Cardiovascular disease risk reduction in diabetes through conventional and natural approaches

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Type 2 diabetes mellitus (DM) is a significant cause of premature complications and mortality in patients with cardiovascular disease (CVD). In addition to lifestyle modifications, conventional treatment of DM consists of oral hypoglycemic agents, insulin sensitizers, and subcutaneous insulin. In diabetic individuals with or at risk for CVD, aspirin and statin therapy reduce CVD morbidity and mortality. Several natural or herbal supplements have shown potential benefit in patients with CVD and DM. We provide an overview of the current guidelines for treatment of DM and CVD. We then review the literature to describe the efficacy of natural approaches to CVD risk reduction in diabetic patients, with a focus on physical activity, dietary modification, and natural/herbal supplements. Activity and diet improve cardiovascular outcomes in patients with CVD and DM.

Introduction

Diabetes mellitus (DM) affects more than 29 million individuals in the USA alone [1]. The predilection of diabetes to cause premature complications and mortality from cardiovascular disease (CVD) has long been appreciated, with CVD death rates ~1.7 times higher in adults diagnosed with DM [1,2]. Lifestyle modifications and conventional medications are the mainstay of treatment in diabetic patients with or at risk for CVD. Natural approaches to CVD risk reduction, including diet, exercise, and herbal supplements, have demonstrated promising results in diabetic patients (Table 1). Herein, we provide an overview of conventional treatments and review the literature supporting natural approaches to CVD risk reduction in DM. We focus on natural and herbal supplements which have shown promise in treating DM alone or the CVD complications of DM.

Complications of diabetes mellitus

DM is well-recognized as a potent risk factor for vascular injury, owing in part to its effect on oxidative stress [3,4]. Hyperglycemia-induced overproduction of superoxide dismutase by the mitochondrial electron-transport chain activates downstream deleterious pathways and results in production of free radicals, which leads to oxidative stress and systemic inflammation [5–8]. Persistent hyperglycemia also causes the formation of advanced glycation end products through nonenzymatic glycation, which further

Natural and herbal supplements have potential for benefit but require further research to determine their efficacy and safety. *Cardiovasc Endocrinol* 6:128–135 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Cardiovascular Endocrinology 2017, 6:128–135

Keywords: cardiovascular disease, diabetes mellitus, herbal supplements, natural products

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Received 27 March 2017 Accepted 4 September 2017

contributes to oxidative stress production [9,10]. The markers of oxidative stress most commonly associated with DM include superoxide dismutase, nitrogen dioxide, and peroxynitrite [11,12]. Oxidative stress and advanced glycation end products combine to activate the protein kinase C pathway [13]. Activation of protein kinase C is linked to cardiomyopathy, atherosclerosis, diabetic retinopathy, and diabetic nephropathy [13]. The polyol and hexosamine pathways are also associated with elevated levels of oxidative stress and contribute to vascular complications of DM [6]. Inflammatory biomarkers, such as high-sensitivity C-reactive protein and fibrinogen, reflect oxidative stress and have been shown to prospectively predict the risk of adverse cardiac events [14].

Table 1 Natural products and their proposed mechanisms of cardiovascular disease risk reduction in diabetes mellitus

Natural products	Proposed mechanism for cardiovascular disease risk reduction
Quercetin	Multifactorial; antioxidant, modulation of PPAR-α
Resveratrol	Multifactorial; antioxidant, anti-inflammatory
Bitter melon	Multifactorial; increased hepatic glucose consumption and decreased gluconeogenesis
<i>Panax ginseng</i>	Mediation of AMP-activated protein kinase pathway
Vitamin C	Antioxidant
Vitamin E	Antioxidant

PPAR-α, peroxisome proliferator-activated receptor-α.

The accumulation of vascular injury over time leads to the microvascular and macrovascular complications seen in DM. Microvascular complications include retinopathy, macular edema, neuropathy, and nephropathy [1]. The macrovascular complications of coronary artery disease, peripheral vascular disease, and cerebrovascular disease contribute to most mortality in DM [15]. Individuals with DM, once adjusted for population age differences, have a relative risk of 1.7 for cardiovascular death and 1.8 for hospitalization for myocardial infarction (MI), and are 1.5 times more likely to experience a stroke [1]. After acute MI, patients with DM have an 18-month mortality of 36.4% compared with 25.7% in the nondiabetic population [16]. In addition, many of the metabolic risk factors for atherosclerotic cardiovascular disease (ASCVD), including hypertension, dyslipidemia, and increased visceral adipose tissue, are comorbid in individuals with DM [17,18].

Guidelines for the treatment of diabetes mellitus

The ADA and American Heart Association (AHA) have issued a combined scientific statement for prevention of CVD in DM [19]. The cornerstone of current recommendations is therapeutic lifestyle management, including regular physical activity (PA), improved nutrition, and weight loss. Blood pressure targets of less than 140/90 mmHg should be achieved in all patients with DM; lower targets (i.e. <130 mmHg systolic) may be appropriate in select populations [19].

The current recommendation for blood glucose control is to treat to a glycated hemoglobin (HbA1c) of 7.0% primarily to reduce microvascular complications [20]. Despite an established association between hyperglycemia and CVD, intensive lowering of HbA1c has not been clearly shown to decrease the macrovascular complications of DM [21].

Conventional pharmacotherapy for diabetes mellitus

Since 1980, the prevalence of diabetes has remained stable or increased in all countries tracking these data [22]. Included in the first line of defense against vascular disease in DM patients is the control of blood glucose. For patients with type 2 DM, metformin remains the cornerstone of oral hypoglycemic therapy through its augmentation of hepatic insulin sensitivity. Dipeptidyl peptidase-4 inhibitors improve functioning of the pancreatic islet cells by preventing degradation of incretin hormones [23]. Insulin, in both its long-acting and short-acting forms, is utilized after failure of oral hypoglycemic therapy or in cases of severely uncontrolled DM. In addition to blood glucose management, several other medications are important for reducing CVD risk (Fig. 1).

Aspirin

Aspirin is the foundation for antiplatelet therapy, used for the primary and secondary prevention of coronary and cerebrovascular events. By acetylating cyclooxygenase-1's serine residue 529 in prehepatic circulation, aspirin prevents arachidonic acid from accessing and activating the cyclooxygenase-1 enzyme, which would otherwise activate thromboxane A₂-induced platelet aggregation [24,25]. Dosing of aspirin remains a topic of discussion. There has been no demonstrated additional benefit of high-dose (300–325 mg) as opposed to low-dose (75–100 mg) aspirin in the setting of MI, stroke, or overall cardiovascular mortality [26]. The ADA recommends primary prevention with aspirin intake of 75–162 mg for diabetic individuals with a 10-year ASCVD risk more than 10% who are not at increased risk for bleeding, whereas aspirin is not recommended if the 10-year ASCVD risk is less than 5% [27]. For 10-year ASCVD risk between 5 and 10%, the ADA recommends clinical judgment for aspirin initiation [27].

Statins

Statin therapy remains another cornerstone of therapy in the prevention of CVD in diabetics. These medications function through inhibition of 3-hydroxy-3-methyl-glutaryl coenzyme-A reductase. Statins have been associated with a statistically significant risk of new-onset diabetes [28–30]. Practitioners are asked to remain mindful of risk factors for diabetes when placing their patients on statins [31]. This risk is never meant to preclude treatment or provide contraindication to the initiation of statin therapy in a patient at significant risk for CVD. The ADA, with slight variants to the aforementioned criteria, cites trials demonstrating evidence of both primary [32,33] and secondary [34] prevention of CVD with statin therapy [35]. The ADA guidelines for statin use in the diabetic population are based on age and the presence of ASCVD or ASCVD risk factors [27]. All patients with established ASCVD, regardless of age, should be considered for treatment with a high-intensity statin [27].

Natural approaches for cardiovascular disease risk reduction in diabetes

Diet

The ADA published nutritional therapy recommendations for diabetic patients focusing on achieving glycemic control, as well as reducing CVD risk factors such as hypertension and dyslipidemia. The ADA recognized the challenges of creating a 'one-size-fits-all' dietary approach, as there is no ideal mix of macronutrients proven to meet the needs of all patients. Overall, the guidelines are intentionally broad to promote individualized nutritional therapy. The ADA recommends consuming minimally processed, nutrient-dense foods in appropriate portions. Carbohydrates – for example, should be derived from mostly vegetables, fruits, whole grains, and legumes. Dietary patterns should also include

Fig. 1

Conventional therapies for the prevention and treatment of cardiovascular risk in patients with diabetes mellitus. ASCVD, atherosclerotic cardiovascular disease; DPP-IV, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter 2.

more foods containing omega-3 fatty acids, such as fatty fish, which favorably affects lipoproteins and may prevent heart disease [36–38].

The AHA, in collaboration with the ADA, issued a 2015 Scientific Statement with nutritional guidelines for CVD risk reduction in diabetics. Dietary patterns such as DASH (Dietary Approaches to Stop Hypertension) and Mediterranean, which emphasize intake of fruits, vegetables, and low-fat dairy, have been shown to lower CVD risk factors [19]. The DASH diet can reduce low-density lipoprotein cholesterol by an average of 17.2 mg/dl, increase high-density lipoprotein (HDL) cholesterol by 4.3 mg/dl, and lower systolic and diastolic blood pressure by 13.6 and 9.5 mmHg, respectively [39]. The Mediterranean diet may also raise HDL and decrease triglyceride levels, but more importantly, was shown to lower the incidence of CVD by 30% in diabetic patients [40,41].

Other AHA/ADA recommendations include limiting alcohol consumption to moderate intake and substituting healthy fats (monounsaturated and polyunsaturated fatty acids) for saturated and trans fats [19]. The AHA uniquely recommends limiting sodium to less than 1500 mg/day, which differs from the ADA limit of 2300 mg/day [42]. Reducing caloric intake is also recommended for overweight patients to improve CVD risk factors; however, weight loss was not shown to reduce the incidence of cardiovascular events in a large 10-year trial [43].

Physical activity

Reduction in CVD incidence, death from CVD, and all-cause mortality is believed to be attainable in the diabetic population with regular PA [44,45]. A 2013 meta-analysis of 17 observational cohort studies involving diabetic

patients supported the existence of an inverse, dose-dependent relationship of all-cause mortality and CVD risk with increased PA [46]. The highest levels of PA were associated with a 40% reduction in all-cause mortality and 29% reduction in CVD, but any amount of PA resulted in risk reduction when compared with sedentary lifestyles [46]. Similarly, a meta-analysis by Sluik *et al.* [47] found that higher levels of walking, leisure-time PA, and total PA resulted in lower CVD and total mortality in patients with type 2 DM. The study deviated from most others in the presence of a slight J-shaped association between PA and mortality as opposed to the more frequently reported linear association, which warrants further investigation [47]. Although these data are promising and encourage the implementation of PA to affect cardiovascular complications in DM, randomized control trials (RCTs) supporting these results are needed as most of the existing evidence is from observational, cohort studies. Studies incorporating objective methods of assessing PA, as opposed to self-reporting by patients, would also be beneficial. Objective measures for exercise were used in a 2016 study by Lamb *et al.* [48] involving 308 recently diagnosed diabetic patients (mean age: 61 years, 66% male), and the study found that increasing exercise energy expenditure over 4 years resulted in greater reduction of clustered cardiometabolic risk, a precursor to CVD. In fact, a physically active lifestyle may eliminate the additional CVD risk in diabetic individuals relative to the nondiabetic population [49–51].

The spectrum of PA includes various forms of exercise, such as aerobic exercise (AE) and resistance training (RT). The type of exercise undertaken by a diabetic individual may affect health outcomes. Church *et al.* [52] randomized sedentary patients with DM to either an AE

only group, a RT only group, a combined AE and RT group, or a nonexercising control group. The study found that only the combined group experienced a significant reduction in HbA1c after completion of the 9-month exercise program [52]. The Diabetic Aerobic and Resistance Exercise trial found similar improvement in glycemic control with combined exercise as opposed to each exercise type alone after a 6-month exercise program [53].

A recent interest in the effects of high-intensity interval training (HIIT) on cardiovascular risk reduction has developed. HIIT involves very short spurts of high-intensity exercise intermingled with brief recovery periods. A randomized pilot study by Hollekim-Strand *et al.* [54] showed that HIIT was more effective than moderate intensity exercise in improving mean peak oxygen consumption, systolic function, and diastolic function in patients with DM. Cassidy *et al.* [55] found similar results with a 12-week HIIT program, noting improvement in cardiac structure in DM, namely left ventricular wall mass and systolic and diastolic function, which suggests that exercise intensity can improve diabetic cardiac dysfunction and lower cardiometabolic risk. Further research is needed to assess the long-term benefits of HIIT in relation to CVD-related complications.

Recommendations from leading health organizations emphasize the incorporation of exercise as routine health behavior for diabetic patients. The American College of Sports Medicine and the ADA released a joint position statement in 2010 asserting the decreased risk of all-cause and CV mortality provided by greater PA and fitness (American College of Sports Medicine evidence category C), recommending that people with diabetes engage in at least 150 min/week of moderate to vigorous AE without more than 2 consecutive days between aerobic sessions; moderate to vigorous RT 2–3 days/weekly should ideally be incorporated into the routine [56]. The AHA released similar guidelines in 2009, recommending 150 min/week of moderate intensity AE (class I, level of evidence A) or 90 min/week of vigorous intensity AE (class I, level of evidence A), in addition to encouraging RT 3 days/week (class I, level of evidence A) [57].

Natural/herbal supplements

Quercetin

Quercetin, a flavonoid found in many common dietary sources, including onions, kale, broccoli, grapes, and blueberries, has been shown to improve hyperglycemia in animal and human studies [58–60]. In addition to its hypoglycemic effects, quercetin may provide further benefits to patients with DM by reducing comorbid CVD risk factors.

A study of obese rats with DM evaluated the effects of high-dose (10 mg/kg/day) and low-dose (2 mg/kg/day)

quercetin supplementation on parameters of metabolic syndrome after 10 weeks [61]. Despite similar initial body weights and food intake throughout the study, rats receiving high-dose quercetin had a lower body weight at the end of the study compared with obese controls (504.8 vs. 535.1 g, respectively, $P < 0.05$) [61]. Lean rats receiving high-dose quercetin also experienced a reduction in final body weight compared with their lean control counterparts (411.0 vs. 437.0 g, respectively, $P < 0.05$) [61]. Low-dose quercetin was not associated with decreased final body weight in either the lean or obese rats [61]. However, the obese group receiving low-dose quercetin supplementation had significantly reduced total cholesterol (17.7%), triglycerides (29.5%), and free fatty acids (21.2%) compared with the obese controls ($P < 0.05$ for all parameters) [61]. The effects were mirrored in the obese, high-dose quercetin group (17.6, 33.3, and 24.6% reduction respectively, $P < 0.05$ for all parameters) [61]. There was no difference in the improvements between high-dose and low-dose groups [61]. High-dose quercetin was also shown to decrease triglycerides (24%, $P < 0.01$) and total cholesterol (18%, $P < 0.05$), while increasing HDL cholesterol (15%, $P < 0.05$), in mouse models of DM [59]. The effects of quercetin are multifactorial and likely driven primarily by antioxidant properties and modulation of peroxisome proliferator-activated receptor- α [59].

Quercetin must be used with caution owing to its inhibition of the cytochrome P450 system. In particular, its use in conjunction with tamsulosin may potentiate vasodilation and orthostatic symptoms [62]. Animal studies provide promising evidence that quercetin improves CVD risk factors; however, further human studies are required to prove its efficacy and safety.

Resveratrol

Resveratrol is a polyphenol found in several fruits and nuts that has demonstrated potential beneficial effects in DM and the prevention of CVD [63]. Interest in resveratrol supplementation has increased owing to its hyperglycemia-attenuating properties in animal models of DM [64,65]. Results of early human studies are promising but conflicting in their effect on parameters of blood glucose and insulin resistance [66–70].

An RCT evaluating the effect of adjunctive resveratrol supplementation in DM for 3 months, in addition to standard oral hypoglycemic therapy, found an improvement in HbA1c, as well as reductions in total cholesterol (-14.32 vs. $+6.90$, $P < 0.0001$), and systolic blood pressure (-11.78 vs. $+7.76$ mmHg, $P < 0.0001$) in the resveratrol group compared with the group receiving oral hypoglycemic therapy alone, respectively [68]. A similar, single-center RCT of 70 patients with DM demonstrated reduced systolic blood pressure and increased HDL cholesterol in patients receiving resveratrol supplementation [71]. Unfortunately, other clinical studies have

been less encouraging. A meta-analysis of seven studies found no change in lipid profiles with resveratrol [72]. Further investigation into the efficacy of resveratrol, especially with respect to diabetic patients, is needed.

Resveratrol may exert its CVD-risk-reducing effects through antioxidant and anti-inflammatory properties. In a triple-blinded, RCT evaluating the effect of resveratrol in primary prevention of CVD (43% with DM), the group receiving resveratrol had significantly reduced markers of inflammation, including high-sensitivity C-reactive protein, after 1 year [63]. Adverse effects of resveratrol supplementation have been rarely reported and include fever and cytopenia [73].

Bitter melon

Bitter melon (*Momordica charantia*) is a shrub native to Asia, Africa, and Australia that has been used in these regions as a folk medicine for many years. More recently, bitter melon has been studied as a treatment for DM, hypertension, and hyperlipidemia [74,75].

The protective effects of bitter melon on CVD risk factors have been noted in animal models. For example, bitter melon extract given to diabetic rats significantly lowered systolic blood pressure compared with control, but did not affect diastolic blood pressure. There was also a trend toward lower cholesterol and triacylglycerol in the rats given bitter melon, but the association did not reach statistical significance [76]. Human studies are sparse but have demonstrated similar findings. In one human RCT, diabetic patients receiving 4 g/day of bitter melon had a significant reduction in systolic blood pressure and triglycerides compared with baseline [77].

The antidiabetic and lipid-lowering effects of bitter melon are thought to act through several mechanisms. Extracts of bitter melon were shown to increase glucose consumption in the liver and decrease gluconeogenesis by enhancing insulin secretion and inhibiting fructose-1,6-bisphosphatase and glucose-6-phosphatase activity [78,79]. It may also lower cholesterol by increasing fecal excretion of neutral steroids [75]. The blood pressure-lowering effects of bitter melon are less understood, but may be mediated through adrenergic pathways [80].

Panax ginseng

Panax ginseng (PG), also called Asian or Korean ginseng, is a perennial herb native to Korea and China. The name Panax is derived from the Greek words pan (all) and akos (healing), which is a testament to its popularity in Asian medicine to treat illness and promote longevity. More recently, it has been identified as an alternative therapy for diabetes, hypercholesterolemia, and hypertension [81–84].

In an RCT of 19 patients with DM, PG supplementation as an adjunct to usual therapy demonstrated a 34% decrease in fasting plasma insulin [85]. In contrast, a

systematic review of four human trials found no anti-diabetic effects of PG [86]. The data are even less conclusive for the benefits of PG in lipid and blood pressure control. In one systematic review, five of nine studies on lipid control showed some improvement in one or more lipid parameters, including total cholesterol, triglycerides, and HDL. However, the trials were limited by size and design [87]. In another meta-analysis of 17 trials, there was no effect on blood pressure with PG use, but a trend toward improvement in systolic blood pressure in diabetic patients was noted [88].

The medicinal properties of PG are thought to be mediated by AMP-activated protein kinase. In mouse models, ginsenosides, the pharmacologically active component of PG, were shown to lower blood glucose and triglyceride levels and protect against hepatic steatosis [83,84,89]. However, human studies have shown mixed results with limited support of PG use for cardiovascular risk reduction. Larger, more standardized studies are still needed.

Antioxidants

Oxidative stress, through previously described mechanisms, is a potential target for therapy owing to its association with vascular disease and endothelial dysfunction. Two such antioxidants that are commonly available as supplements are vitamin C (ascorbic acid) and vitamin E (α -tocopherol). Observational studies have indicated potential benefit with increased antioxidant intake [90]. However, intervention trials to date have yielded mixed results [91]. Endothelial function, as measured by flow-mediated dilation, was shown to improve with vitamins C and E supplementation in a small, uncontrolled trial, though there was no improvement in postischemic forearm hyperemia, another validated measurement of endothelial function and vascular stiffness [92]. In a larger, randomized placebo-controlled trial, there was no improvement seen in flow-mediated dilation with the combination of vitamins C and E [93]. Vitamins C and E individually have also shown similar mixed results [94,95]. In addition, high-dose vitamin E supplementation may increase all-cause mortality [96]. To date, the safety and efficacy of vitamins C and E supplementation remains to be established and should be avoided in the general population.

Conclusion

Diabetic patients are at substantially increased risk for CVD complications compared with their nondiabetic counterparts. In addition to therapy with conventional medications, several natural approaches have demonstrated efficacy in reducing CVD in DM. Lifestyle modification, which encompasses diet and PA, remains the mainstay of therapy. Several natural products have demonstrated potential favorable effects in DM, but no RCTs have shown definitive outcome benefits for

reducing CVD events. Additional high-quality research is required to better characterize the beneficial and adverse effects of these supplements.

Acknowledgements

Dr Sandesara is supported by the Abraham J. and Phyllis Katz Foundation (Atlanta, GA, USA).

Conflicts of interest

There are no conflicts of interest.

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