METABOLISM (CJ BILLINGTON, SECTION EDITOR)

Dietary Patterns and Cardiovascular Disease Risk in People with Type 2 Diabetes

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Abstract

Purpose of Review The primary objective of this review is to identify dietary patterns with beneficial effects on cardiovascular health of adults with type 2 diabetes.

Recent Findings The prevalence of diabetes is increasing globally. People with diabetes have a greater risk for cardio-vascular disease. Mediterranean diet, dietary approaches to stop hypertension diet, vegetarian diet, traditional Korean diet, Japanese diet, and low-glycemic-index diet can reduce cardio-vascular disease risk in people with diabetes.

Summary Dietary intake is a key modifiable factor in the management of diabetes and plays a significant role in limiting the incidence of cardiovascular diseases.

Keywords Type 2 diabetes · Cardiovascular disease · Dietary pattern · Cardiovascular risk factors · Mediterranean diet · Low

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GI diet \cdot Traditional Korean diet \cdot Vegetarian diet \cdot Japanese diet \cdot DASH diet

Introduction

Over 70% of deaths occurring globally in 2015 were attributed to non-communicable diseases (NCDs), of which cardiovascular disease (CVD) accounted for 45% and type 2 diabetes (T2D) for 4% [1]. CVD and diabetes represent substantial economic burdens, with a projected global cost of US\$1044 billion and US\$745 billion, respectively, by 2030 [2]. Further, the global prevalence of T2D has risen from 4.7 to 8.5% in the last two decades [3], a rise that has been accompanied by an increase in four major risk factors: poor diet, physical inactivity, and tobacco and alcohol use, which represent the hallmark of NCDs [1].

T2D is a chronic metabolic condition characterized by the presence of high blood sugar, insulin resistance, and relative insufficiency of insulin secretion by the pancreas [4]. It accounts for 90% of people with diabetes and most often occurs in adults and elderly, but recently, its prevalence has increased in younger people. Medical nutrition therapy and lifestyle changes with or without anti-hyperglycemic medical treatment are essential for effective management of T2D. Poor control of T2D is associated with increased risk for premature mortality and comorbidities including heart attack, stroke, kidney failure, blindness, non-traumatic limb amputation, and depression [5].

As the prevalence of T2D has risen, the proportion of CVD attributable to diabetes has also increased in the last 50 years [6]. People with T2D have twofold excess risk for a wide range of vascular diseases [7]. The pathophysiology of CVD and T2D is complex and multifactorial, physically affecting macro- and microvasculatures as well as different cellular and



molecular mechanisms in the human body [8]. A crucial part of diabetes care and CVD prevention involves the adoption of ideal health behaviors (non-smoking, healthy weight, healthy diet, physical activity) and ideal health factors (blood pressure, cholesterol, and blood glucose); from these, cardiovascular health status can be designated as poor, intermediate, or ideal in the general population [9].

The American Heart Association's "healthy diet" definition focuses on whole foods and dietary patterns rather than specific nutrients [9]. These recommendations parallel the most recent 2015 Dietary Guidelines for Americans, with the primary focus on moving from single nutrient recommendations toward beneficial dietary patterns [10•]. This shift in focus requires healthcare professionals and researchers to reorient their practices and research objectives. Therefore, the primary objective of this review is to discuss and integrate current knowledge on dietary patterns and their potential health outcomes for minimizing CVD risk of adults with T2D. The review is organized by the features of pathophysiology of CVD manifestation including (i) macrovasculature, (ii) microvasculature, (iii) inflammation and oxidative stress, (iv) hypercoagulation, and (v) heart failure [8], which impact individuals' cardiovascular health and in turn affect their quality of life. The benefits of dietary patterns and their impact on these disease mechanisms are addressed in this review. Patterns that focus on macronutrients rather than foods, e.g., low carbohydrate diets, are not included.

Methods

We searched MEDLINE and PubMed databases for prospective cohort studies, randomized controlled trials (RCTs), and systematic reviews using the following keywords: "diabetes mellitus, type 2, T2D or non-insulin dependent diabetes or NIDDM," "cardiovascular disease*," diet, "diet therp*" or "diet modification*" or "dietary patterns" or nutrition. Human studies in the English language, published between 2012 and June 2017, describing dietary patterns, and comparing various interventions were included. Primary outcomes included cardiovascular risk factors in adults (\geq 18 years) with T2D. The results from the studies extracted were heterogeneous in terms of the dietary interventions, length of followup, participant demographics, data collection, and data reporting. Hence, a narrative review approach was adopted in drafting this manuscript.

Focus Shift from Single Nutrients to Dietary Patterns

The 2015–2020 Dietary Guidelines for Americans focuses on describing the common characteristics of healthy diet patterns [10•]. Even though the new approach sounds "simplistic" or

"logical," almost a century of scientific research had to evolve. The first link of a disease with a specific dietary nutrient deficiency was observed in 1747 by Captain James Lind [11]. Preventing deficiencies was the focus of recommendations until the 1980s [12], when a shift occurred to include avoidance of single-nutrient overconsumption (fat, saturated fat, cholesterol, sugar, sodium), due to possible links to chronic diseases in specific CVD and T2D [12]. These recommendations led to decreased consumption of fat intake; however, a dramatic growth in the prevalence of obesity, CVD, and T2D was concurrently observed [13]. Recent evidence establishes that metabolic health is less influenced by single nutrients and more by intake of specific foods and overall dietary patterns, which have synergistic effects [14]. The amount of fat or carbohydrate consumed is now regarded as less important than the type of fat or carbohydrate [15]. This transition has galvanized the study of different dietary patterns and their effects on cardiovascular health in people with T2D as summarized in Table 1. It is generally accepted that dietary patterns have a strong impact on specific cardiovascular risk factors. Evidence from the general population indicates that the intake of a typical "westernized diet," which includes consuming red and processed meat, sugar-sweetened foods and drinks, and fried foods, is generally associated with insulin resistance, hyperlipidemia, and pro-inflammatory state thus increasing T2D and CVD risks, while intake of a prudent diet characterized by intake of vegetables, fruits, whole grains, fish, and low-fat dairy products is associated with a reduced risk from all-cause mortality and CVD [35•].

Dietary Patterns that Protect the Macrovasculature

In general, patients with T2D and CVD have an impaired lipid profile or dyslipidemia [8]. Small, dense LDL cholesterol (LDL-C) is highly susceptible to oxidation and glycation resulting in increased atherogenic properties [36]. T2D individuals present decreased levels of HDL-C contributing to the development of atherosclerosis [37], given that HDL plays a main function in reverse cholesterol transport or cholesterol efflux [38], crucial for protection from atherosclerosis [39]. Thus, a therapeutic goal is to create a healthier balance of LDL- and HDL-C in people with T2D in order to prevent CVD complications. The Korean traditional diet (KTD), traditional Mediterranean diet (TMD), dietary approaches to stop hypertension (DASH) diet, and low-glycemic-index (GI) diet were identified as providing macrovascular benefits. Vegetarian diets were also protective against certain CVD although the number of T2D patients studied is small (Table 1).

Consumption of a KTD for 12 weeks in older adults with T2D improved including anthropometric parameters and total serum cholesterol, LDL-C, triglyceride (TG), and glycated hemoglobin (HbA1c) in addition to lowering the heart rate

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Low GI diet [27, Includes foods high in dietary fiber such meat Improved HDL and TG Insufficient evidence Insufficient evidence Insufficient evidence Insufficient evidence 28] as whole grains, vegetables, fruit, and team meat In DL and TG Insufficient evidence	DASH diet [21, 22•, 23–26]	Includes low intake of total fat, sweets, added sugars, sugar-containing beverages, and sodium and a high intake of fruits and vegetables, whole grains, fish, poultry, nuts, and fat-free or low-fat dairy foods	Reduction in body weight, waist circumference, fasting blood glucose, HbA1C, and LDL-C and improvement in insulin resistance and	Insufficient evidence	Reduction in inflammatory markers (CRP), oxidative stress. Improvements in total antioxidant capacity and total	Decrease in fibrinogen	Reduction in systolic and diastolic blood pressures
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	Vegetarian diet [30, 31, 32•, 33, 34]	Improves glycernic control, abdominal obesity, hypertension, and metabolic syndrome. Lower risks of mortality from ischemic heart disease, cardiovascular disease, and cerebrovascular disease	Improves endothelial function	Improvement in inflammatory markers	Insufficient evidence	Improvements in blood viscosity, erythrocyte sedimentation rate, and fibrinogen and hematocrit levels. Improvement in plasmin-dependent fibrinolytic pathway	Insufficient evidence

and diastolic blood pressure (DBP), all of which reduce the risk of atherosclerosis [29•]. The KTD pattern is based on steam-cooked rice and soups, vegetables, fish or meat, sesame oil, soy sauce, and fermented plant products. It excludes bread and dairy products but does not restrict caloric or sodium intake [29•]. Participants on KTD dramatically increased their fiber consumption by ~ 22 g/day, which might explain the improvement in their lipid profile [29•], because similar effects were seen in other high-fiber diet patterns, such as a study reporting improved glycemic control, abdominal obesity, hypertension, metabolic syndrome, and inflammatory markers in Japanese T2D patients [27] or improved endothelial function in T2D patients on an 8-week high-fiber brown rice diet [40]. Observational studies concur that consumption of high-fiber whole grain diets reduces CVD risk [41], and a meta-analysis of prospective studies evaluating the association between dietary fiber and diabetes risk found an inverse association, with a 6% reduced risk for every 2 g/day increase in fiber intake [42]. There is a growing appreciation that the modulation of the gut microbiota by fiber plays a role in its beneficial effects on CVD risk [43•].

The improvement in HbA1c levels shown after following a KTD was not found with other dietary patterns discussed above [40, 44]. A unique aspect of the KTD is the high amount of fermented food consumed. Fermented soy products are high in isoflavones that impact hepatic glucose and lipid metabolism to reduce blood glucose and HbA1c levels [45]. Fermented chili, for example, is rich in capsaicin, flavonoids, and other bioactive compounds and is reported to be an appetite suppressant leading to a decrease in TG, visceral adiposity, and apolipoprotein B levels [46•]. The combined benefits of fiber and isoflavones point to the synergistic effects of constituents of the dietary pattern.

A more well-known, well-balanced dietary pattern is the TMD, characterized in part for its high fiber content. Adherents to the TMD consume olive oil (main lipid source), fruits and vegetables (F&V), legumes, and fish and poultry but have lower consumption of red or processed meat, butter, fast food, sweets, pastries, and sugar-sweetened beverages [47]. Trials of the TMD reported an overall improvement in cardiovascular risk factors including lipid profile and waist-hip ratio [16•]. Furthermore, the TMD not only increased HDL-C concentrations but also improved several HDL-C functions including cholesterol efflux capacity [48••], a more clinically relevant measurement than the HDL-C concentration [49]. Additional benefits of the TMD relative to other CVD endpoints are discussed further below.

The DASH diet was originally designed to help people with hypertension. However, $\sim 50\%$ of people with T2D suffer from hypertension, which contributes to both macrovascular and microvascular damages; hence, the DASH diet is suitable for effective diabetes management [4]. The DASH diet includes low intake of total fat, sweets, added

sugars, sugar-containing beverages, and sodium and high intake of F&V, whole grains, fish, poultry, nuts, and fat-free or low-fat dairy foods. In an 8-week RCT of T2D adults with hypertension, following the DASH diet was associated with significant reduction in body weight, waist circumference, fasting blood glucose, HbA1C, and LDL-C and an increase in HDL-C [21] consistent with earlier literature [22•, 23, 50–52].

Additional dietary patterns have also been beneficially associated with CVD health outcomes in people with T2D. In a meta-analysis of RCTs (> 6-month duration) conducted in T2D adults, low-GI diets improved HDL-C and HbA1c levels in comparison to control diets (various high-fiber cereal diets, the American Diabetes Association (ADA) diet, and lowcarbohydrate diet) [53]. Although the beneficial effects of vegetarian diets in people with T2D per se have not been examined recently, a meta-analysis of 11 studies of which 2 included T2D patients found not only significant lowering of total cholesterol and LDL-C but also reduced HDL-C compared with omnivorous diets [30]. A review of prospective cohort studies not focused on people with T2D reported that in comparison to non-vegetarians, vegetarians had 26-68% lower risk of mortality from ischemic heart, cardiovascular, and cerebrovascular diseases, along with lower incident hypertension and T2D [31]. A recent systematic review and meta-analysis of ~ 90 cross-sectional and prospective studies reported that vegetarian and vegan diets, in comparison to omnivorous diets, significantly reduced BMI, total cholesterol, LDL-C, and glucose levels. Vegetarian diets also offered protection against incident and/or ischemic heart disease mortality; however, there was no significant difference in total cardiovascular and cerebrovascular diseases [32•]. Higher intake of total/soluble fiber, nuts, soy, plant sterols, and lower levels of saturated fat as observed in vegetarian diets could exert a beneficial effect on the lipid profile [33].

Dietary Patterns that Protect the Microvasculature

Nephropathy, retinopathy, and neuropathy encompass the more common microvascular complications in T2D [54]. Damage to the small vessels results from a hyperconstricted state as a consequence of decreased bioavailability of nitric oxide (NO) and increased secretion of endothelin-1 [54]. Further, chronic hyperglycemia promotes membrane thickening [55] resulting in impaired selective transport and increased permeability of large molecules resulting in endothelial dysfunction [56].

The PREDIMED study, a nutritional intervention based on the TMD, with daily supplementation of extra virgin olive oil (EVOO) or nuts and a frequent use of "sofrito" sauce for the dressing of dishes, reported a 43% relative risk reduction for retinopathy in those supplemented with EVOO and high adherence to the TMD compared to the lowest adherence after a 6-year follow-up [17•]. These benefits were attributed to the bioactive compounds and nutrients found in EVOO [17•]. While the anti-inflammatory, anti-atherogenic, and hypoglycemic properties of EVOO have been well-documented [57], its benefits to the microvasculature are not fully understood. However, since a chronic hyperglycemic state results in excessive reactive oxygen species (ROS) production, which are implicated in microvascular comorbidities [58], the TMD and EVOO may decrease ROS [17•]. Future research to understand the effects of dietary patterns/macronutrient composition on ROS, NO bioavailability, and impaired microvascular permeability is warranted, as are studies of other dietary patterns examining microvascular endpoints.

Dietary Patterns that Reduce Inflammation and Oxidative Stress

During the progression of diabetes and cardio-metabolic comorbidities, increased oxidative stress and inflammation have been consistently reported [8, 58–60]. The chronic hyperglycemic state characteristic of T2D involves the activation of the immune system via production of pro-inflammatory cytokines [61]. This long-term, chronic inflammation exacerbates vascular injury and promotes mitochondrial production of ROS [60] culminating in cardiac tissue damage [59].

The effects of the TMD on inflammation and oxidative stress were investigated in the ATTICA cohort study in a 10-year follow-up [62•]. The authors observed improvements in biomarkers of oxidative stress, inflammation, and coagulation, concluding that high adherence to the TMD decreased oxidative stress and subclinical inflammation with resultant 60% decrease in diabetes risk, whereas a medium level of adherence reduced the risk by 50% [62•]. The greatest benefit was observed in individuals who shifted from low to medium adherence, particularly in those with greater waist circumference [62•].

Other dietary patterns also have anti-inflammatory properties. Increasing F&V intake enhanced the antioxidant capacity in subjects with T2D after an 8-week intervention [63]. Blood carotenoid levels were associated with enhanced antioxidant properties of HDL-C, consequently boosting its antiatherogenic properties [63]. The DASH diet likewise reduced inflammation and oxidative stress in people with T2D as evidenced by significant reduction in C-reactive protein (CRP), fibrinogen, and liver enzymes in T2D adults after 8 weeks [24]. In a RCT of pregnant women (24–28-week gestation) with gestational diabetes, intake of DASH diet for 4 weeks improved fasting plasma glucose and insulin, HOMA-IR, total antioxidant capacity, and total glutathione levels in comparison with the control diet; however, no significant differences in CRP levels were observed [25].

Dietary Patterns that Reduce Hypercoagulability

Heart attack and stroke as results of clots are leading causes of mortality in people with T2D [64]. Hyperglycemia and insulin resistance lead to increased levels of thrombin generation by the platelets, IL-6 expression inducing hepatocyte production of fibrinogen, and tissue factor expression resulting in hypercoagulation [64]. Several anti-thrombotic drugs aimed at different coagulation and platelet activation targets moderate these problems [65], but they can also be managed through diet [34, 66•, 67]. At present, few studies have examined the relationship between dietary patterns per se and prothrombotic parameters in overt T2D. Supplementation of 300 g of F&V with no other changes to usual dietary intake for 8 weeks was associated with improved blood viscosity, erythrocyte sedimentation rate, and fibrinogen and hematocrit levels in adults with T2D [68]. Similar improvements in plasmin-dependent fibrinolytic pathway were reported in a 3-week controlled feeding trial of low-fat and high-complexcarbohydrate diet (35-45-g dietary fiber per 1000 kcal, with the majority of protein derived from plant sources) with significant reductions in plasminogen, tissue plasminogen activator, plasminogen activator inhibitor, and lipid and lipoprotein profiles [69]. Further, in an 8-year follow-up study of T2D adults with no previous coronary heart disease history, higher intake of F&V and total dietary fiber was associated with a significantly lower risk of stroke [70].

Dietary Patterns Associated with Reduced Heart Failure

Even though the prevalence of T2D has risen during the past two decades, cardiovascular and cardiac deaths have declined in diabetic patients [71] as a result of advances in medication [72] and healthcare systems' efficacy of diabetes care [73]. The general features of diabetes physiopathology such as impaired glucose tolerance, dyslipidemia, elevated inflammation, and oxidative stress increase the risk of left ventricular hypertrophy, myocardial fibrosis, and diastolic/systolic dysfunction associated with diabetic cardiomyopathy (DCM) [74], which is the final pathway of heart failure. Diabetic patients with ischemic heart diseases or hypertension are at higher risk of DCM [75]. Hence, in order to improve heart failure outcomes, it is recommend that people with diabetes achieve and maintain blood pressure of < 130/80 mm Hg [4, 76].

An 8-week RCT of DASH diet was sufficient to lower systolic and diastolic blood pressures [21], while DASH diet plus physical activity also showed effective blood pressure reduction [77]. Interestingly, the consumption of F&V typical of the DASH diet was associated with reduced blood pressure in patients with T2D, possibly playing a protective role in part

through the increased intake of vitamin K [26] because insufficient levels of vitamin K are associated with increased vascular calcification [78]. The KTD for 12 weeks also reduced heart rate and DBP [29•]. Further, results from the PREDIMED study indicate that 1 year of following the TMD (TMD + EVOO or TMD + nuts) in comparison to a low-fat diet decreased both a biomarker of heart failure and oxidized low-density lipoprotein in patients with increased CVD risk [18].

Discussion

This review presents the cardiovascular pathogenesis associated with T2D and provides evidence that balanced dietary patterns can be effective in managing T2D and limiting the risk of cardiovascular comorbidities. Balanced dietary patterns, which include adequate amount of a variety of foods to provide the macro- and micronutrients to meet an individual's daily nutrient requirements, are essential for proper functioning of the body and overall health [79]. For example, diets such as the TMD and DASH diets are protective against chronic diseases including T2D and cardiovascular diseases [19, 51, 80]. Several mechanisms come together to explain these benefits: whole grains and F&V are sources of dietary fiber beneficial in improving hyperglycemia and dyslipidemia and hematological parameters including hypercoagulability, thus supporting optimal macrovascular health [70]. Further, these foods are rich sources of micronutrients including vitamins, minerals, and phytochemicals, all of which regulate metabolic, anti-inflammatory, and antioxidant pathways to improve microvascular status. A recent prospective cohort study from several countries, with a median follow-up of 7.4 years, reported that lower risk of major CVD can be attained even with a relatively moderate consumption of 375-500 g/day (three to four servings) of fruit, vegetables, and legumes [81]. Similarly, these positive health outcomes are reported in individuals who consume vegetarian diets, which limit or exclude foods of animal origin [30]. Careful planning and a varied plant-based diet with supplementation of limiting micronutrients such as homocysteine, folate, and calcium [33] make vegetarian diets suitable for management of CVD risks in T2D. Very few studies have examined the effects of low-GI diet in reducing cardiovascular complications in T2D per se, although there is extensive evidence indicating its effectiveness in weight and blood pressure management in the general population [28]. Given that low-GI foods tend to fall into the categories of F&V, whole grains, and legumes, it can be anticipated that following such diet will have CVD risk benefits for people with T2D.

Recent studies focusing on traditional dietary practices such as KTD have shown improved cardiovascular benefits in people with T2D. These diets promote traditional, local foods and ingredients with an emphasis on grains, vegetables, seafood, and fermented plant-based products. The fiber, probiotics, and phytochemicals found in these foods plausibly explain their cardio-protective effects. It should be also noted that the TMD and vegetarian diets are also rooted in traditional practices. Newer evidence supports beneficial effects of other local dietary practices, such as the traditional Japanese diet; people from Japan are known to have long and high expectancy (89 years) [82], and this can be attributed to their dietary and lifestyle practices. A traditional Japanese diet (JD) is high in grains and vegetables (including seaweeds), with moderate amounts of fish and soy but minimal dairy and fruit intakes. Green tea and fermented soy products are also staples of the diet [83]. A prospective cohort study with a 15-year follow-up period indicated that adherence to Japanese dietary guidelines was associated with a lower risk of total mortality, mortality from cardiovascular disease, and cerebrovascular disease [83].

One commonality in the diets presented in this review is a complex dietary pattern including a variety of foods with a large focus on plant-based products such as whole grains, F&V, legumes (TMD, DASH, VD, GI), seafood, and/or poultry (TMD, DASH, KTD, JD, GI). Further, a newer conceptual framework termed "cooking behavior" which includes cooking frequency (frequency of cooking at home versus restaurant eating or takeout); techniques and methods of cooking impacting the nutritional quality of food (e.g., low-fat cooking methods, avoiding high-temperature cooking and heavy browning of food); minimal usage of added sugars, sweeteners, animal fats, processed foods, and red meat; and flavoring of foods (use of herbs and spices and avoiding salt) may play an important role in improving dietary intake and prevention of chronic disease risk such as CVD and obesity [84]. Many of the characteristics discussed above are a cultural norm of the diets reviewed in this paper (TMD, KTD, JD). Additionally, in these diets, the major source of fat is plant- or seafood-based, providing essential fatty acids, poly-/monounsaturated fatty acids, which demonstrate anti-atherogenic properties and other health benefits [20, 85, 86]. Liu et al. (2017) presented evidence that rather than total fat, it is far more important to consider the overall dietary patterns and type of foods (particularly carbohydrate and fat) consumed, for improving cardiovascular health [87•]. However, public confusion of dietary recommendations particularly regarding fats remains problematic [88]. The 2015 Dietary Guidelines Advisory Committee led the shift toward moving from single nutrients to focusing on dietary patterns and types of foods [10•], with the potential benefit of reducing confusion and misperceptions of what a healthy dietary pattern should include.

The diets described in this review will also have the effect of increasing nutrient density while lowering caloric density achieved by moderate intake of dairy, lean protein lower in saturated fats, and restriction of processed meats and added sugars. A recent study reported people who experienced a long-term change to a higher-quality diet reduced their risk of death from any cause over 12 years regardless of the approach taken (risk reduction 14% by alternate healthy eating index score, 11% by alternate Mediterranean diet score, and 9% by DASH score) [89••] providing evidence to support the shift from focusing on single nutrients/diets to healthy eating patterns since these diets, even though different, constitute balanced patterns and incorporate cooking methods associated with healthy eating patterns [17•, 26, 29•, 32•, 68, 83, 90]. Furthermore, associations between dietary environment factors (portion size and increased availability) [91, 92], as well as increased dietary variability, might also play an important role as risk factors for obesity [93]. Thus, the role of nutrition in T2D and CVD risks goes beyond the collection of nutrients ingested and include many personal and environmental factors that need to be taken into consideration, both in research and in practice.

Conclusion

Based on the review of diets presented here (Mediterranean diet, DASH diet, Vegetarian diet, traditional Korean diet, Japanese diet, low-glycemic-index diet), there is a range of dietary options available to people with T2D to manage CVD risk. However, considering the overall set of scientific evidence is necessary when making cardiovascular health recommendations since adherence to dietary practices is highly individualistic and influenced by various social and environmental factors. Future interventions to educate and build skills in patients and healthcare professionals can help them make informed choices to meet individual needs.

Compliance with Ethics Guidelines

Conflict of Interest *M. Carolina* Archundia Herrera, Fatheema B. Subhan, and Catherine B. Chan declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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