REVIEW

Food of the Gods: The Role of Chocolate in Cardiovascular Health

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ABSTRACT

The benefits of chocolate in cardiovascular health have long been considered since an observational study in Panama found that an indigenous people who drank salt–enriched cocoa daily suffered fewer age–related increases in blood pressure. Since then, epidemiological studies have reported a decrease in certain cardiometabolic disorders in individuals who consume moderate amounts of cocoa. The compounds responsible for the benefits of cocoa are thought to be flavonoid epicatechin monomers, which exert both an antioxidant effect as well as lead to upregulation of nitric oxide (NO) to promote vasodilation. Animal studies have also shown that cardiovascular disease (CVD) progression is significantly reduced with cocoa consumption. Although many of these studies possess limitations, including small sample sizes and incomplete blinding, the data nevertheless suggest that cocoa consumption can reduce the risk of certain cardiometabolic disorders.

KEYWORDS: *flavanoids, cardiovascular health, chocolate, cocoa benefits, preventative health*

INTRODUCTION

Chocolate has been considered a sinful pleasure for centuries. The Latin name for the cocoa tree, the seeds of which are refined into chocolate, is Theobroma cacao, which can be translated into "food of the gods." A study on the Kuna Indians in Panama, who traditionally drink several cups of salt–enriched cocoa daily, first ignited interest in the health benefits of cocoa, as it was observed that this population had reduced age–related hypertension and vascular problems.[1] Furthermore, such a reduction was not observed in those Kuna Indians who had relocated to urban centers and no longer consumed cocoa to the same degree as their rural counterparts.[1] Since then, a number of studies have published associations between chocolate consumption and positive cardiovascular outcomes.[2,3] Furthermore, other studies have demonstrated that certain compounds in chocolate have antioxidant properties,[4-6] and promote vasodilation.[7-11] Several of these studies have low Jaddad method scores, which are scores allocated based on a series of criteria that critique the rigorousness of clinical trial methods.[12] Notably, other trials with higher Jaddad scores have found no change in vascular markers with increased cocoa consumption.[13,14] Given these inconsistencies, an evaluation of the literature on cocoa is necessary to determine whether epidemiological, clinical, and in vitro studies provide sufficient evidence that cocoa is beneficial for cardiovascular health.

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EPIDEMIOLOGICAL EVIDENCE

The initial observational study on the Kuna evaluated their diet, genetics, and physiology, concluding that cocoa was the largest factor accounting for their reduced risk of developing hypertension.[1] Several other epidemiological studies have since been conducted on various sociological factors. The Zutphen Elderly Study followed 470 male seniors who were free of chronic diseases for a period of 15 years at baseline. Their vital signs were monitored every five years and any cardiovascular events that occurred during this period were recorded. Cross–sectional analysis demonstrated that individuals who reported higher cocoa consumption had a 50 % reduction in mortality from cardiovascular events and a lower mean blood pressure compared to senior men who reported no chocolate consumption.[2] This result held even after adjustments were made for possible confounding factors, yet medications were not accounted for in this study.

Another study followed patients after their first myocardial infarction and examined their vital signs three months after hospital discharge, comparing populations who consumed chocolate over the past year with those who did not. A significant decrease in cardiac mortality with increasing chocolate consumption was found.[10] Two other prospective observational studies that followed post–menopausal women for eight[15] and 16[16] years performed similar analyses. One of these studies found that diets rich in flavonoids, a naturally–derived polyphenolic compound found in cocoa beans and many other flora including coffee beans and grapes, led to a reduced cardiovascular mortality in post–menopausal women.[16] Interestingly, the other study found that the incidence of heart failure requiring hospitalization was only

decreased in women who consumed chocolate in moderation; women who reported consuming more than one serving per day showed similar results to those who did not consume chocolate at all.[15] Recently, another meta–analysis focused on the effects of chocolate on general cardiometabolic disease incidence. The authors pooled data from seven cohort studies, concluding that higher levels of chocolate consumption reduced the overall risk of CVD by 37 % when compared to the lowest consumption level reported.[17] Likewise, the risk of diabetes was reduced by 31 % and stroke by 29 %, although no association was found for heart failure.[17] This study had a sufficiently large sample size to calculate a percentage risk reduction for CVD development, making it a review of great importance and providing the most concrete evidence for the benefits of chocolate on the reduction of cardiometabolic disorders.

IN VITRO STUDIES AND MECHANISM OF ACTION

It is generally accepted that diets high in polyphenols reduce the risk of CVD, and cocoa seeds contain high levels of flavonoids at about 6-8 % of dry weight per bean.[18] However, the amount of flavonoids in a cocoa bean depend on the level of processing, the time of harvest, and the growing location.[19] In general, the greater the percentage of cocoa in chocolate, the more flavonoids it contains and the more pronounced the cardiovascular effects were. Spectrographs have shown that all flavonoids share a common C6-C3-C6 linkage in their structures,[19] and the type of polyphenols contained in cocoa are mainly (+)catechin and (-)epicatechin monomers.[5] Additionally, there is a dose–dependent relationship between flavonoid ingestion and plasma concentration of epicatechins/catechins. Epicatechin is the most readily absorbed flavonol and is the most abundant in human plasma following cocoa ingestion.[20] Flavonoids are antioxidants that bind to low–density lipoprotein (LDL) and other molecules in plasma to prevent their oxidation into free radicals.[5] These epicatechins/catechins also upregulate the expression of proteins that synthesize NO (known as endothelial nitric oxide synthase, or eNOS), as well as inhibit NAPH oxidase in endothelial cells, further reducing LDL oxidation.[19] The common system for dealing with free radicals in the cardiovascular system is complex, but it involves binding of NO to LDL. Therefore, if there is a high level of either LDL or free radicals, the circulating concentration of NO will be decreased and less will be available to exert other protective physiological functions including vasodilation, decreasing smooth muscle proliferation, and inhibiting leukocyte and platelet adhesion.[18,19] Dysfunction in some or all of these vascular factors promotes the development of cardiometabolic disorders such as atherosclerosis.

ANIMAL STUDIES

The evidence supporting a mechanism of action for cocoa is somewhat unique. While proof for the biological effects of other compounds, such as cinnamon, come from in vitro evidence that is supported (or refuted) by clinical data, with cocoa it is in vivo tests measuring physiological responses to cocoa flavonoids that provide most of the evidence for its biological effects. There are not many animal studies, however one small experiment provided a dose–response relationship for cocoa in five rats, finding epicatechin to be highest in plasma 30-60 minutes after ingestion, which correlated with a lag time in LDL oxidation.[4] Another study used hypercholesterolemic rabbits that lack LDL receptors and, being unable to process fats, are predisposed to developing atherosclerosis.[6] Fifteen rabbits were split into cocoa and control groups. The cocoa groups were fed cocoa liquor extracts and were observed to have significantly reduced numbers of foam cells in vessel walls, reduced platelet numbers, and reduced inflammatory mediators in the blood.[6] A second study done in healthy hamsters also found a reduction in these factors, which are considered atherosclerotic precursors.[22] This data supports the notion that compounds in cocoa promote vascular integrity, possibly through vasodilatory and anti–inflammatory properties, reducing the tendency towards vascular injury and atherosclerosis. A recent study noted a decrease in blood pressure and a potential decrease in angiotensin II, a mediator of hypertension, in 20 healthy rats fed an extract made from polyphenol–rich cocoa seed husks.[24] Overall, these studies provide evidence that cocoa may prevent vascular inflammation, and that NO upregulation may be the mechanism by which this effect is mediated.

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HUMAN CLINICAL TRIALS

In general, subjects for clinical trials were selected based on specific pre–determined criteria, randomized into control or cocoa groups, and followed the guided dose regimen for the duration of the experiment. One of the earliest studies found a significant decrease in systolic blood pressure in the cocoa group compared to the control group in 11 patients recently diagnosed with early–stage hypertension.[25] Decreases in blood pressure with cocoa consumption were also found in patients with essential hypertension[9] and in healthy subjects.[26] Early reviews summarized this literature[11,20,22] and two meta–analyses[27,28] pooled the results and concluded that a reduction in blood pressure and an increase in vasodilation are general effects of cocoa consumption. An improvement in insulin sensitivity in glucose–intolerant subjects was observed in two separate studies,[3,9] and a later meta–analysis showed that increased chocolate consumption was associated with decreased diabetes incidence.[17] Two other studies found no change in blood pressure, insulin sensitivity,[14] or levels of coronary artery disease (CAD) biomarkers.[11] These two studies were of high methodological quality based on Jaddad scores,[12] and one of them tested for the placebo effect. On the other hand, these studies used doses of cocoa extract that were

much higher than average consumption and could have been too high to show a physiologically relevant effect. Previous studies showed cardioprotective effects in women who consumed only moderate, but not high, amounts of chocolate.[12,15] Furthermore, one of the studies did not measure as many serum biomarkers and inflammatory mediators as previous in vivo blood pressure experiments.[12]

Other human studies have focused on the effects of chocolate consumption on vasodilation and inflammatory factors in the blood. Vasodilation has been observed in the majority of studies,[7,8,21,29] and seems to be both transient and dose–dependent within the range of cocoa doses tested.[7] However, it appears to be insignificant in people with atherosclerosis,[8] and therefore some level of baseline endothelial function may be required to observe the vasodilatory effects of NO. Other parameters studied have included wound closure time as an indication of platelet inhibition; one study reported an increased closure time indicating a decrease in platelet activity,[29] as well as downregulation of plasma inflammatory markers.[30] This evidence is not as widespread or as consistent as the noted effects on blood pressure and cardiovascular mortality.[20, 21] However, given that one of the functions of NO is to promote endothelial health, this could be an additional benefit.[19]

CONCLUSION

Many studies that have examined the effects of cocoa on cardiovascular health were not fully controlled, incompletely blinded, or used small sample sizes.[18,20-22,31,32] This may be partially explained by the fact that these studies had very rigorous inclusion criteria, making it difficult to recruit large numbers of individuals while simultaneously controlling for other factors.[25] Overall, the evidence that supports cocoa as reducing the risk of cardiometabolic disorders is growing, as epidemiological studies demonstrate this association which correlates with outcomes generated in animal studies and clinical trials. The beneficial effects of cocoa appear to be related to endothelial NO synthesis. While the optimal dose of cocoa per day is still undetermined,[12] studies have shown that moderate doses per week lead to a significant reduction of cardiometabolic disorders such as stroke, diabetes and CVD. Existing data do not allow a clear recommendation to eat large amounts of chocolate, and further meta–analyses are needed to include the results from smaller studies that on their own might not have statistical significance. Nevertheless, the current literature suggests that flavonoid–containing cocoa products, including chocolate, are beneficial for cardiovascular health.

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Management of Retinopathy and Neuropathy in Diabetes

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ABSTRACT

A combination of metabolic and vascular dysfunction in patients with diabetes can often lead to the development of microvascular complications such as retinopathy and neuropathy. These complications are the cause of significant morbidity and mortality in patients with diabetes, potentially leading to blindness and lower limb amputation. A key aim in diabetes management is to slow the development of microvascular disease, as there are limited options for treatment of established disease. Past studies have demonstrated the importance of strict control of blood glucose levels in preventing or slowing progression of microvascular complications. There is strong evidence that aggressive treatment of hypertension, dyslipidemia, and lifestyle modifications are also important in preventing complications. This review aims to help future physicians understand the pathogenesis of diabetic retinopathy and neuropathy, and provides a summary of the current literature and evidence–based recommendations for screening and management of both conditions.

KEYWORDS: *diabetes mellitus, diabetes complications, diabetic retinopathy, diabetic neuropathy*

INTRODUCTION

Diabetes mellitus currently affects greater than 285 million people, a figure that is expected to increase to 366 million by the year 2030.[1] Diabetes is characterized by a state of chronic hyperglycemia resulting in many downstream effects including eventual organ dysfunction. Microvascular complications include diabetic nephropathy, retinopathy, and neuropathy, all of which can result in serious consequences if left untreated. The topic of chronic kidney disease and end–stage renal disease in diabetes has been reviewed in recent publications.[2,3] This review will focus on the pathophysiology and management of diabetic retinopathy and neuropathy.

The effects of microvascular disease in diabetes are most prominent in the kidneys, retina, and vascular endothelium, tissues in which glucose uptake is independent of insulin levels.[4] Metabolic changes, including increased production of reactive oxygen species, formation of advanced glycation end products (AGEs), activation of protein kinase C isoforms, and hyperactivity of the hexosamine pathway,[5] lead to altered blood flow, endothelial permeability, and extravascular protein deposition.[6] The U.K. Prospective Diabetes Study Group (UKPDS) and the Diabetes Control and Complications Trial Research Group (DCCT) have shown a direct relationship between microvascular disease and inappropriate glycemic control.[7,8] Other factors also contribute to the risk of developing complications, including the patient's type of diabetes, gender, duration of diabetes, and hemoglobin A1c level.[9] The importance of controlling cardiovascular risk factors to prevent the development of microvascular complications is well–established.[1] For example, reduction of arterial hypertension, cessation of smoking, reduction of body mass index, and treatment

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