Chapter 3

Dietary Recommendations for Patients with Cardiovascular Disease and Diabetes

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Additional information is available at the end of the chapter

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Abstract

Cardiovascular disease remains the main cause of death and disability among patients suffering from diabetes mellitus. All forms of diabetes are characterized by chronic hyperglycemia and the development of diabetes-specific macrovascular disease affecting the coronary arteries that supply the heart. Healthy diet plays an important role in the prevention and management of cardiovascular diseases and diabetes. The information in this chapter is divided into the following sections: mechanisms by which diabetes increases cardiovascular disease, the relationship between diet and disease, the potential of foods in preventing cardiovascular disease and diabetes, and dietary items and patterns.

Keywords: cardiovascular disease, type 2 diabetes mellitus, healthy diet, dietary patterns, nutrients

1. Introduction

Atherosclerotic cardiovascular disease (CVD) remains the main cause of disability and death among patients with diabetes mellitus, especially those with type 2 diabetes mellitus (T2DM). On average, CVD typically occurs 14.6 years earlier in patients with T2DM being characterized by greater severity than in individuals without diabetes mellitus [1, 2]. It is estimated that 90% of atherosclerotic CVD is preventable [3]. The dramatic increase of T2DM has developed into a major public health concern worldwide [4]. Several clinical studies have demonstrated that preventive strategies reduce significantly the risk of developing T2DM [4]. Understanding the mechanisms, strategies, and challenges as well as the potential cardiovascular risks and benefits of glucose-lowering diets are important in managing CVD in T2DM.

2. Mechanisms by which diabetes increases cardiovascular disease

All forms of diabetes are characterized by chronic hyperglycemia and the development of diabetes-specific macrovascular disease affecting the coronary arteries. Large prospective clinical studies show a strong correlation between hyperglycemia, insulin resistance and diabetic macrovascular complications in both type 1 and type 2 diabetes mellitus [5]. Five major molecular mechanisms have been implicated in hyperglycemia-induced tissue damage [6]: (1) increased polyol pathway flux, (2) increased advanced glycation end products (AGEs), (3) activation of protein kinase C (PKC), (4) increased hexosamine pathway flux, and (5) activation of the 12/15-lipoxygenase (12/15-LO) pathway [5]. Hyperglycemia-induced overproduction of superoxide is the causal link between high glucose concentration and the pathways responsible for hyperglycemic damage [5] (**Figure 1**).

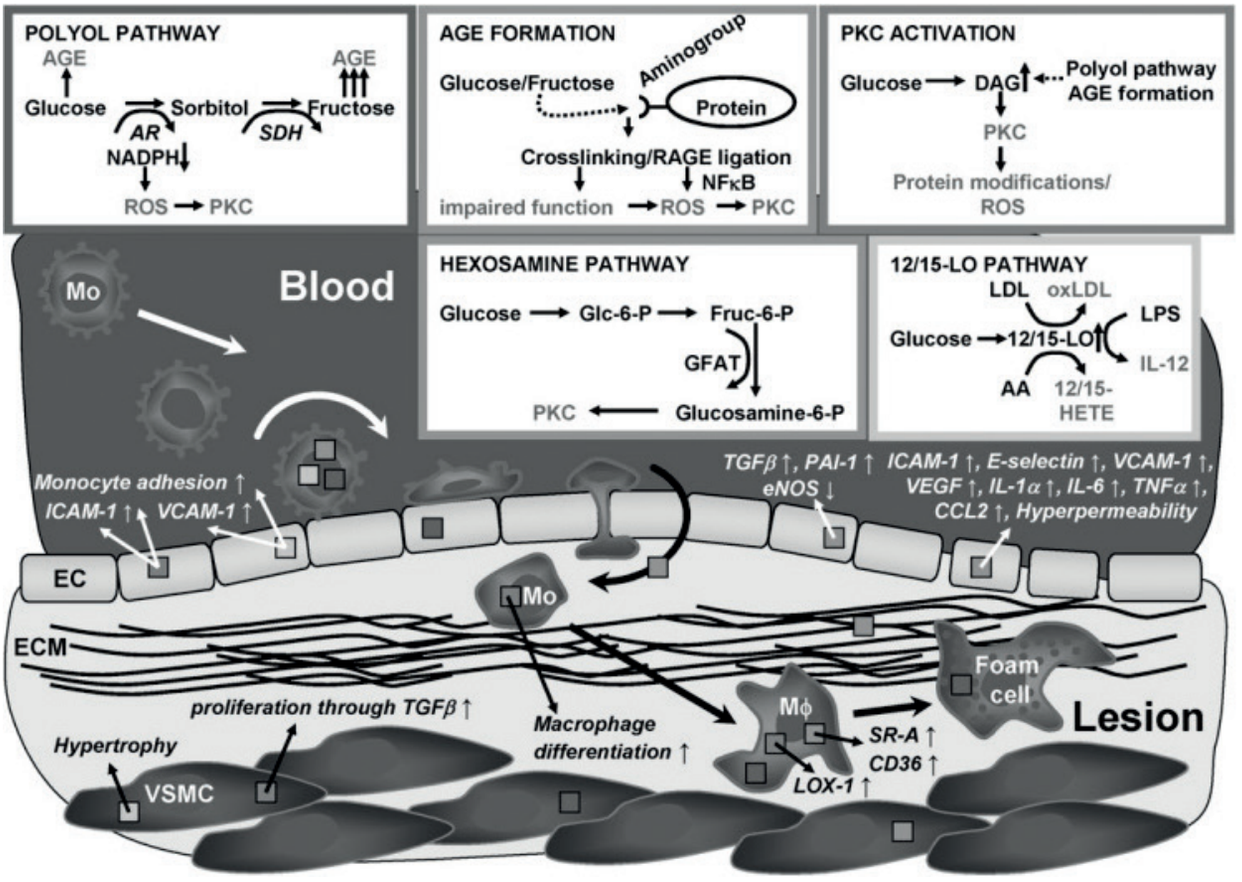

Figure 1. Pro-atherogenic mechanisms of diabetes associated with hyperglycemia. Four hyperglycemia-related mechanisms may promote diabetic atherosclerosis: (1) the polyol pathway, (2) formation of advanced glycation end products (AGEs), (3) activation of protein kinase C (PKC) isoforms, (4) the 12/15-lipoxyenase pathway, and (5) the hexosamine pathway. All four mechanisms result in increased formation of reactive oxygen species (ROS) and promote diabetic atherosclerosis by various mechanisms as depicted in the figure. Boxes in arrows, cells and ECM indicate relevant pathway. 12/15-LO = 12-/15-lipoxygenase, AR = aldose reductase, EC = endothelial cell, ECM = extracellular matrix, Fruc = fructose, GFAT = glutamine-fructose-6-phopshate amidotransferase, Glc = glucose, Mo = monocyte, Mϕ = macrophage, RAGE = receptor for advanced glycation end products, SDH = sorbitol dehydrogenase, VSMC = vascular smooth muscle cell, other abbreviations are explained in the text. Reprinted with permission from [5].

2.1. Increased polyol pathway flux

Aldose reductase (alditol:NADP+ 1-oxidoreductase) is a cytosolic NADPH-dependent oxidoreductase that catalyzes the reduction of glucose to sorbitol, which is further processed to fructose [7]. Aldose reductase (AR) has a low affinity (high *K*m) for glucose and, under euglycemic conditions, this pathway plays a minor role in glucose metabolism [6]. Excess glucose is also channeled into the accessory polyol pathway, where it is reduced to polyalcohol sorbitol by AR, an NADPH-dependent enzyme [8]. In the polyol pathway, sorbitol is oxidized to fructose by sorbitol dehydrogenase, with NAD+ reduced to NADH. Under hyperglycemia, this pathway can account for 25–30% of total glucose metabolism [9]. Overexpression of human AR in low-density lipoprotein (LDL) receptor (LDLR) deficient mice resulted in increased atherosclerotic lesion size if mice became diabetic by administration of streptozotocin (STZ) [5, 10]. Atherosclerotic lesions in normoglycemic LDLR−/− did not differ significantly between AR-overexpressing mice and mice with normal AR expression [11]. Long-term polyol pathway activation also increased intimal thickening in dog coronary arteries, an effect that could be blunted by AR inhibition [12]. Polyol pathway activation also triggered abnormalities in endothelium-dependent relaxation in aortas from STZ-diabetic rats and decreased nitric oxide (NO) release and functionality [13, 14].

2.2. Increased intracellular formation of advanced glycation end products (AGEs)

One of the important mechanisms responsible for accelerated atherosclerosis in diabetes is the Maillard reaction—a type of non-enzymic browning which involves the reaction of carbonyl compounds, especially reducing sugars, with compounds which possess a free amino group, such as amino acids, amines, and proteins [15]. This reaction is subdivided into three main stages. In an early stage, the protein glycation process starts with a nucleophilic addition between free ε-amino or NH_2-terminal groups of proteins and the carbonyl group of reducing sugars (normally glucose or glyceraldehyde) to form a reversible Schiff base [16]. By structural irreversible rearrangements, more Amadori products—stable keto-amines—are formed (i.e., hemoglobin A1c (Hb A1c) [17]. In an intermediate stage, breakdown of Amadori products results in a variety of reactive dicarbonyl compounds such as glyoxal, methylglyoxal, and deoxyglucosones. In the late stage of glycation due to oxidation, dehydration, and cyclization reactions, irreversible compounds called AGEs are formed [18]. AGEs act either by modifying substrates, or by interacting with specific receptors [16]. AGEs-induced damage can occur to the vasculature, vascular cells, and cells implicated in vascular homeostasis via at least the following 4 mechanisms [19, 20]: (1) AGEs modify intracellular proteins, including those involved in the regulation of gene transcription; (2) precursors of AGEs leave the cells via diffusion and modify nearby extracellular matrix molecules, subsequently altering the signaling between matrix and cells and ultimately causing cellular dysfunction; (3) AGEs and their precursors modify circulating proteins in the bloodstream, thereby altering their function; (4) circulating proteins modified by AGEs bind to and activate AGE receptors, thereby altering the production of inflammatory cytokines and growth factors and causing tissue damage [19, 20].

The deleterious effects of AGEs on the vasculature can also be classified either as follow:

2.2.1. Receptor-independent effects of AGEs

Collagen in the blood vessel wall has a relatively long biological half-life, and with time undergoes significant non-enzymatic glycation, which may have a considerable bearing on atherosclerosis [21]. Soluble plasma proteins, such as low-density lipoprotein cholesterol (LDL-C) and immunoglobulin G (IgG), are also entrapped and covalently cross-linked by AGEs on collagen [20, 22]. Glycation of LDL-C decreases recognition of LDL-C particles by the LDL-receptor and enhances the uptake of LDL-C by a low-affinity high-capacity receptor pathway on macrophages. Decreased LDLR affinity of glycated LDL-C may result in increased oxidation of particles and may sufficiently alter their structure to render them immunogenic [23]. Glycated LDL-C is more susceptible to oxidative modification than non-glycated LDL-C. Being immunogenic, glycated LDL-C accumulates in plasma and may enhance cholesterol ester accumulation in macrophages and thus may increase the risk of atherogenic complications [23]. Glycation of apolipoprotein A1 (Apo-AI), the major protein of the protective HDL-C (high-density lipoprotein cholesterol) complex is increased in T2DM and has been shown to induce conformational changes and decreased stability of the lipid-protein interaction, as well as a reduction in the ability of the lipoprotein to self-associate [24, 25]. HDL-C glycated in vitro and Apo-AI isolated from diabetic subjects show decreased ability to activate lecithin-cholesterol acyltransferase, which drives reverse cholesterol transport by esterifying the cellular cholesterol removed by HDL-C [26, 27]. In human aortic endothelial cells, glycated and glycoxidized HDL-C induces H_2O_2 formation, dampens the expression of endothelial nitric oxide synthases (eNOS) decreases NO production, promotes apoptosis associated with increased caspase 3 expression, attenuates caspase 3 inhibition, and increases release of cytochrome c into the cytosol [28, 29].

2.2.2. Receptor-dependent effects of AGEs

AGEs initiate diabetic micro- and macrovascular complications through the structural modification and functional alteration of the extracellular matrix proteins [30]. The receptor for AGEs (RAGE) is a multiligand receptor of the immunoglobulin superfamily of cell surface molecules, acting as a counter-receptor for these diverse molecules [31]. AGE/RAGE signaling elicits activation of multiple intracellular signal pathways involving NADPH oxidase, PKC, and mitogen-activated protein kinases (MAPKs), resulting in nuclear factor NF-kappaB activity [31]. In human diabetic atherosclerotic plaques, RAGE was demonstrated to be upregulated and its expression colocalized with inflammatory markers such as cyclooxygenase 2 and matrix metalloproteinases, particularly in macrophages at the vulnerable regions of atherosclerotic plaques [32, 33]. Administration of the soluble form of RAGE (sRAGE) could work as a decoy receptor for AGEs and might inhibit the binding of AGEs to RAGE, preventing the development and progression of atherosclerosis in animal subjects [34]. The augmented response to arterial injury in diabetes was shown to be associated with RAGE, because administration of sRAGE caused decreased neointimal expansion in hyperglycemic fatty Zucker rats [35].

2.3. Activation of protein kinase C

Protein kinase C (PKC), a multifunctional serine/threonine-specific protein kinase, plays a crucial role in many cellular functions and affects many signal transduction pathways. The AGC

group is named after the protein kinase A, G, and C families that are closely related to the cAMP-dependent protein kinase [36]. Twelve PKC isoforms have thus far been identified, which differ in terms of structure and substrate requirements [37]. Eight isoforms are activated by diacylglycerol (DAG) [6, 38]. Hyperglycemia can contribute to the direct and indirect production of ROS via the activation of the DAG-PKC pathway [6, 38]. Indirect PKC activation may be due to RAGE engagement or polyol pathway activation or activation of the12/15-lipoxygenase (12/15-LO) pathway [39]. Increased PKC levels associated with diabetes are found in several tissues including the aorta and the heart [40, 41]. Higher PKC activation triggers hyperglycemia-induced cardiometabolic perturbations such as changes in blood flow, basement membrane thickening, vascular permeability, angiogenesis, cell growth, and enzymatic activity alterations [42, 43]. PKC activation directly increases the permeability of albumin and other macromolecules through barriers formed by endothelial cells [44]. PKCβ_1 and PKCβ_2 are two of the classical isoforms (α, β, and γ) of PKC [45]. Of the two isoforms, PKCβ_2 overexpression and activation facilitates the development of cardiac hypertrophy and fibrosis, which eventually leads to left ventricular dysfunction suggesting that PKCβ may play a central role in the development of diabetic cardiomyopathy (DCM) [46, 47]. PKCβ_2 activation has been implicated in diabetes-associated abnormalities via inhibition of Akt (protein kinase B)-dependent endothelial nitric eNOS activity [48]. Restoration of Akt-eNOS-NO signaling has been shown to attenuate DCM and myocardial dysfunction [49]. Quantitative immunoblotting revealed a significant increase in membrane fraction expression of PKC-β1 and -β2 in failed human hearts [50]. Among the processes induced by hyperglycemia, activation of PKC may contribute to DCM by inhibiting the metabolic actions of insulin [51]. The PKC-β inhibitor ruboxistaurin (LY333531) is a class of bisindolylmaleimide [52]. In vivo LY333531 treatment prevents excessive PKCβ_2 activation and attenuates cardiac diastolic dysfunction in rats with STZ-induced diabetes. LY333531 suppresses the decreased expression of myocardial NO and phosphate endothelial eNOS [53]. Peroxisome proliferator-activated receptors gamma (PPARs-γ), could directly affect vascular function because of their expression in endothelial cells and smooth vascular muscle cells [54, 55].

2.4. Increased glucose flux through the hexosamine pathway

The hexosamine biosynthesis pathway (HBP) is another side branch of glycolysis [56]. The reaction in which glucose 6-phosphate is changed to fructose 6-phosphate is catalyzed by glutamine fructose-6-phosphate amidotransferase (GFAT) [57]. The major product of HBP is UDP-N-acetylglucosamine (UDP-GlcNAc) [57]. UDP-GlcNAc regulates flux through HBP by regulating GFAT activity and is the obligatory substrate of O-GlcNAc transferase [57, 58]. Hyperglycemia stimulates the expression of PAI-1 in smooth vascular muscle cells and aortic endothelial cells. This effect is thought to be an important factor in the development of vascular disease in diabetes [59, 60]. Sp1 (a protein that in humans is encoded by the SP1 gene) was the first transcription factor identified as an O-GlcNAc modified protein [60]. It has multiple O-GlcNAc modification sites, and its phosphorylation on serine–threonine is inversely proportional to its O-GlcNAc modification [57, 61]. The glycosylated form of Sp1 seems to be more transcriptionally active than the deglycosylated form [62]. The major mechanism of glucose toxicity is the increased mitochondrial superoxide production; this event can account for the diverse manifestations in vascular cells, i.e., increased polyol pathway flux, increased AGE products, activation of PKC, and increased HBP [6, 63]. Inhibition of the rate-limiting

enzyme in the conversion of glucose to GFAT blocks hyperglycemia-induced increases in the transcription of TGF-b1 and plasminogen activator inhibitor-1 [64, 65]. This pathway also plays an important role in hyperglycemia-induced and fat-induced insulin resistance [66, 67]. A prospective study examined the effect of strict blood glucose control through intravenous insulin aimed at euglycemia on the concentration of UDP-GlcNAc and UDP-GalNAc in the muscles of severely insulin resistant, uncontrolled, obese, T2DM patients [67, 68].

2.5. 12/15-lipoxygenase (12/15-LO) pathway

12/15-LOs are enzymes that insert molecular oxygen into polyunsaturated fatty acids, such as arachidonic acids, leading to formation of 12(S)- and 15(S)-hydroxyeicosatetraeonic acid [69]. 12/15-LO enzymes and their products, namely HETEs (hydroxyeicosatetraeonic acid) and hydroxyoctadecadienoic acids, have been implicated in the pathogenesis of atherosclerosis [70]. Several studies have shown that the 12/15-LO pathway is also able to mediate oxidative modification of LDL-C [71, 72]. 12/15-LO seems to be involved in hyperglycemia, as well as minimally modified LDL-mediated adhesion of monocytes to the endothelium and promotes smooth vascular muscle cell hypertrophy [73]. Also 12(S)- HETE promotes monocyte adhesion to endothelial cells, probably in part by inducing the fibronectin splice variant CS-1 (C-terminal fragment of the connecting segment 1) and VCAM-1 on endothelial cells [73]. Some metabolites of the 12/15-LO system, i.e., 13-hydroxyoctadecadieonic acid (13-HODE) reduces platelet adhesion to endothelial cells and binds to PPARγ thereby reducing macrophage expression of matrix metallopeptidase 9 and proinflammatory cytokines [74].

3. The potential of diet in preventing cardiovascular disease and diabetes

The 2016 American Diabetes Association (ADA) Lifestyle Guidelines support the idea of a healthy diet to improve overall health, in light of achieving body weight, individualized glycemic, blood pressure, and lipid goals [75]. The 2016 European Guidelines on CVD prevention in clinical practice acknowledge that the Mediterranean diet is the most studied specific dietary pattern, which comprises many of the foods and nutrients that have been recommended previously, such as high intake of fruits, vegetables, whole grain products, fish, and unsaturated fatty acids [76]. The PREDIMED study (Prevention with Mediterranean Diet) demonstrated that Mediterranean diet reached a statistically significant reduction in the rate of the composite cardiovascular primary end-point of myocardial infarction (MI), stroke, or cardiovascular death [77]. The Mediterranean diet protects the heart, improves lipid profile, reduces blood pressure, and improves glucose tolerance [78]. Current evidence indicates that the Mediterranean diet is effective in improving glycemic control and reducing cardiovascular risk factors in people with T2DM and should therefore be considered in the overall strategy for the management of people with diabetes [79]. In the most extensive study assessing the effects of the Mediterranean diet on patients with newly diagnosed T2DM, the follow-up results over 8.1 years show that compared to a traditional low-fat diet, the rate of regression in the intima-media thickness of the carotid artery was higher by 49%, and the rate of progression lower by 25% in the Mediterranean diet group [80, 81].

4. Using food to meet dietary guidelines

Evidence-based nutrition practice guidelines are devised to guide clinicians in assisting dietitians and patients/clients in taking appropriate decisions regarding nutrition care for specific disease, or conditions in typical settings [82, 83]. The 2015–2020 US Dietary Guidelines are a critical tool for professionals to help Americans make healthy choices in their daily lives to help prevent chronic disease. It serves as the evidence-based foundation for nutrition education materials that are developed by the US Federal Government for the public [77]. Strong evidence reflects a large, high-quality, and/or consistent body of evidence. Moderate evidence reflects sufficient evidence to draw conclusions. Limited evidence reflects a small number of studies, studies of weak design or with inconsistent results, and/or limitations on the generalizability of the findings [77, 84]. The ADA uses the Create Your Plate system, which divides a plate into three sections: non-starchy vegetables (the largest section), starchy foods, and meat or meat substitutes [85]. The Harvard School of Public Health uses the Healthy Eating Pyramid, which is split into nine sections, including a base of daily exercise and weight control [86]. The LiveWell for LIFE project uses National Plates to show the ideal composition of diets in various European Union countries which are both healthy, environmentally sustainable and affordable [87]. Prospective Urban Rural Epidemiology (PURE study) is an epidemiological study carried out in 18 countries, examining associations between diet and total mortality, CVD mortality, CVD events, and non-CVD mortality. [88] The PURE study carried out between 2003 and 2009 on 153,996 adults, aged 35–70 from urban and rural communities in low, middle, and high-income households, found that elevated carbohydrate diets (74.4–80.7% of daily calories from carbs) had a mortality hazard ratio 1.28 (1.12–1.46) times greater the median follow-up period of 7.4 years [88]. Total fat and individual types of fat were associated with lower risk of total mortality, but were not significantly associated with risk of CVD mortality [89]. Reducing saturated fatty acid intake and replacing it with carbohydrate have an adverse effect on blood lipids [88]. Global dietary guidelines should be reconsidered in light of these findings.

5. Dietary items

5.1. Dietary fiber

Dietary fiber can be classified in different ways: soluble versus insoluble based on water solubility; fermentable versus non-fermentable based on whether or not it can be fermented by the microbiota in the large intestine; and viscous versus non-viscous related to its viscosity [90]. Fruit, vegetables, and cereals are the major sources of dietary fiber. The analysis of 67 clinical trials on diets high in soluble fibers suggested that these fibers lower total cholesterol and LDL-C [91]. Water insoluble fibers remain unchanged during digestion and have no effect unless they displace foods supplying saturated fats and cholesterol [92]. Most of the available epidemiologic studies suggest that dietary fiber is inversely related to coronary artery disease [93]. Diet rich in dietary fiber is beneficial for the treatment of T2DM [94], as dietary fiber ameliorates postprandial hyperglycemia by delaying digestion and absorption of carbohydrates [95]. A recent systematic review of the literature reported that moderate

amounts of fiber supplements (4–19 g/day) achieved little improvement in glycemic control or CVD risk factors [96]. It has been reported that increased intake of dietary fiber and low GI diet with legumes reduced blood pressure compared with wheat fiber diet in T2DM patients [95]. A cross-sectional study in adults men and women indicated that the highest total dietary fiber and insoluble dietary fiber intakes were associated with a significantly lower risk of overweight, high blood pressure, plasma apolipoprotein (apo) B, apo B, apo A–I, cholesterol, triacylglycerols, and homocysteine [97]. The fiber intake should, ideally, be 40 g/day (or 20 g/1000 kcal/day) or more and about half should be of the water-soluble type. People with T2DM are encouraged to choose ≥5 servings of fiber-rich vegetables or fruit and ≥4 servings of legumes per week to achieve the fiber intake goals set for the general population [98].

5.2. Polyphenols

A number of antioxidants showed beneficial effect in experimental models of atherosclerosis and CVD [99, 100]. The main polyphenol dietary sources are fruit and beverages (fruit juice, wine, tea, coffee, chocolate, and beer), dry legumes, and cereals [101]. Dietary polyphenols have been shown to possess cardioprotective effects. Oleuropein inhibits the oxidation of LDL-C in vitro [102]. Dietary quercetin decreases lipid peroxidation and upregulates the expression of serum HDL-associated paraoxonase-1 (PON-1) in the liver [101]. PON-1 may mediate anti-atherogenic properties by protecting LDL-C from oxidation. Several studies have indicated that red wine polyphenolic compounds (RWPCs) were able to inhibit proliferation and migration of vascular cells. RWPCs induced NO-mediated endothelium-dependent relaxations in isolated arteries. The activation of eNOS led to an increase in $[Ca^{2+}]_i$ and phosphorylation of eNOS by the PI3-kinase/Akt pathway [103]. RWPCs also increased endothelial prostacyclin release and inhibited the synthesis and the effects of endothelin-1 in endothelial cells [101].

5.3. Lycopene

Lycopene is a natural carotenoid found in tomatoes, which has biochemical functions as an antioxidant scavenger, hypolipidemic agent, and inhibitor of pro-inflammatory and prothrombotic factors [104]. Red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, apricots, and pink guavas, contain lycopene. Processed tomato products are good dietary sources of lycopene [105]. Two major hypotheses have been proposed to explain the anti-atherogenic activities of lycopene. The non-oxidative action of lycopene results in an increase of gap-junction communication between cells and modulation of immune function [106] .The oxidative hypothesis supports the prevention of the oxidization of LDL-C as the initial step leading to its uptake by the macrophages inside the arterial wall and the formation of foam cells and atherosclerotic plaque [105]. A possible mechanism for the protective role of lycopene in CVD is via the inhibition of cellular 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis [107]. Results from the Harvard Medical School's Women's Health Study showed that women with the highest intake of tomato-based foods rich in lycopene had a reduced risk for CVD compared to women with a low intake of these foods [108]. The European multicenter case-control study on antioxidants,

myocardial infarction, and breast cancer (EURAMIC) study found that the risk of MI was 60% lower for the highest quintile of adipose lycopene concentration compared to the lowest quintile, after adjustment for age, family history of CVD and cigarette smoking [109]. In a cross-sectional study comparing Lithuanian and Swedish populations showing diverging mortality rates from CVD, lower blood lycopene levels were found to be associated with increased risk and mortality from CVD [110]. Many studies show that high consumption of tomato products can improve resistance to oxidation in people with T2DM [111]. Eating a lycopene-rich Mediterranean diet increases lycopene levels and can reduce the levels of hemoglobin A1c from 7.1 to 6.8% [112]. In a case-control study on serum β-carotene and the risk of T2DM, participants in the highest tertile of serum β-carotene levels had a 55% lower risk of developing T2DM [113]. In a quasi-experimental study, 32 T2DM patients received 200 g raw tomato daily for 8 weeks. There were significant decreases in systolic and diastolic blood pressure and also a significant increase in apoA-I compared with initial values, which suggests the beneficial role of tomato consumption in reducing cardiovascular risk associated with T2DM [114, 115].

5.4. Fatty acids

N−3 fatty acids including α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) have a significant role in the prevention of CVD [116]. The evidence supports a dietary recommendation of ≈500 mg/day of eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) for CVD risk reduction [117]. A meta-analysis suggests that ALA consumption may also confer cardiovascular benefits, and each 1 g/d increment in ALA intake was associated with a 10% lower risk of CVD death [118]. Dietary sources of ALA include flaxseeds and flaxseed oil, walnuts and walnut oil, soybeans and soybean oil, pumpkin seeds, rapeseed oil, and olive oil [119]. In the GISSI Prevention Study, treatment with n-3 PUFA significantly lowered the risk of the primary endpoint (death, non-fatal MI, and stroke) [120]. Several mechanisms explaining the cardioprotective effect of the n-3 PUFA have been suggested including antiarrhythmic and antithrombotic roles [119].

5.5. Ethanol and non-ethanolic components of wine

Several groups are now beginning to use animal models of myocardial ischemia and reperfusion to explore whether certain nutrients, including ethanol and non-ethanolic components of wine, may have a specific protective effect on the myocardium, independently from the classical risk factors for coronary disease involved in vascular atherosclerosis and thrombosis [121]. Most epidemiological studies have suggested an inverse association between regular light to moderate drinking and the risks of CVD [122]. Researchers have wondered whether moderate alcohol consumption mediates some of its cardioprotective effects by stimulating NO, and conversely, whether binge drinking diminishes NO availability [123]. In a swine model of chronic ischemia, alcohol administration promoted angiogenesis, increased capillary and arteriolar density in non-ischemic myocardium [122]. Numerous studies indicate that moderate red wine consumption is associated with a protective effect on the cardiovascular system, which has largely been attributed to the rich content of phenolic compounds [124, 125]. Polyphenolic antioxidants scavenge the free radicals, inhibit lipid peroxidation (lipoproteins,

membranes), attenuate platelet aggregation, produce coronary vasorelaxation, and protect from cellular injury [126]. Sudden death was examined in US males who participated in the Physicians' Health Study over 12 years of follow-up. Men who consumed light to moderate amounts of alcohol (2–6 drinks/week) had a significantly reduced risk of CVD compared to those who never or rarely consumed alcohol [127]. Daily intake of red wine decreased plasma malondialdehyde and oxidized LDL-C, indicating the antioxidant activity of wine polyphenols [128]. The NO-mediated vasorelaxant effects of red wine phenolic extracts acted mainly through activating endothelial NO synthase [129]. Mild to moderate beer drinking (12.5–25 g/day) provides cardiac protection, improves endothelial function by inhibiting vascular oxidative damage and modulating the Akt/eNOS pathway, which should be attributed to the non-alcohol components in beer [130]. PPARγ plays an important role in glucose and lipid metabolism [131]. Ellagic acid and epicatechin gallate, active components of wine, were reported to have similar affinity to PPARγ of rosiglitazone, which is a standard drug for the treatment of T2DM [132]. Xanthohumol is a flavonoid which was reported to exist in hops and beer could decrease the activity of alpha glucosidase in a non-competitive and reversible way via directly binding to the enzyme and triggering conformational alterations [131].

6. Dietary patterns

6.1. Low-fat diets

Low-fat diets may improve quality of life and extend life expectancy in healthy people, as well as in patients with overweight issues, diabetes, and CVD [77]. Due to the high risk of CVD in individuals diagnosed with T2DM, the goal in dietary fat intake (amount and type) is similar to that of patients with CVD without diabetes [77]. Certain saturated fatty acids (SFA), trans fatty acids (TFA), conjugated linoleic acids (CLA), and cholesterol adversely affect blood lipid levels, whereas viscous fiber, unsaturated MUFA and PUFA, plant sterols/stanols, and to a certain extent, polyphenols have favorable effects [113]. Diet recommendations include obtaining 25 to 35% of daily calories from fats, and restricting saturated fats to less than 7% of total calories, TFA less than 1%, and cholesterol to less than 200 mg/day [133]. These levels can be achieved by eating more grain products, vegetables and fruits, low-fat dairy products, and fat-free milk, and by reducing food containing TFA [134]. A randomized controlled trial found that diets containing ≥7% SFA and ≥200 mg/day cholesterol led to a reduction of the LDL-C level by 9–12% compared to baseline values or to a more standard Western-type diet [135].

6.2. Low-carbohydrate diets

Low-carbohydrate diets are preferable to a low-fat diet in reducing triglycerides (TG) levels and for increasing HDL-C blood levels [77]. A low-carbohydrate diet is defined as consumption of 30–130 g of carbohydrates per day or up to 45% of total calories [136]. There is no justification for the recommendation of very low carbohydrate diets in T2DM. Carbohydrate quantities, sources, and distribution should be selected to facilitate near-normal long-term

glycemic control [137]. A two-year international Dietary Intervention Randomized Controlled (DIRECT) study found that compared to the other diets, the low-carbohydrate diet was most effective for weight loss, and changes in biomarkers (TG, HDL-C, glucose, and insulin) [138].

6.3. A Mediterranean diet

A Mediterranean diet characterized by a relatively high fat intake (40–50% of total daily calories), of which SFA comprises ≤8%, and MUFA 5–25% of calories is associated with a higher life expectancy in healthy people, as well as with lower rates of stroke, coronary heart disease, and diabetes [77]. Mediterranean-style diets are preferable to a low-fat diet in reducing cardiovascular events, increasing blood HDL-C levels, decreasing plasma TG levels, and improving insulin sensitivity [77]. This diet is characterized by abundant legumes, unrefined cereals, vegetables, fresh fruit, olive oil as the principal source of fat, moderate to high consumption of fish, dairy products (mostly as cheese and yogurt), wine consumed in low to moderate amounts, and red meat consumed in low amounts [139]. The Mediterranean-style eating pattern has been observed to improve cardiovascular risk factors in individuals with diabetes [140]. Interventional studies demonstrate the beneficial role of the Mediterranean diet in T2DM management, greater improvements in glycemic control, and reduction of CVD risk factors [141]. The Mediterranean diet is associated with a lower incidence of all-cause mortality [142].

6.4. The dietary approach to stop hypertension (DASH) diet

The dietary approach to stop hypertension (DASH) diet is a dietary pattern to prevent and control hypertension. Its main target is to lower blood pressure, and therefore CVD incidence, by dietary means [77]. The DASH diet includes a relatively high daily content of fruit, vegetables, and grain; moderate amounts of low-fat dairy products, fats, and oils; a decreased content of meat, regular-fat dairy products, snacks, and sweets. All meals have similar sodium content (approximately 3000 mg/day) [77, 143]. Several observational studies in adults have shown that adherence to a DASH-like diet has positive effects on cardiovascular health, including reduced risk of hypertension, T2DM, heart failure, coronary heart disease, stroke [144]. The PREMIER trial reported that standard dietary treatment of hypertensive patients often showed unfavorable control of lipid profile and other cardiovascular risk factors [145]. In the Diabetes Control and Complications Trial, intensive glucose control significantly reduced total cholesterol and LDL-C and TG. The DASH-sodium results indicate that low sodium levels are correlated with the largest reductions in blood pressure for participants at both pre-hypertensive and hypertensive levels [146].

7. Conclusions

To maintain a healthy weight, diet should include a variety of foods, increased intake of fruits and vegetables, whole grains, olive oil, and nuts. Moderate intake of fish, poultry, and red wine is recommended. Consumption of foods high in sodium and sugar should be minimized. The Mediterranean diet has been shown to reduce the incidence of major cardiovascular events

among patients with T2DM. Low-fat dietary patterns have been shown to reduce the risk of CVD in both primary and secondary prevention. The healthy DASH diet plan was developed to lower blood pressure and is associated with a lower risk for developing T2DM. Low-carbohydrate diets may help prevent obesity, T2DM, and atherosclerosis.

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