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EDITORIAL

Chocolate consumption, blood pressure, and cardiovascular risk

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This editorial refers to 'Chocolate consumption in relation to blood pressure and risk of cardiovascular disease in German adults'†, by B. Buijsse *et al.*, on page 1616

Diet is a lifestyle factor that plays a major role in the primary and secondary prevention of numerous chronic diseases, including certain cancers, cardiovascular disease, and diabetes.[1] Current dietary recommendations endorse the consumption of a diet rich in fruit and vegetables, as it is now recognized that these are healthy for multiple reasons.[2] In addition to being low in calories and fat, and high in fibre, plant-based foods can also contain a number of potentially health-promoting bioactive phytochemicals. Recently, flavanols, a subgroup of plant-derived compounds called flavonoids, have gained increasing attention as epidemiological investigations have revealed an inverse correlation between the dietary intake of flavanol-containing foods and coronary artery disease (CAD) mortality, with a reduction of mortality risk of up to 51% (*Figure 1*).[3] In the context of human nutrition, major flavanol sources in the western diet include tea, grapes and wine, cocoa products including chocolate, as well as various fruits, especially apples, and certain berries. While subject to agricultural practices and food processing, particularly high flavanol levels can be present in cocoa.[4] Several controlled human dietary intervention studies utilizing flavanol-containing foods in concert with nutrient-matched low-flavanol controls have demonstrated a causal relationship between flavanol intake and the modulation of (patho)physiological functions involved in the development and progression of vascular disease. In this context, the attenuation of endothelial dysfunction, decreases in blood pressure, reductions in platelet aggregation, and improvements in insulin sensitivity have been observed following clinical dietary interventions with flavanol-containing foods and beverages.[5]

Buijsse and colleagues have presented an epidemiological study that demonstrates an inverse relationship between chocolate consumption (at the time of enrolment in the study) and cardiovascular disease risk (myocardial infarction and stroke over the following 8 years).[6] Buijsse *et al.* studied a large cohort (n = 19 357) of middle-aged German participants of both sexes, without cardiovascular disease at inclusion, and observed that in the quartile characterized by the lowest chocolate consumption (1.7 g/day) 106 myocardial infarctions and strokes occurred, whereas only 61 events occurred (combined relative risk of 0.61) in the quartile with the highest chocolate consumption (7.5 g/day). In the latter group, both systolic and diastolic blood pressure were found to be 1 mmHg lower as compared with the referent low chocolate consumption quartile. Baseline blood pressure explained 10–12% of the risk reduction. Counterintuitively to the accepted view that high vegetable intake is associated with cardiovascular benefits, the subgroup with the lowest risk was also the group with the lowest vegetable intake while also having the highest chocolate intake. Generally, the results of the study by Buijsse *et al.* corroborate previous findings emanating from other western countries that show an association between higher intake of flavanol-rich foods, including chocolate, and lower incidence of cardiovascular events in elderly Dutch men (Zutphen Elderly Study)[7] and post-menopausal American women (Iowa Women's Health Study).[8] The study by Buijsse *et al.* extends these findings to German middle-aged subjects of both sexes, and statistically links a small proportion of the cardiovascular benefit (11%) to higher chocolate consumption and lower blood pressure.

While these findings certainly spark interest, it is inherent to epidemiological investigations that they cannot provide direct proof for the existence of a cause and effect relationship. However, are there conclusive prospective intervention studies that support a causal relationship between chocolate intake and blood pressure lowering? Ideally, such studies should be performed over a meaningful period of time, be adequately powered, and they need to be well controlled in order to yield sufficiently conclusive

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results. As cocoa and therefore chocolate contains various bioactives, i.e. flavanols, theobromine, caffeine, and others, the content of these bioactive compounds needs to be considered in the design of a proper control product. In order to reduce bias, the macro- and micronutrient composition as well as flavour and appearance need to be taken into account. Although no published study currently exists that meets all of the above criteria, in the context of a dietary intervention based on chocolate, the study by Taubert *et al.*[9] perhaps comes closest and has gained much attention. In the latter study, participants with untreated essential hypertension received 6.3 g of dark chocolate per day over 18 weeks, and a significant drop in systolic and diastolic blood pressure was observed. One major limitation of this data set is the fact that white chocolate was used as a control food product, which makes masking of patients and observers impossible, thus increasing the risk of bias. Furthermore, the different compositions of white and dark chocolate makes it difficult to identify bioactive compounds, such as flavanols, in the context of blood pressure lowering. Whereas white chocolate lacks flavanols, it also lacks methylxanthines and has a different fat composition. Overall, it might be argued that we do not have conclusive data from sufficiently controlled interventional trials to support the notion that chocolate consumption can lower blood pressure.

As outlined above, epidemiological studies have statistically linked the cardiovascular protective effects of certain foods including tea, various fruits, and cocoa to their high flavanol content. As cocoa is the main flavanol-delivering ingredient in chocolate, the findings from cocoa intervention studies may be used, with certain limitations kept in mind, to construct a feasible physiological link between chocolate consumption and cardiovascular risk reduction. Indeed, well-controlled small-scale human intervention studies have established a causal relationship between the intake of flavanols and the increase of endothelium-dependent vasodilation. In these intervention studies, flavanol-rich cocoa products were tested against micro- and macronutrient-matched controls in randomized trials ensuring proper blinding. It was shown that high flavanol interventions can induce an acute and sustained increase or restoration, respectively, of endothelium-dependent vasodilation in healthy subjects with cardiovascular risk factors (smoking, diabetes mellitus, hypertension, hypercholesterolaemia), heart transplant recipients, or patients with manifest coronary artery disease. In most studies, endothelium-dependent vasodilation was measured as flow-mediated vasodilation (FMD) which represents a prospectively validated surrogate endpoint predicting cardiovascular prognosis. These effects were shown to be dose dependent, inhibited by nitric oxide synthase blockers, and were paralleled by an increase in nitric oxide stores in blood, suggesting a mechanistic role for this pathway in this context. Importantly, a causality chain between flavanols in food and nitric oxide-dependent vascular function was first experimentally closed by Schroeter *et al.* and then further substantiated by another independent group who showed that intake of chemically pure flavanols [(−)-epicatechin] mimics the vascular effects observed after ingestion of flavanol-rich cocoa.[10,11]

In the context of the study by Buijsse *et al.*[6], one of the major shortcomings is that chocolate consumption was only estimated as one item on the food-frequency questionnaire, making a more qualified evaluation of the associated intake of potential bioactives including favanols impossible. This is an important limitation as not every chocolate, or cocoa for that matter, is created equally. The

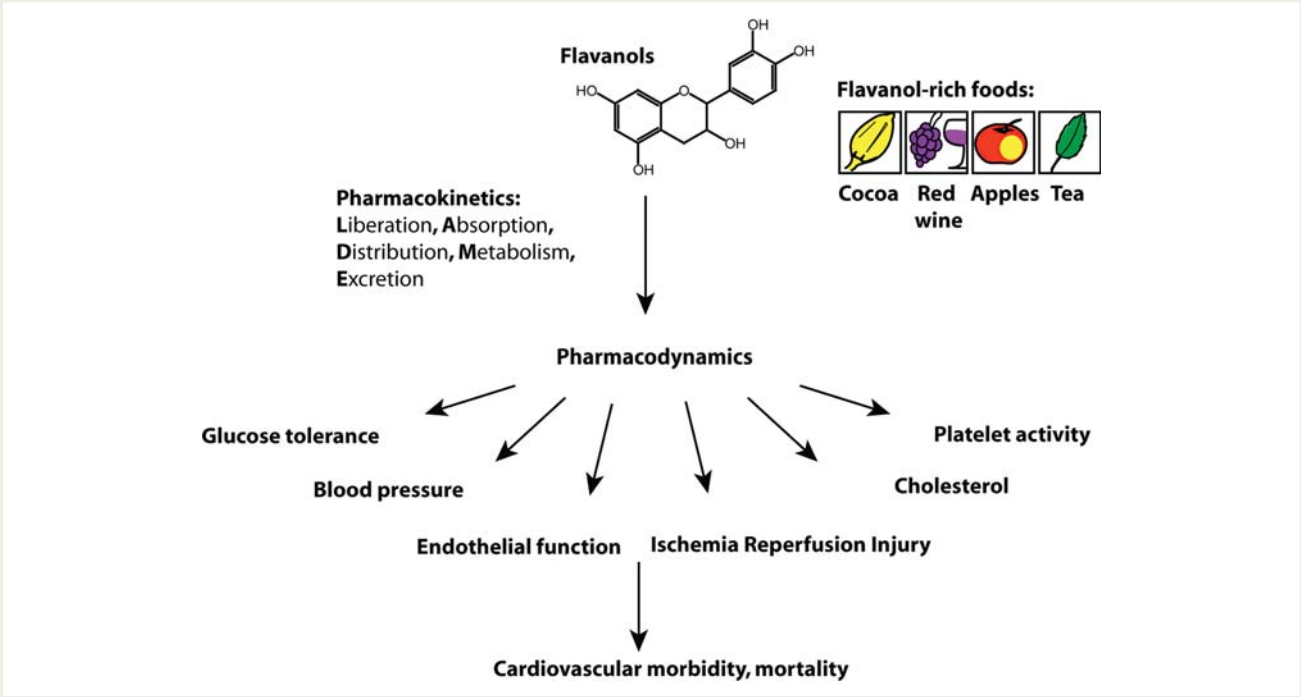

Figure 1 Schematic of flavanol effects on the cardiovascular system.

cocoa content varies greatly between chocolates, and the flavanol content and profile differ greatly between cocoas. Yet another layer of complexity should be considered carefully, namely that flavanols exist in distinct stereochemical configurations. This topic has not yet been comprehensively explored, but as stereochemistry is a known factor influencing bioactivity, and as food processing affects the stereochemical configuration of favanols, this topic should be considered in the context of both epidemiological studies and dietary interventions.

While chocolate represents a wonderfully delicious treat that can doubtlessly be a healthy part of a balanced diet, cardiologists need to consider how best to communicate such findings and ask the important question as to whether or not they should directly or indirectly recommend to their patients an increased consumption of chocolate, a food relatively high in saturated fat, sugar, and calories.

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