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Dietary Recommendations for Patients with Cardiovascular Disease and Diabetes

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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).

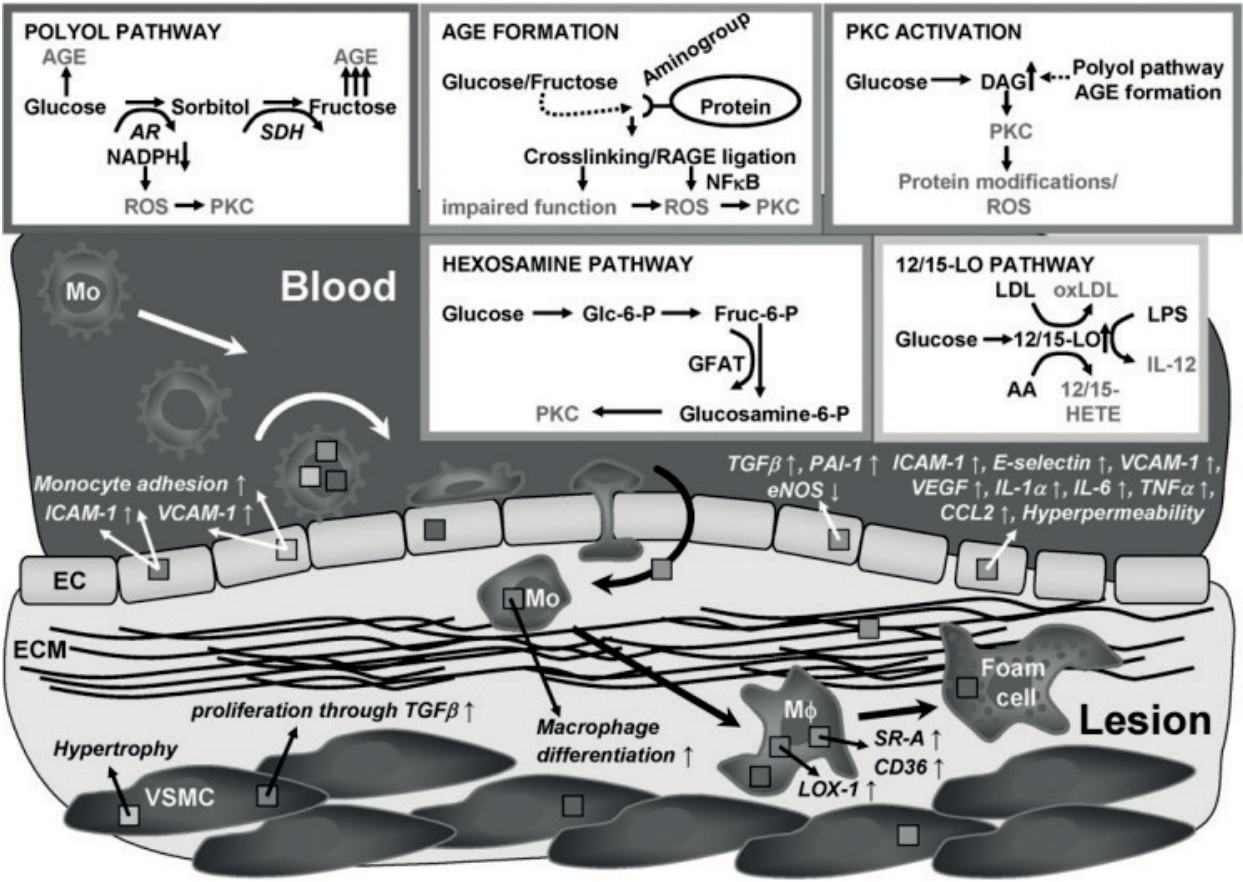


Figure 1. Pro-atherogenic mechanisms of diabetes associated with hyperglycemia. Four hyperglycemia-related mechanisms may promote diabetic atherosclerosis: (1) the polyol pathway, (2) formation of advanced glycation end products (AGEs), (3) activation of protein kinase C (PKC) isoforms, (4) the 12/15-lipoxygenase 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-phosphate 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 NH₂-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 the 12/15-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]. PKC β_1 and PKC β_2 are two of the classical isoforms (α , β , and γ) of PKC [45]. Of the two isoforms, PKC β_2 overexpression and activation facilitates the development of cardiac hypertrophy and fibrosis, which eventually leads to left ventricular dysfunction suggesting that PKC β may play a central role in the development of diabetic cardiomyopathy (DCM) [46, 47]. PKC β_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- β_1 and - β_2 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 PKC β_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- β 1 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)-hydroxyeicosatetraenoic acid [69]. 12/15-LO enzymes and their products, namely HETEs (hydroxyeicosatetraenoic 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-hydroxyoctadecadienoic acid (13-HODE) reduces platelet adhesion to endothelial cells and binds to PPAR γ thereby reducing macrophage expression of matrix metalloproteinase 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 pro-thrombotic 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]. PPAR γ 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 PPAR γ 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 $\geq 7\%$ 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 $\leq 8\%$, 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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References

- [1] Beckman JA, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part II. *European Heart Journal*. 2013;**34**(31):2436-2443. DOI: 10.1093/eurheartj/eh149
- [2] World Health Organization. Cardiovascular diseases (CVDs). Available from: <http://www.who.int/mediacentre/factsheets/fs317/en/>. [Accessed: 2017-July-10]
- [3] McGill HC, McMahan CA, Gidding SS. Preventing heart disease in the 21st century: Implications of the Pathobiological determinants of atherosclerosis in youth (PDAY) study. *Circulation*. 2008;**117**(9):1216-1227. DOI: 10.1161/Circulation.AHA.107.717033
- [4] Schwarz PE, et al. How should the clinician most effectively prevent type 2 diabetes in the obese person at high risk? *Current Diabetes Reports*. 2007;**7**(5):353-362
- [5] Gleissner CA, Galkina E, Nadler JL, Ley K. Mechanisms by which diabetes increases cardiovascular disease. *Drug Discovery Today. Disease Mechanisms*. 2007;**4**(3):131-140. DOI: 10.1016/j.ddmec.2007.12.005
- [6] Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001;**414**(6865):813-820. DOI: 10.1038/414813a
- [7] Vikramadithyan RK, Hu Y, Noh HL, Liang CP, Hallam K, Tall AR, Goldberg IJ. Human aldose reductase expression accelerates diabetic atherosclerosis in transgenic mice. *Journal of Clinical Investigation*. 2005;**115**(9):2434-2443 DOI.org/10.1172/JCI24819
- [8] Chung SS, Ho EC, Lam KS, Chung SK. Contribution of polyol pathway to diabetes-induced oxidative stress. *Journal of the American Society of Nephrology*. 2003;**14**:S233-S236. DOI: 10.1097/01.ASN.0000077408.15865.06

- [9] Srivastava SK, Ramana KV, Bhatnagar A. Role of aldose reductase and oxidative damage in diabetes and the consequent potential for therapeutic options. *Endocrine Reviews*. 2005;**26**:380-392. DOI: 10.1210/er.2004-0028
- [10] Reaven P, Merat S, Casanada F, Sutphin M, Palinski W. Effect of streptozotocin-induced hyperglycemia on lipid profiles, formation of advanced glycation endproducts in lesions, and extent of atherosclerosis in ldl receptor-deficient mice. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1997;**17**:2250-2256. DOI: 10.1161/01.ATV.17.10.2250
- [11] Wu L, et al. Addition of dietary fat to cholesterol in the diets of LDL receptor knock-out mice: Effects on plasma insulin, lipoproteins, and atherosclerosis. *Journal of Lipid Research*. 2006;**47**(10):2215-2222. DOI: 10.1194/jlr.M600146-JLR200
- [12] Ramana KV. Aldose Reductase: New insights for an old enzyme. *Biomolecular Concepts*. 2011;**2**(1-2):103-114. DOI: 10.1515/BMC.2011.002
- [13] Cameron NE, Cotter MA. Contraction and relaxation of aortas from galactosaemic rats and the effects of aldose reductase inhibition. *European Journal of Pharmacology*. 1993;**243**:47-53. DOI: 10.1016/0014-2999(93)90166-F
- [14] Mulhern M, Docherty JR. Effects of experimental diabetes on the responsiveness of rat aorta. *British Journal of Pharmacology*. 1989;**97**(4):1007-1012. DOI: 10.1111/j.1476-5381.1989.tb12555.x
- [15] Nursten HE. The Maillard reaction: Chemistry, biochemistry and implications. *Journal of the American Chemical Society*. 2005;**127**(41):14527-14528. DOI: 10.1021/ja059794d
- [16] Ahmed MU, Dunn JA, Walla MD, Thorpe SR, Baynes JW. Oxidative degradation of glucose adducts to protein. *Journal of Biological Chemistry*. 1988;**263**:8816-8821
- [17] Ahmed N. Advanced glycation endproducts—Role in pathology of diabetic complications. *Diabetes Research and Clinical Practice*. 2005;**67**:3-21. DOI: 10.1016/j.diabres.2004.09.004
- [18] Singh VP, Bali A, Singh N, Jaggi AS. Advanced glycation end products and diabetic complications. *The Korean Journal of Physiology & Pharmacology*. 2014;**18**(1):1-14. DOI: 10.4196/kjpp.2014.18.1.1
- [19] Stirban A, Gawlowski T, Roden M. Vascular effects of advanced glycation endproducts: Clinical effects and molecular mechanisms. *Molecular Metabolism*. 2014;**3**(2):94-108. DOI: 10.1016/j.molmet.2013.11.006
- [20] Vlassara H. Advanced glycation end-products and atherosclerosis. *Annals of Medicine*. 1996;**28**:419-426. DOI: 10.3109/07853899608999102
- [21] Brownlee M, Vlassara H, Kooney T, Ulrich P, Cerami A. Aminoguanidine prevents diabetes-induced arterial wall protein cross-linking. *Science*. 1986;**232**:1629-1632
- [22] Meng J, Sakata N, Takebayashi S, et al. Glycooxidation in aortic collagen from STZ-induced diabetic rats and its relevance to vascular damage. *Atherosclerosis*. 1998;**136**:355-365

- [23] Hunt JV, Bottoms MA, Clare K, Skamarauskas JT, Mitchinson MJ. Glucose oxidation and low-density lipoprotein-induced macrophage ceroid accumulation: Possible implications for diabetic atherosclerosis. *Biochemical Journal*. 1994;**300**(1):243-249
- [24] Smith JD. Dysfunctional HDL as a diagnostic and therapeutic target. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2010;**30**(2):151-155. DOI: 10.1161/ATVBAHA. 108. 179226
- [25] Hedrick CC, Thorpe SR, Fu MX, Harper CM, Yoo J, Kim SM, Wong H, Peters AL. Glycation impairs high-density lipoprotein function. *Diabetologia*. 2000;**43**:312-320. DOI: 10.1007/s001250050049
- [26] Calvo C, Ulloa N, Del Pozo R, Verdugo C. Decreased activation of lecithin: Cholesterol acyltransferase by glycated apolipoprotein A-I. *European Journal of Clinical Chemistry and Clinical Biochemistry*. 1993;**31**:217-202
- [27] Fournier N, Myara I, Atger V, Moatti N. Reactivity of lecithin-cholesterol acyltransferase (LCAT) toward glycated high density lipoproteins. *Clinica Chimica Acta*. 1995;**234**:47-61
- [28] Matsunaga T, et al. Glycated high-density lipoprotein species regulates reactive oxygen species and reactive nitrogen species in endothelial cells. *Metabolism*. 2003;**52**:42-49. DOI: 10.1053/meta.2003.50013
- [29] Matsunaga T, Iguchi K, Nakajima T, Koyama I, Miyazaki T, Inoue I, Kawai S, Katagama S, Hirano K, Hokari S, Komoda T. Glycated high density lipoprotein induces apoptosis of endothelial cells via mitochondrial dysfunction. *Biochemical and Biophysical Research Communications*. 2001;**387**:714-720
- [30] Fukami K, Yamagishi S, Okuda S. Role of AGEs-RAGE system in cardiovascular disease. *Current Pharmaceutical Design*. 2014;**20**(14):2395-2402
- [31] Bierhaus A, Humpert PM, Morcos M, Wendt T, Chavakis T, Arnold B, Stern DM, Nawroth PP. Understanding RAGE, the receptor for advanced glycation end products. *Journal of Molecular Medicine*. 2005;**83**:876-886. DOI: 10.1007/s00109-005-0688-7
- [32] Koyama H, Yamamoto H, Nishizawa Y. RAGE and soluble RAGE: Potential therapeutic targets for cardiovascular diseases. *Molecular Medicine*. 2007;**13**(11-12):625-635. DOI: 10.2119/2007-00087
- [33] Cipollone F, Iezzi A, Fazia M, et al. The receptor RAGE as a progression factor amplifying arachidonate-dependent inflammatory and proteolytic response in human atherosclerotic plaques: Role of glycemic control. *Circulation*. 2003;**108**:1070-1077. DOI: 10.1161/01.CIR. 0000086014.80477.0D
- [34] Burke AP, Kolodgie FD, Zieske A, et al. Morphologic findings of coronary atherosclerotic plaques in diabetics: A postmortem study. *Arteriosclerosis Thrombosis and Vascular Biology*. 2004;**24**:1266-1271
- [35] Zhou Z, Wang K, Penn MS, et al. Receptor for AGE (RAGE) mediates neointimal formation in response to arterial injury. *Circulation*. 2003;**107**:2238-2243. DOI: 10.1161/01.CIR. 0000063577.32819.23

- [36] Newton AC. Regulation of the abc kinases by phosphorylation: Protein kinase C as a paradigm. *Biochemical Journal*. 2003;**370**:361-371. DOI: 10.1042/BJ20021626
- [37] Gerald P, King GL. Activation of protein kinase C isoforms and its impact on diabetic complications. *Circulation Research*. 2010;**106**:1319-1331. DOI: 10.1161/CIRCRESAHA . 110.217117
- [38] Das Evcimen N, King GL. The role of protein kinase C activation and the vascular complications of diabetes. *Pharmacological Research*. 2007;**55**(6):498-510. DOI: 10.1016/j. phrs. 2007.04.016
- [39] Williams MD, Nadler JL. Inflammatory mechanisms of diabetic complications. *Current Diabetes Reports*. 2007;**7**(3):242-248
- [40] Mapanga RF, Joseph D, Symington B, Garson KL, Kimar C, Kelly-Laubscher R, Essop MF. Detrimental effects of acute hyperglycaemia on the rat heart. *American Journal of Physiology Heart and Circulatory Physiology*. 2016;**310**:H153-H173. DOI: 10.1152/ajp-heart. 00206.2015
- [41] Inoguchi T, Battan R, Handler E, Sportsman JR, Heath W, King GL. Preferential elevation of protein kinase C isoform beta II and diacylglycerol levels in the aorta and heart of diabetic rats: Differential reversibility to glycemic control by islet cell transplantation. *Proceedings of the National Academy of Sciences of the United States of America*. 1992;**89**(22):11059-11063
- [42] Xia P, Inoguchi T, Kern TS, Engerman RL, Oates PJ, King GL. Characterization of the mechanism for the chronic activation of diacylglycerol-protein kinase C pathway in diabetes and hypergalactosemia. *Diabetes*. 1994;**43**:1122-1129. DOI: 10.2337/diab.43.9.1122
- [43] Xia P, Kramer RM, King GL. Identification of the mechanism for the inhibition of Na⁺,K⁺-adenosine triphosphatase by hyperglycemia involving activation of protein kinase C and cytosolic phospholipase A2. *Journal of Clinical Investigation*. 1995;**96**(2):733-740. DOI: 10.1172/JCI118117
- [44] Inoguchi T, Ueda F, Umeda F, Yamashita T, Nawata H. Inhibition of intercellular communication via gap junction in cultured aortic endothelial cells by elevated glucose and phorbol ester. *Biochemical and Biophysical Research Communications*. 1995;**208**:492-497. DOI: 10.1006/bbrc.1995.1365
- [45] Clarke M, Dodson PM. PKC inhibition and diabetic microvascular complications. *Best Practice Research: Clinical Endocrinology Metabolism*. 2007;**21**:573-586. DOI: 10.1016/j. beem.2007.09.007
- [46] Yang L, Doshi D, Morrow J, Katchman A, Chen X, Marx SO. PKC isoforms differentially phosphorylate Ca_v1.2 α_{1c} . *Biochemistry*. 2009;**48**(28):6674-6683. DOI: 10.1021/bi900322a
- [47] Liu Y, et al. PKC β inhibition with ruboxistaurin reduces oxidative stress and attenuates left ventricular hypertrophy and dysfunction in rats with streptozotocin-induced diabetes. *Clinical Science*. 2012;**122**:161-173. DOI: 10.1042/CS20110176

- [48] Naruse K, Rask-Madsen C, Takahara N, et al. Activation of vascular protein kinase C-beta inhibits Akt-dependent endothelial nitric oxide synthase function in obesity-associated insulin resistance. *Diabetes*. 2006;**55**:691-698. DOI: 10.2337/diabetes.55.03.06.db05-0771
- [49] Ren J, Duan J, Thomas DP, et al. IGF-I alleviates diabetes-induced RhoA activation, eNOS uncoupling, and myocardial dysfunction. *American Journal of Physiology Regulatory Integrative and Comparative Physiology*. 2008;**294**:R793-R802
- [50] Bowling N, Walsh RA, Song G, Estridge T, Sandusky GE, Fouts RL, Mintze K, Pickard T, Roden R, Bristow MR, Sabbah HN, Mizrahi JL, Gromo G, King GL, Vlahos CJ. Increased protein kinase C activity and expression of Ca²⁺-sensitive isoforms in the failing human heart. *Circulation*. 1999;**99**:384-391. DOI: 10.1161/01.CIR.99.3.384
- [51] Kolter T, Uphues I, Eckel J. Molecular analysis of insulin resistance in isolated ventricular cardiomyocytes of obese Zucker rats. *American Journal of Physiology - Endocrinology and Metabolism*. 1997;**273**:E59-E67
- [52] Ishii H, Jirousek MR, Koya D, Takagi C, Xia P, Clermont A, Bursell SE, Kern TS, Ballas LM, Heath WF, Stramm LE, Feener EP, King GL. Amelioration of vascular dysfunctions in diabetic rats by an oral PKC beta inhibitor. *Science*. 1996;**272**:728-731
- [53] Lei S, Li H, Xu J, et al. Hyperglycemia-induced protein kinase C β_2 activation induces diastolic cardiac dysfunction in diabetic rats by impairing Caveolin-3 expression and Akt/eNOS signaling. *Diabetes*. 2013;**62**(7):2318-2328. DOI: 10.2337/db12-1391
- [54] Kume S, Uzu T, Isshiki K, Koya D. Peroxisome proliferator-activated receptors in diabetic nephropathy. *PPAR Research*. 2008;**11**:4. DOI:10.1155/2008/879523
- [55] Takagi T, Akasaka T, Yamamuro A, Honda Y. Troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with non-insulin dependent diabetes mellitus: A serial intravascular ultrasound study. *Journal of the American College of Cardiology*. 2000;**36**(5):1529-1535. DOI: 10.1016/S0735-1097(00)00895-0
- [56] Buse MG. Hexosamines, insulin resistance and the complications of diabetes: Current status. *American Journal of Physiology Endocrinology and Metabolism*. 2006;**290**(1):E1-E8. DOI: 10.1152/ajpendo.00329.2005
- [57] Kreppel LK, Blomberg MA, Hart GW. Dynamic glycosylation of nuclear and cytosolic proteins. Cloning and characterization of a unique O-GlcNAc transferase with multiple tetratricopeptide repeats. *Journal of Biological Chemistry*. 1997;**272**:9308-9315. DOI: 10.1074/jbc.272.14.9308
- [58] Laczy B, Hill BG, Wang K, Paterson AJ, White CR, Xing D, Chatham JC. Protein O-GlcNAcylation: A new signaling paradigm for the cardiovascular system. *American Journal of Physiology—Heart and Circulatory Physiology*. 2009;**296**(1):H13-H28. DOI: 10.1152/ajpheart.01056.2008
- [59] Chen YQ, Su M, Walia RR, Hao Q, Covington JW, Vaughan DE. Sp1 sites mediate activation of the plasminogen activator inhibitor-1 promoter by glucose in vascular smooth muscle cells. *Journal of Biological Chemistry*. 1998;**273**:8225-8231. DOI: 10.1167/iov.14-14048

- [60] Du XL, Edelstein D, Rossetti L, Fantus IG, Goldberg H, Ziyadeh F, Wu J, Brownlee M. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *Proceedings of the National Academy of Sciences of the United States of America*. 2000;**97**:12222-12226. DOI: 10.1073/pnas.97.22.12222
- [61] Roos MD, Su K, Baker JR, Kudlow JE. O glycosylation of an Sp1-derived peptide blocks known Sp1 protein interactions. *Molecular and Cellular Biology*. 1997;**17**(11):6472-6480
- [62] Kadonaga JT, Courey AJ, Ladika J, Tjian R. Distinct regions of Sp1 modulate DNA binding and transcriptional activation. *Proceedings of the National Academy of Sciences of the United States of America*. 1986;**83**(16):5889-5893
- [63] Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. *Diabetes*. 2005;**54**:1615-1625. DOI: 10.2337/diabetes.54.6.1615
- [64] Chen G, Liu P, Thurmond DC, Elmendorf JS. Glucosamine-induced insulin resistance is coupled to O-linked glycosylation of Munc18c. *FEBS Letters*. 2003;**534**:54-60. DOI: 10.1016/S0014-5793(02)03774-2
- [65] Toleman C, Paterson AJ, Whisenhunt TR, Kudlow JE. Characterization of the histone acetyltransferase (HAT) domain of a bifunctional protein with activable O-GlcNAcase and HAT activities. *Journal of Biological Chemistry*. 2004;**279**:53665-53673. DOI: 10.1074/jbc.M410406200
- [66] van Dam EM, Govers R, James DE. Akt activation is required at a late stage of insulin-induced GLUT4 translocation to the plasma membrane. *Molecular Endocrinology*. 2005;**19**:1067-1077. DOI: 10.1074/jbc.M410406200
- [67] Virkamaki A, Yki-Jarvinen H. Allosteric regulation of glycogen synthase and hexokinase by glucosamine-6-phosphate during glucosamine-induced insulin resistance in skeletal muscle and heart. *Diabetes*. 1999;**48**:1101-1107. DOI: 10.2337/diabetes.48.5.1101
- [68] Pouwels MJ, Span PN, Tack CJ, Olthaar AJ, Sweep CG, van Engelen BG, de Jong JG, Lutterman JA, Hermus AR. Muscle uridine diphosphate-hexosamines do not decrease despite correction of hyperglycemia-induced insulin resistance in type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism*. 2002;**87**(11):5179-5184
- [69] Natarajan R, Nadler JL. Lipid inflammatory mediators in diabetic vascular disease. *Arteriosclerosis Thrombosis and Vascular Biology*. 2004;**24**(9):1542-1548. DOI: 10.1161/01.ATV.0000133606.69732.4c
- [70] Ma K, Nunemaker CS, Wu R, Chakrabarti SK, Taylor-Fishwick DA, Nadler JL. 12-Lipoxygenase products reduce insulin secretion and β -cell viability in human islets. *The Journal of Clinical Endocrinology and Metabolism*. 2010;**95**(2):887-893. DOI:10.1210/jc.2009-1102
- [71] Benz D, Mol JM, Ezaki M, et al. Enhanced levels of lipoperoxides in low density lipoprotein incubated with murine fibroblasts expressing high levels of human 15-lipoxygenase. *Journal of Biological Chemistry*. 1995;**270**:5191-5197. DOI: 10.1074/jbc.270.10.5191

- [72] Daugherty A, Manning, MW,& Cassis LA. Antagonism of AT2 receptors augments Angiotensin II-induced abdominal aortic aneurysms and atherosclerosis. *British Journal of Pharmacology*. 2001;**134**(4):865-870. DOI:10.1038/sj.bjp.0704331
- [73] Scheidegger KJ, Butler S, Witztum JL. Angiotensin II increases macrophage-mediated modification of low-density lipoprotein via a lipoxygenase-dependent pathway. *Journal of Biological Chemistry*. 1997;**272**:21609-21615. DOI: 10.1074/jbc.272.34.21609
- [74] Wittwer J, Hersberger M. The two faces of the 15-lipoxygenase in atherosclerosis. *Prostaglandins, Leukotrienes and Essential Fatty Acids*. 2007;**77**(2):67-77. DOI: 10.1016/j.plefa.2007.08.001
- [75] Jensen MD, et al. AHA/ACC/TOS guideline for the management of overweight and obesity in adults. *Circulation*. 2013. DOI: 10.1161/01.cir. 0000437739.71477.ee
- [76] Catapano AL. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *European Heart Journal*. 2016;**37**(39):2999-3058. DOI: 10.1093/eurheartj/ehw272
- [77] Estruch R, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *New England Journal of Medicine*. 2013;**368**:1279-1290. DOI: 10.1056/NEJMoa1200303
- [78] Esposito K. A journey into a Mediterranean diet and type 2 diabetes: A systematic review with meta-analyses *British Medical Journal Open*. 2015;**5**(8):6. DOI:10.1136/bmjopen-2015-008222
- [79] Evert AB, et al. Nutrition therapy recommendations for the Management of Adults with Diabetes. *Diabetes Care*. 2013;**36**(11):3821-3842. DOI: 10.2337/dc13-2042
- [80] Esposito K, Maiorino MI, Petrizzo M, et al. The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: Follow-up of a randomized trial. *Diabetes Care*. 2014;**37**:1824-1830. DOI: 10.2337/dc13-2899
- [81] Esposito K, Chiodini P, Bellastella G, Maiorino MI, Giugliano D. Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: Systematic review of 218 randomized controlled trials with 78 945 patients. *Diabetes Obesity and Metabolism*. 2012;**14**(3):228-233. DOI: 10.1111/j.1463-1326.2011.01512.x
- [82] Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: Dietary components and nutritional strategies. *Lancet*. 2014;**383**(9933):10. DOI:10.1016/S0140-6736(14)60613-9
- [83] Position of the academy of nutrition and dietetics: Food and nutrition for older adults: Promoting health and wellness. *Journal of Academy of Nutrition and Dietetics*. 2012;**112**:2212-2672. DOI: 10.1016/j.jand.2012.06.015
- [84] Lennon SL, DellaValle DM, Rodder SG, Prest M, Sinley RC, Hoy MK, Papoutsakis C. Evidence analysis library evidence-based nutrition practice guideline for the management of hypertension in adults. *Journal of the Academy of Nutrition and Dietetics*. 2017; pii: S2212-2672(17)30348-9. DOI: 10.1016/j.jand.2017.04.008

- [85] Murphy M, et al. Phytonutrient intake by adults in the United States in relation to fruit and vegetable consumption. *Journal of the Academy of Nutrition and Dietetics*. 2012;**2**:222-229. DOI: 10.1016/j.jada.2011.08.044
- [86] Skerrett PJ, Willett WC. Essentials of healthy eating: A guide. *Journal of Midwifery & Women's Health*. 2010;**55**(6):492-501. DOI: 10.1016/j.jmwh.2010.06.019
- [87] Wallace-Jones J. LiveWell for LIFE - Livewell plate for low impact food in Europe. Available from: <http://ec.europa.eu/environment/life/project/Projects/index.cfm?fuseaction=search>. [Accessed 2017-July- 27]
- [88] The Press Conference Hot Line—Late Breaking Registry. ESC, Barcelona, Spain – 29 Aug 2017. Available from: <https://www.escardio.org/The-ESC/Press-Office/Press-releases/revisiting-dietary-fat-guidelines-pure-results>. [Accessed: 31-08-2017]
- [89] Mente A, Yusuf S, et al. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: A cross-sectional analysis from the PURE study. *The Lancet Diabetes & Endocrinology*. 2017;Aug 29: [Epub ahead of print]. DOI: 10.1016/S2213-8587(17)30283-8
- [90] Brown L, et al. Cholesterol-lowering effects of dietary fiber: A meta-analysis. *American Journal of Clinical Nutrition*. 1999;**69**(1):30-42. Available from: <http://ajcn.nutrition.org/content/72/4/922.full> [Accessed 2017-July-27]
- [91] Truswell AS. Dietary fibre and plasma lipids. *European Journal of Clinical Nutrition*. 1995;**49**(2):105-113
- [92] Kris-Etherton PM, Krummel D, Russell ME, et al. The effect of diet on plasma lipids, lipoproteins, and coronary heart disease. *Journal of the American Dietetic Association*. 1988;**88**:1373-1400
- [93] Kromhout D, Bosschieter EB, de Lezenne Coulander C. Dietary fiber and 10-year mortality from coronary heart disease, cancer and all causes: The Zutphen study. *Lancet* 1982;**2**:518-521
- [94] Pastors JG, Franz MJ, Warshaw H, Daly A, Arnold MS. How effective is medical nutrition therapy in diabetes care? *Journal of the American Dietetic Association*. 2003;**103**:827-831. DOI: 10.1053/jada.2003.50186
- [95] Kaczmarczyk MM, Miller MJ, Freund GG. The health benefits of dietary fiber: Beyond the usual suspects of type 2 diabetes, cardiovascular disease and colon cancer. *Metabolism*. 2012;**61**(8):1058-1066. DOI: 10.1016/j.metabol.2012.01.017
- [96] Wheeler ML, Dunbar SA, Jaacks LM, et al. Macronutrients, food groups, and eating patterns in the Management of Diabetes: A systematic review of the literature, 2010. *Diabetes Care*. 2012;**35**(2):434-445. DOI: 10.2337/dc11-2216
- [97] Ignarro LJ, Balestrieri ML, Napoli C. Nutrition, physical activity, and cardiovascular disease. An update. *Cardiovascular Research*. 2007;**73**(2):326-340. DOI: 10.1016/j. cardiores. 2006.06.030

- [98] Rydén L, et al. ESC Guidelines on Diabetes, Pre-diabetes, and Cardiovascular Diseases Developed in Collaboration with the EASD: The Task Force on Diabetes in Collaboration with the European Association for the Study of Diabetes (EASD). Available from: <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Diabetes-Pre-Diabetes-and-Cardiovascular-Diseases-developed-with-the-EASD>. [Accessed 2017-July- 27]
- [99] Ames BN, Gold LS, Willet WC. Causes and prevention of cancer. *Proceedings of the National Academy of Sciences of the United States of America*. 1995;**92**:5258-5265
- [100] Ignarro LJ, Napoli C. Novel features on nitric oxide, endothelial nitric oxide synthase and atherosclerosis. *Current Atherosclerosis Reports*. 2004;**6**:278-287
- [101] Han X, Shen T, Lou H. Dietary polyphenols and their biological significance. *International Journal of Molecular Sciences*. 2007;**8**(9):950-988
- [102] Visioli F, Galli C. Oleuropein protects low density lipoprotein from oxidation. *Life Sciences*. 1994;**55**(24):1965-1971
- [103] Ndiaye M, Chataigneau T, Chataigneau M, Schini-Kerth VB. Red wine polyphenols induce EDHF-mediated relaxations in porcine coronary arteries through the redox-sensitive activation of the PI3-kinase/Akt pathway. *British Journal of Pharmacology*. 2004;**142**(7):1131-1136. DOI: 10.1038/sj.bjp.0705774
- [104] Riccioni G, Mancini B, Di Ilio E, Bucciarelli T, D'Orazio N. Protective effect of lycopene in cardiovascular disease. *European Review for Medical and Pharmacological Sciences*. 2008;**12**(3):183-190
- [105] Agarwal S, Rao AV. Tomato lycopene and its role in human health and chronic diseases. *CMAJ: Canadian Medical Association Journal*. 2000;**163**(6):739-744
- [106] Lee R, Margaritis M, Channon K, Antoniades C. Evaluating oxidative stress in human cardiovascular disease: Methodological aspects and considerations. *Current Medicinal Chemistry*. 2012;**19**(16):2504-2520. DOI: 10.2174/092986712800493057
- [107] Fuhrman B, Elis A, Aviram M. Hypocholesterolemic effect of lycopene and beta-carotene is related to suppression of cholesterol synthesis and augmentation of LDL receptor activity in macrophages. *Biochemical and Biophysical Research Communication*. 1997;**233**(3):658-662. DOI: 10.1006/bbrc.1997.6520
- [108] Sesso HD, Liu S, Gaziano JM, Buring JE. Dietary lycopene, tomato-based food products and cardiovascular disease in women. *Journal of Nutrition*. 2003;**133**(7):2336-2341
- [109] Gomez-Aracena J, Sloots J, Garcia-Rodriguez A, et al. Antioxidants in adipose tissue and myocardial infarction in a Mediterranean area. The EURAMIC study in Malaga. *Nutrition, Metabolism & Cardiovascular*. 1997;**7**:376-382
- [110] Kristenson M, Ziedén B, Kucinskienė Z, et al. Antioxidant state and mortality from coronary heart disease in Lithuanian and Swedish men: Concomitant cross sectional study of men aged 50. *BMJ : British Medical Journal*. 1997;**314**(7081):629-633

- [111] Raiola A, Rigano MM, Calafiore R, Frusciante L, Barone A. Enhancing the health-promoting effects of tomato fruit for biofortified food. *Mediators of Inflammation*. 2014; **2014**:139873. DOI: 10.1155/2014/139873
- [112] Itsiopoulos C, Brazionis L, Kaimakamis M, et al. Can the Mediterranean diet lower HbA1c in type 2 diabetes? Results from a randomized cross-over study. *Nutrition, Metabolism & Cardiovascular Diseases*. 2011; **21**(9):740-747. DOI: 10.1016/j.numecd.2010.03.005
- [113] Simin L, Ajani U, Chae C, et al. Long-term β -carotene supplementation and risk of type 2 diabetes mellitus. A randomized controlled trial. *Journal of the American Medical Association*. 1999; **282**(11):1073-1075. DOI: 10.1001/jama.282.11.1073
- [114] Li W, Wang G, Lu X, Jiang Y, Xu L, Zhao X. Lycopene ameliorates renal function in rats with streptozotocin-induced diabetes. *International Journal of Clinical and Experimental Pathology*. 2014; **15**(8):5008-5015 eCollection 2014
- [115] Shidfar F, Froghifar N, Vafa M, Rajab A, Hosseini S, Shidfar S, Gohari M. The effects of tomato consumption on serum glucose, apolipoprotein B, apolipoprotein A-I, homocysteine and blood pressure in type 2 diabetic patients. *International Journal of Food Sciences and Nutrition*. 2011; **62**(3):289-294. DOI: 10.3109/09637486.2010.529072
- [116] Harper CR, Jacobson TA. Beyond the Mediterranean diet: The role of omega-3 fatty acids in the prevention of coronary heart disease. *European Journal of Preventive Cardiology*. 2003; **6**:136-146. DOI: 10.1016/j.numecd.2010.03.005
- [117] Gebauer SK, Psota TL, Harris WS, Kris-Etherton PM. n-3 fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. *American Journal of Clinical Nutrition*. 2006; **83**(6):S1526-1535S
- [118] Pan A, Chen M, Chowdhury R, Wu JH, Sun Q, Campos H, Hu FB. α -Linolenic acid and risk of cardiovascular disease: A systematic review and meta-analysis. *The American Journal of Clinical Nutrition*. 2012; **96**(6):1262-1273. DOI: 10.3945/ajcn.112.044040
- [119] Djousse L, Pankow JS, Eckfeldt JH, et al. Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute family heart study. *American Journal of Clinical Nutrition*. 2001; **74**:612-619
- [120] Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet*. 1999; **354**:447-455
- [121] Rakotovao A, Berthonneche C, Guiraud A, de Lorgeril M, Salen P, de Leiris J. Ethanol, wine, and experimental cardioprotection in ischemia/reperfusion: Role of the prooxidant/antioxidant balance. *Antioxidants & Redox Signaling*. 2004; **6**:431-438
- [122] Zhou Y, Zheng J, Li S, Zhou T, Zhang P, Li H-B. Alcoholic Beverage Consumption and Chronic Diseases. Hayley A, Verster JC, eds. *International Journal of Environmental Research and Public Health*. 2016; **13**(6):522. DOI: 10.3390/ijerph13060522

- [123] Davda RK, Chandler LJ, Crews FT, Guzman NJ. Ethanol enhances the endothelial nitric oxide synthase response to agonists. *Hypertension* 1993;**21**:939-943
- [124] Tsang C, Higgins S, Duthie GG, Duthie SJ, Howie M, Mullen W, Lean MEJ, Crozier A. The influence of moderate red wine consumption on antioxidant status and indices of oxidative stress associated with CHD in healthy volunteers. *British Journal of Nutrition*. 2005;**93**:233-240. DOI: 10.1079/BJN20041311
- [125] Huang PH, Tsai HY, Wang CH, Chen YH, Chen JS, Lin FY, Lin CP, Wu TC, Sata M, Chen JW, et al. Moderate intake of red wine improves ischemia-induced neovascularization in diabetic mice—Roles of endothelial progenitor cells and nitric oxide. *Atherosclerosis*. 2010;**212**:426-435. DOI: 10.1016/j.atherosclerosis.2010.06.034
- [126] Das S, Santani DD, Dhalla NS. Experimental evidence for the cardioprotective effects of red wine. *Experimental & Clinical Cardiology*. 2007;**12**(1):5-10
- [127] Kristenson M, Ziedén B, Kucinskienė Z, Elinder LS, Bergdahl B, Elwing B, Olsson AG. Antioxidant state and mortality from coronary heart disease in Lithuanian and Swedish men: Concomitant cross sectional study of men aged 50. *BMJ: British Medical Journal*. 1997;**314**(7081):629-633
- [128] Kaliora AC, et al. Dietary antioxidants in preventing atherogenesis. *Atherosclerosis*. 2005;**187**(1):1-17. DOI: 10.1016/j.atherosclerosis.2005.11.001
- [129] Auger C, Chaabi M, Anselm E, Lobstein A, Schini-Kerth VB. The red wine extract-induced activation of endothelial nitric oxide synthase is mediated by a great variety of polyphenolic compounds. *Molecular Nutrition & Food Research*. 2010;**54**(Suppl. 2): S171-S183. DOI: 10.1002/mnfr. 200900602
- [130] Vilahur G, Casani L, Mendieta G, Lamuela-Raventos RM, Estruch R, Badimon L. Beer elicits vasculoprotective effects through Akt/eNOS activation. *European Journal of Clinical Investigation*. 2014;**44**:1177-1188. DOI: 10.1111/eci.12352
- [131] Koloverou E, Panagiotakos DB, Pitsavos C, Chryschoou C, Georgousopoulou EN, Metaxa V, Stefanadis C. Effects of alcohol consumption and the metabolic syndrome on 10-year incidence of diabetes: The ATTICA study. *Diabetes & Metabolism*. 2015;**41**:152-159. DOI: 10.1016/j.diabet.2014.06.003
- [132] Avior Y, Bomze D, Ramon O, Nahmias Y. Flavonoids as dietary regulators of nuclear receptor activity. *Food & function*. 2013;**4**(6):831-844. DOI: 10.1039/c3fo60063g
- [133] Position and Practice Paper Update for 2017 *Journal of the Academy of Nutrition and Dietetics* 2017;**117**(2):278-279. Available from: <http://jandonline.org/content/positionPapers?JournalCode=jand&filterModify=true&dateYear1field> [Accessed: 2017-August-9]
- [134] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;**106**(25):3143-3421

- [135] Feldman EB. The scientific evidence for a beneficial health relationship between walnuts and coronary heart disease. *The Journal of Nutrition*. 2002;**132**(5):1062S-1101S
- [136] Accurso A, Bernstein RK, Dahlqvist A, Draznin B, Feinman RD, et al. Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: Time for a critical appraisal. *Nutrition and Metabolism*. 2008;**9**:2. DOI:10.1186/1743-7075-5-9
- [137] Hashimoto Y, Fukuda T, Oyabu C, Tanaka M, Asano M, Yamazaki M, Fukui M. Impact of low-carbohydrate diet on body composition: Meta-analysis of randomized controlled studies. *Obesity Review*. 2016;**17**(6):499-509. DOI: 10.1111/obr.12405
- [138] Shai I. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *New England Journal of Medicine*. 2008;**359**:229. DOI: 10.1056/NEJMoa0708681
- [139] Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: A systematic review and meta-analysis of intervention trials. *Nutrition, Metabolism & Cardiovascular Diseases*. 2014;**24**(9):929-939. DOI: 10.1016/j.numecd.2014.03.003
- [140] Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: A 1-year prospective randomized intervention study. *Diabetes, Obesity and Metabolism*. 2010;**12**:204-209
- [141] Georgoulis M, Kontogianni MD, Yiannakouris N. Mediterranean diet and diabetes: Prevention and treatment. *Nutrients*. 2014;**6**(4):1406-1423. DOI: 10.3390/nu 6041406
- [142] Mitrou PN, Kipnis V, Thiébaud AC, Reedy J, Subar AF, Wirfält E, Flood A, Mouw T, Hollenbeck AR, Leitzmann MF, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: Results from the NIH-AARP diet and health study. *Archives of Internal Medicine*. 2007;**167**:2461-2468. DOI: 10.1001/archinte. 167.22.2461
- [143] Sacks FM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *New England Journal of Medicine*. 2001;**344**:3-10. DOI: 10.1056/NEJM200101043440101
- [144] Liese AD, Bortsov A, Günther AL, et al. Association of DASH diet with cardiovascular risk factors in youth with diabetes mellitus the SEARCH for diabetes in youth study. *Circulation*. 2011;**123**(13):1410-1417. DOI: 10.1161/CIRCULATIONAHA110. 955922
- [145] Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: Main results of the PREMIER clinical trial. *Journal of the American Medical Association*. 2003;**289**:2083-2093
- [146] Ha SK. Dietary salt intake and hypertension. *Electrolytes & Blood Pressure: E & BP*. 2014;**12**(1):7-18. DOI: 10.5049/EBP.2014.12.1.7

