for T2D.

Since oxidative stress and inflammation are considered pathophysiological mediators in the progression of T2D complications, a recent study focused on measuring postprandial oxidative and dicarbonyl stress, inflammatory markers, and appetite hormones after having a vegan meal vs a conventional one.[53] This randomized crossover intervention used three groups of men. One group included 20 adult males diagnosed with T2D, the second group had 20 obese males with normal glucose tolerance and the control group was comprised of 20 healthy males. All participants consumed two energy- and macronutrient-matched test meals in random order, one meal was vegan and the other was omnivorous. After a week washout period, all participants switched meal plan. Results indicated no change in inflammatory markers in either of the groups between PBD and control meals, however in the T2D subjects, postprandial concentrations of oxidized glutathione were significantly decreased ($p < 0.001$) and glutathione peroxidase activity was significantly increased ($p = 0.045$) after the vegan meal consumption, compared with the control meal, suggesting that is less postprandial oxidative stress after having a PBD meal.[53]

Positive effects following a PBD are not only acute since they can be observed in longer interventions. Barnard et al.[54] conducted a randomized controlled trial to investigate whether a PBD was as or more effective than the American Diabetes Associations (ADA) guidelines to improve glycemic index, plasma lipids and weight control. Eligible subjects (n=99) were randomly allocated to follow a low-fat vegan diet (n=49) or to follow the ADA guidelines (n=50) for 22 weeks. Weight, plasma lipids and HbA1c were measured at the beginning and at the end of the study. After 22 weeks, participants from both groups had improved their glycemic control and cardiovascular risk, however, those who had the vegan diet showed significantly greater reduction in weight, HbA1c and LDL-C, suggesting that following a low-fat plant-based diet is an excellent approach for T2D patients[54]. In a large prospective study, Satija et al.[55] evaluated T2D incidence according to dietary choices using the Nurses' Health Study, the Nurses' Health Study II and the Health Professionals follow up study. In this investigation, plant foods received positive scores and food items from animal origin (including dairy and eggs) were assigned a negative score. Less healthy plant-based foods such as fruit juices, sweetened beverages, refined grains, potatoes, sweets/desserts also received reverse scores. Independently of BMI and other risk factors, individuals who had higher scores had up to 34% lower risk of developing T2D when compared to individuals who had more animal products.[55]

The benefits of PBD can be attributed not only to the increased intake of whole foods and dietary fiber sources like legumes, whole grains, fruits, vegetables, and nuts, which also add antioxidants, vitamins, minerals and healthy fatty acids to the diet[49] but also to the exclusion of animal-based foods that increase the risk of developing insulin resistance, such as red meat[47,56] or saturated fat.[57]

However, it is important to note that not all plant-derived foods are considered healthy food choices, food items such refined grains, potatoes, fruit juices and sugar sweetened beverages can be part of a PBD and when eaten in high amounts, can contribute to a greater risk of inflammation and chronic diseases.[58,59,60] Some relevant studies that were successful in T2D patients utilizing PBD are presented in **Table 1.**

### 2.4 DASH Diet

The Dietary Approaches to Stop Hypertension (DASH) intervention originated in the 1990s as a lifestyle strategy to lower systolic blood pressure. This dietary pattern limits the consumption of red meat, sweets and sugary beverages and encourages a high intake of fruits, vegetables, whole grains, nuts, low-fat dairy products and lean meats such as poultry and fish.[61,62] Overall, this diet is high in fiber, antioxidants, magnesium, potassium and calcium and poly/monounsaturated fats while it is low in sodium, cholesterol, total and saturated fat and high glycemic foods[63] Despite being a dietary approach designed for hypertensive patients, the eating plan proposed by the DASH diet can be favorable to improve body weight, lipid profile, glucose control and cardiovascular risk, which means that is an acceptable eating pattern for T2D patients[64, 65] In fact, a metanalysis of clinical trials using the DASH diet with some risk factors for developing T2DM concluded that this dietary pattern may lead to an improvement in insulin sensitivity and glycemic control.[66]

The DASH diet has shown to be a good strategy to lower low-grade inflammation, which is involved in the pathogenesis of many chronic diseases, including T2D. Studies have shown that people following the DASH diet have improved circulating serum inflammatory biomarkers, such as C-reactive protein, an acute phase protein in which raised levels have been associated with both development and complications of T2DM.[67,68, 69,70]

In a randomized crossover study conducted with diabetic patients, Azadbakht et al.[67] demonstrated that following a DASH diet for 8 weeks had greater reductions in CRP levels than following a control diet (-26.9 % vs 5.1%) when compared to baseline. In this study, other cardiometabolic parameters such as plasma fibrinogen and liver enzymes were also improved after the DASH diet.[67] In a more recent study[71], the effects of the DASH diet were compared to the American Diabetes Association (ADA) guidelines on the lipid profiles of patients with T2DM. In this intervention, 80 adult diabetic patients were randomly allocated in the DASH diet group (n=12) or the control (ADA guidelines) diet group (n=40) for 12 weeks. At the end of this period, both groups showed improvements on their plasma lipids (lower TG, TC and VLDL). Moreover, circulating free fatty acids (FAA) which are known risk factors for muscular and hepatic insulin resistance[72], significantly decreased in both groups, but this reduction was greater in the DASH diet group.[71] The anti-inflammatory effects of the DASH diet can be attributed to a high fiber, fruits and vegetables intake[73] and the limited amount of sodium.[74] Studies using DASH diet in T2D patients are presented in **Table 1**.

## 3.0 Protective Nutrients against inflammation in type-2 Diabetes

In the next paragraphs specific nutrients that protect against inflammation and type-2 diabetes and their mode of action will be reviewed.

**Table 1.** Dietary regimes that have been useful for T2D patients. These studies include carbohydrate restricted diet (CRD), the Mediterranean diet (MD), Plant-based diets (PBD) or Dietary approaches to stop hypertension (DASH) on obesity, HbA1c levesl, insulin resistance, dyslipidemias, endothelial function and inflammation.

| **Dietary Regime** | Population | Time | Major outcomes | **Reference** |
|---|---|---|---|---|
| CRD vs BL | 96 Pre-diabetic Patients | 2 years | Decreases in HbA1C, insulin resistance, hepatic steatosis | 25 |
| CRD vs High Carbohydrate | 115 obese patients with T2D | 24weeks | Decreases in plasma TG, HbA1c, increases in HDL | 31 |
| CRD vs Low Fat Diets | 61 adults with T2D | 6 months | Reductions in plasma insulin and increases in HDL-C | 32 |
| CRD vs Low Fat Diets | 102 patients with T2D | 3 months | Reductions in weight loss and increases in HDL-C | 33 |
| CRD vs Low Fat Diets | 34 Patients with T2D | 3 months | Improvements in HbA1c and greater number of patients who reduced medications | 34 |
| CRD vs Low glycemic index | 24 Patients with T2D and high HbA1C | 6 months | Reductions in plasma insulin and HbA1c | 35 |
| MD vs Low fat diet | 805 Patients | 1.5 years | Improvement in endothelial function | 41 |
| MD vs baseline | 72 women with metabolic syndrome | 3 months | Reductions in insulin resistance, in TNF-α and adhesive molecules | 42 |
| MD vs low fat diet | 24 T2D patients | 3 months | | 43 |
| MD vs low fat diets | 215 newly diagnosed T2D patients | 4 years | Increases in endothelial progenitor cells associated with healthy endothelium | 44 |
| PBD vs regular meal | 20 TD2 patients, 20 obese patients, 20 controls | Postprandial | Reduction in postprandial oxidative stress | 54 |
| Low fat PBD vs Regular diet | 75 overweight adults | 16 weeks | Improvement in beta cell function and insulin sensitivity. Reduction in HOMA-IR | 53 |
| Low fat PBD vegan diet vs ADA guidelines | 99 T2D patients | 22 weeks | Greater reduction in HbAiC, weight and LDL-C | 55 |
| DASH vs regular diabetic diet | 44 diabetic patients | 8 weeks | Reduction in CRP, plasma fibrinogen and liver enzymes | 67 |
| DASH vs ADA guidelines recommendations | 80 adults with T2DM | 12 weeks | Improvements in lipid profile: lower TC, TG, VLDL and FFA | 72 |

### 3.1 Fatty Acids

#### 3.1.1 Omega-3 (W-3) Fatty Acids

Dietary W-3 fatty acids have been recognized to play a major role as anti-inflammatory components that protect against chronic disease including CVD, NAFLD, cancer, and T2D.[75] These properties of W-3 fatty acids are attributed to their capacity to be converted into long chain fatty acids (LC-PUFA) with anti-inflammatory and pro-resolving properties.[76]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have a wide range of anti-inflammatory effects.[75] Supplementation with these fatty acids has resulted in increased concentrations of EPA and DHA in the membranes of cells involved in inflammation[21] as well as decreases in inflammatory cytokines.[77] A great number of studies show inverse correlations between W-3 fatty acids and inflammation.[78] Therefore, increasing dietary W-3 fatty acids appears to be an effective way to reduce inflammation in T2D diabetes.

However, systematic reviews show contradictory information. A recent systematic review and meta-analysis concluded that W-3 fatty acids may be associated with lower inflammatory biomarkers[79] although other meta-analysis have opposite results.[80,81] Clinical interventions demonstrate that W-3 fatty acids are effective in lowering TG in diabetic patients[82] while EPA and DHA intake have been shown to reduce inflammation in patients with T2D.[83] The anti-inflammatory effects of W-3 fatty acids might also protect against oxidative stress.[84] Future studies with W-3 fatty acids should be carried out in diverse populations of T2D since the effectiveness of W-3 fatty acids has been associated with diet-gene interactions.[76,77]

#### 3.1.2 Oleic Acid

The replacement of saturated fatty acids by mono or polyunsaturated fat appears to be beneficial in the prevention of T2D.[85] Olive oil has been demonstrated to improve both cardiovascular risk factors and to protect against T2D and these healthy effects are attributed to the higher concentration of oleic acid.[86] Extra virgin olive oil has been shown to have other protective bioactive components including polyphenols that could also affect insulin sensitivity.[87] Guash-Ferre et al[88] reported that higher olive oil intake was associated with a modest lower risk of T2D. Since this study was conducted in US where for the most part, the Mediterranean diet is not followed, the results highlight the specific effects of this fatty acid in the prevention of T2D independent of other dietary components[88].

A meta-analysis that included 29 trials concluded that the highest intake of olive oil showed a reduction of T2D by 16% in the highest compared to the lowest intake.[89] Other studies have demonstrated that replacing carbohydrate with monounsaturated fat had beneficial effects in subjects with T2D.[90] Monounsaturated fatty acids have also shown to be quite effective in reducing HbA1c levels in patients with abnormal glucose metabolism.[91] In summary, data derived from clinical trials and meta-analysis evaluations supports the effectiveness of olive oil in protecting against and in reducing the incidence of T2D.

### 3.2 Carotenoids

Carotenoids are fat soluble red, orange and yellow pigments that are found naturally in plants, algae and photosynthetic microorganisms and are an important component of the human diet. According to their chemical structure carotenoids are classified into highly lipophilic carotenes such as beta carotene and lycopene and oxygen containing, amphipathic xanthophylls like lutein and zeaxanthin. Other classification can be made regarding their capacity to transform into retinol, reason for which some carotenoids are considered vitamin A precursors.[92, 93] In this review we will focus on those that are not pro-vitamin A. Carotenoids are known to be beneficial for human health given their antioxidant capacity an anti-inflammatory effect.[93-94]

Numerous studies have shown an inverse relationship between carotenoid plasma concentration and chronic diseases, including CVD, atherosclerosis[95], NAFLD[96] and T2D.[97]

As previously stated, oxidative stress and inflammation play an important role in the development, progression, and complication of T2D.[98] For this reason, phytochemicals with antioxidant capacity have been widely studied as a prevention or even as a dietary strategy treatment.[99] A recent double-blind, randomized, placebo-controlled trial evaluated the effect of 8 mg of astaxanthin (a carotenoid from the xanthophyll family) supplementation for 8 weeks in T2D patients. The results showed that compared to placebo, astaxanthin supplementation increased serum adiponectin (associated with better insulin sensitivity) decreased serum TG concentrations, and significantly reduced fructosamine concentrations (a marker of glycemic control).[100]Moreover, astaxanthin has shown to protect against diabetic

microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy.[101]

Similar promising results have been found using other xanthophylls: lutein and zeaxanthin. These carotenoids are found mostly in green leafy vegetables, but also in animal products such as egg yolks.[102] Both lutein and zeaxanthin are particularly known for their protective effects against age related macular degeneration and cataracts[103,104]; however, they have also proven to be effective against T2D retinopathy.[105,106] A recent randomized, double-blind, placebo-controlled trial performed with 31 patients with non-proliferative diabetic retinopathy tested the effect 10 mg/d of lutein or placebo for 36 weeks. The results indicated that period of supplementation, the lutein group showed an improvement in visual acuity and contrast sensitivity, most likely due to lutein's antioxidant and anti-inflammatory properties.[107] Using a Ins2Akita/+ mouse model Wang et al.[108] found that a long-term lutein supplementation (4.2 mg/kg/d) suppresses inflammatory responses such as microglial reactivity or VEGF upregulation in the diabetic mice retina.[108] Similarly, when diabetic rats were given a control or supplemented diet with 0.02% or 0.1% powdered zeaxanthin for two months, the treated rats showed a lower retinal damage and lower diabetes-induced increase of VEGF and ICAM-1, independently of their glycemia.[109]

Another non provitamin A carotenoid is lycopene. This red, hydrophilic carotene is particularly abundant in tomatoes; however, it is present in many other fruits and vegetables. Due to its potent antioxidant activity, lycopene has been widely studied on its protective role in several types of cancer and inflammatory diseases, including T2D.[93,110]

The role of inflammation in the pathogenesis of insulin resistance and T2D can be seen as increased interleukin (IL)-1β, tumor necrosis factor alpha (TNF-α) and CRP levels in diabetic patients. Using a mouse model fed a high fat diet, Zeng et al[111] investigated the effect of lycopene on fat-induced insulin resistance. After 12 weeks, lycopene-treated mice showed lower fasting glucose and plasma insulin concentration. Moreover, the supplemented mice had less inflammation, as lycopene prevented the increase of IL-1β, TNFα and CRP levels. In this study, lycopene also improved lipid profile by decreasing total cholesterol, plasma triglycerides and LDL-C and increasing HDL-C[111]

In humans, a recent case-control study with 87 T2D patients and 122 healthy subjects assessed lycopene intake in relation to their glycemic control and antioxidant capacity status. Despite having a significant lower antioxidant capacity when compared to controls, among the T2D group lycopene intake was positively correlated with peripheral antioxidant level. Conversely, glycemic control markers such as HbA1c and fasting plasma glucose where negatively correlated to lycopene consumption, suggesting that this carotenoid may play an important role in diabetes management.[112]

The protective effects of carotenoids for T2D are presented in **Figure 2.**

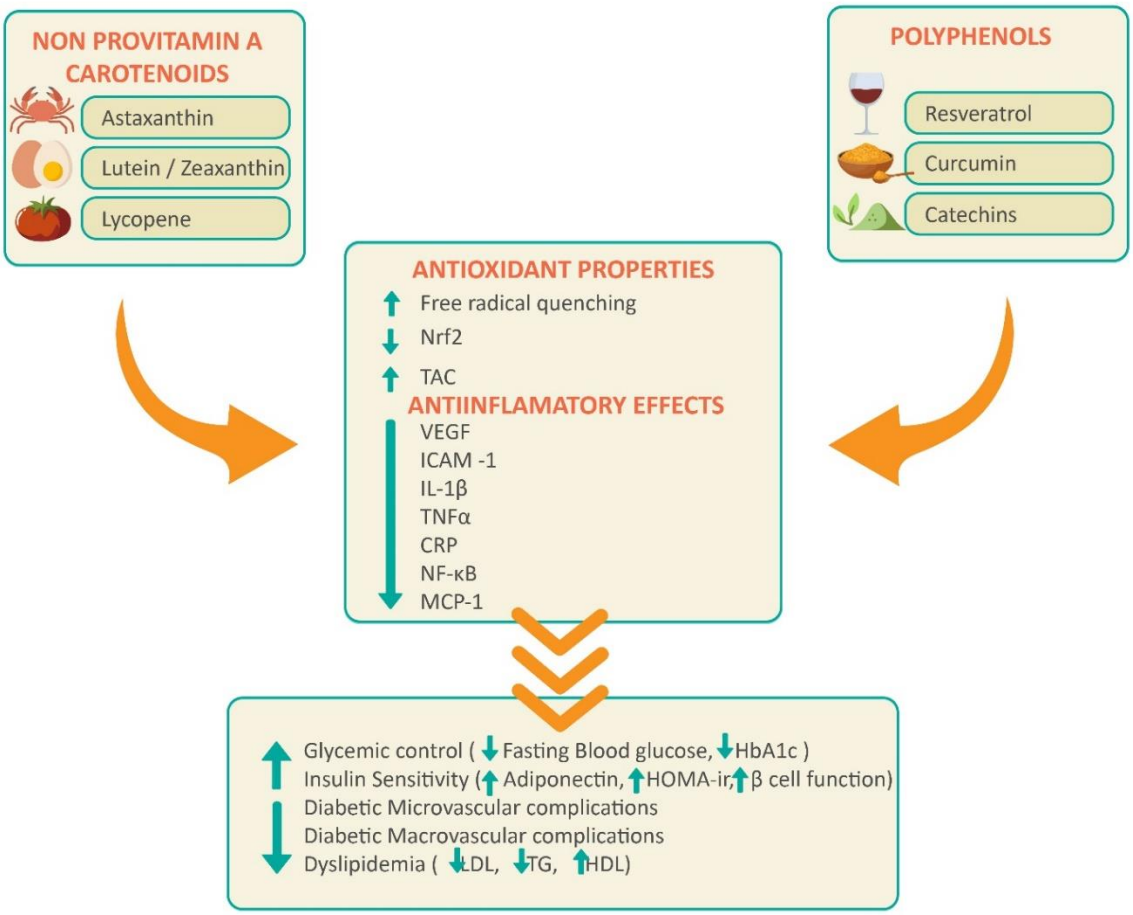


**Figure 2:** Proposed mechanisms by which carotenoids and polyphenols have protective effects against T2D

### 3.3 Polyphenols

Another phytochemical group that has been widely studied for its benefits for human health is the polyphenol family.[113] These organic compounds are found mainly in plant derived foods such as fruits, vegetables, tea, coffee, chocolate, olive oil, wine, seeds, nuts, and condiments.[114] Around 8000 different polyphenols have been identified in the human diet and they can be classified into 4 major groups: Flavonoids, Stilbenes, Lignans and Phenolic acids.[114]

The health benefits of polyphenol intake can be attributed to their considerable antioxidant capacity and anti-inflammatory properties.[115] In fact, several studies have linked polyphenols with therapeutic effects for cardiovascular disease[116,117], cancer[118], obesity[119] and neurodegenerative disorders.[120] Many authors sustain that the protective effects of the Mediterranean diet, Plant Based Diets and DASH diet against non-communicable chronic diseases are due to the increased intake of polyphenols in all these dietary patterns.[120]. In the following paragraphs, the effects of selected polyphenols on T2D and its associated complications are discussed.

#### 3.3.1 Resveratrol

Resveratrol is a non-flavonoid polyphenol produced in fruits such as grapes and cranberries or nuts, like peanuts. The cardioprotective effect of red wine is attributed to this compound.[121] In a randomized, placebo-controlled, double blinded parallel study Movahed et al.[122] investigated the effect of resveratrol supplementation (1g/d) in diabetic patients. After an intervention period of 45 days, data showed that the subjects who received resveratrol supplementation had decreased blood pressure, fasting blood glucose, HbA1c and insulin resistance when compared to baseline. These patients also presented significantly higher HDL-C.[122] Similarly, positive glycemic control results were observed with a much lower dose (250 mg)

and for longer intervention periods (3 months)[123] The mechanism for this polyphenol to be considered antidiabetic relies on reducing inflammation, since it has shown to decrease the expression of pro-inflammatory genes such as NF-κB, IL-1β, IL-6, TNF-α, ICAM-1 and MCP-1 in animal models[124] and clinical trials.[125] Moreover, a cell study with resveratrol and curcumin showed improvement in β cell function in B-Min6 cells.[126]

It is important to note that given its beneficial properties, resveratrol supplements are readily available in the market, however, this compound has low solubility, low bioavailability and harmful side effects when consumed in large quantities which means a challenge for its pharmaceutical uses.[127]

### 3.3.2. Curcumin

Curcumin is another polyphenol that has been widely studied for its health benefits.[128] This compound is less distributed in nature, since it is mostly found in turmeric root, which is member of the ginger family and its widely used in Middle Eastern and Asian countries, as a spice or traditional medicine.[129] The protective effects of curcumin against T2D have been reported in many diabetic rat models.[130] For instance, Soetikno et al[131] tested the effect of curcumin (100mg/kg) for 8 weeks in STZ-induced diabetic Sprague-Dawley rats. As expected, all diabetic rats had increased plasma glucose and inflammatory markers such as TNF-α and IL-1β, however, the curcumin-treated rats reversed this hyperglycemia and decreased proinflammatory cytokines by inhibiting NFκB activation.[131] Similar protective results have been described using 50 mg/kg for 15 days in rats fed a high fat diet[132] or 150 mg/kg/day for over a month in diabetes induced animals. In this latter study, curcumin supplementation also decreased plasma lipids in a dose dependent manner.[133] In humans, a randomized, double-blind, placebo-controlled trial with 53 T2D patients showed that 1500 mg of curcumin per day for 10 weeks decreased anthropometric measures such as body weight, BMI and waist circumference and glycemic control parameters such as blood glucose, when compared to controls. However, in this study, no changes were observed in HbA1c, insulin, malondialdehyde (MDA), total antioxidant capacity (TAC), HOMA-IR or pancreatic β cell function.[134] Authors state that curcumin exert its benefits is via many pathways, such as modulating lipid metabolism, being a strong antioxidant and having antiapoptotic and anti-inflammatory properties.[135]

### 3.3.3 Catechins

Catechins are a group of polyphenols that can be found in many foods, but are highly concentrated in tea leaves, red wine, black grapes or cocoa. These compounds are responsible for the health benefits attributed to green tea, which contains five catechins subgroups: catechin, epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (EGCG).[127, 136]

The consumption of green tea is known to have anti-obesity effects, since catechins, in particular EGCG, suppresses of adipocyte differentiation and proliferation, inhibits fat absorption, induces apoptosis in mature adipocytes, suppresses lipogenesis, and promotes lipolysis and fatty acid β-oxidation.[122,138] Moreover, green tea and catechins have also been associated with protection against cardiovascular disease[137] atherosclerosis[138] and T2D.[139]

Regarding T2D in humans, the evidence is inconsistent. Nagao et al.[140] tested the effect of a catechin-rich drink on glycemic control in diabetic patients in a double-blind controlled study. Participants were told to consume a high catechin (582.8 mg) green tea or a low (96.3 mg) catechin green tea as control per day for 12 weeks. At the end of the intervention, the high catechin group showed lower waist circumference and higher adiponectin when compared to baseline than the control group. However, no changes were reported in fasting plasma glucose or HbA1c[140] Similar results have been reported by other authors, who did not find an effect of catechin supplementation on fasting glucose or other biomarkers of metabolic syndrome.[141] Conversely a meta-analysis of randomized controlled trials found that green tea catechins did result in a significant reduction in fasting blood glucose.[142]

A recent cohort study done with 482,425 healthy participants and 30,300 diabetic patients in China evaluated the relationship between tea consumption and the incidence of diabetes and diabetic complications[143]. During the follow up after 11 years, an inverse association between daily green tea consumption and risk of T2D and all-cause mortality in patients with diabetes was observed. This protective effect was not reported with other type of teas, suggesting that the catechins present in high concentrations in this traditional beverage played an important role on this

antidiabetic effect. In addition, daily tea intake was associated with a lower risk of diabetic microvascular complications but had no effect on macrovascular complications.[143]

Reports of catechins effects on inflammation have stated that these polyphenols can reduce the expression of IL-6 and MCP-1, suppress NFκB binding activity, downregulate CRP expression and increase the production of adiponectin.[127] Nevertheless, further clinical trials are needed to establish catechins usefulness in the prevention or treatment of T2D. A summary of the effects and mechanisms of polyphenols in the prevention and treatment of T2D is shown in figure 2.

### 3.4 Vitamins and Minerals

There is limited information on the effects of vitamins in their protection against T2D. Regarding Vitamin A, the administration of retinoic acid in diabetic patients has been demonstrated to improve insulin sensitivity.[144] Decreases in plasma Vitamin E have been correlated with T2D incidence.[145] Among the B Vitamins, thiamine levels are low in T2D patients, and the administration of thiamine has been shown to decrease plasma glucose[146,] Other B vitamins have not clearly shown a positive correlation with decreased risk of T2D although their functions are associated with glucose metabolism.[147] Plasma Vitamin C levels are inversely correlated with HbA1C and blood glucose levels.[148] Higher intakes of Vitamin K in the PREDIMED study were associated with lower levels of inflammatory cytokines including IL-6 and TNF-α.[149]

It is common knowledge that lower Vitamin D plasma concentrations represent a risk factor for T2D.[150] Patients with T2D and low levels of Vitamin D improve glycemia and insulin secretion by Vitamin D supplementation both directly and by regulating plasma calcium levels.[151] Calcium homeostasis is impaired in diabetes, which may lead to an improper insulin secretion and action.[152]Overall lower concentrations of both calcium and Vitamin D are correlated with the prevalence of diabetes. Vitamin D also protects against cytokine induced apoptosis by direct modulation of expression and activity of IL-1, IL-6 and TNF-α in mononuclear cells from T2DM patients[153]. However, compared to a placebo, supplementation of Vitamin D did not show any effect on diabetes prevention[154] indicating the need of more studies to support the protective role of Vitamin D in T2D.

Although some studies promote that the use of chromium for T2D[155], its effectiveness in decreasing insulin resistance and T2D is controversial. The use of chromium has not always been found to be effective.[156] Selenium, a well-recognized antioxidant has not shown to be effective in treating T2D[157] and high concentrations of selenium have been identified with increased risk for T2D.[158] These data suggest that more well-controlled clinical studies need to be conducted to define the role of these minerals in the pathogenesis of T2D.

## 4.0 Conclusions

The studies presented here clearly demonstrate that specific dietary regimes as well as nutrients recognized as antioxidants protect against inflammation and insulin resistance in T2D patients. The carbohydrate-restricted diet has been demonstrated to affect all the biomarkers that define T2D[31-37]; The Mediterranean diet has shown to be protective against chronic disease in general and there are many studies and meta-analysis that confirm its effectiveness to prevent or treat T2D.[38-45] PBD have also been helpful in controlling T2D[53-55] as well as DASH interventions.[68,73.]

When we look at specific nutrients, oleic acid, although a key component of the MD has been identified as being effective on its own in controlling T2D[87]; W-3 fatty acids protect against inflammation, a typical condition of T2D due to the anti-inflammatory properties of the derived LC-PUFA[78]; the well-known protection of polyphenols and carotenoids against oxidative stress in increasing insulin sensitivity, protecting against oxidation and reducing inflammation support the benefit of frequent consumption of these nutrients by T2D patients.[93-98] Other than Vitamin D[150], vitamins and minerals do not have well documented effects against T2D as derived from clinical trials; however, they are important components of fruits and vegetables and part of dietary strategies (DASH, Mediterranean, PBD) that have proven to be effective for T2D patients. Overall, it is shown that diet plays a crucial role in the development of complication of T2D, which strongly suggest that nutritional guidance and healthy food choices are key to prevent and treat chronic diseases.

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**5.0 References**

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