TOWNSEND LETTER
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Chewing on Chocolate

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Over the years we've witnessed publication of a series of epidemiological studies that suggest chocolate consumption is associated with reduced cardiovascular disease morbidity and mortality. An umbrella review of meta-analyses published in June 2019 by Veronese et al reported that "Among observational studies, including a total of 1,061,637 participants, the best available evidence suggests that chocolate consumption is associated with reduced risk of cardiovascular disease (CVD) death (n = 4 studies), acute myocardial infarction (n = 6), stroke (n = 5) and diabetes (n = 6), ..."[1] This should be enough evidence to encourage our patients to consume chocolate, at least those at risk of CVD.

Yet the recent publication of a clinical trial early in 2021 on chocolate left me wondering if I've been thinking about chocolate the wrong way. In fact, the questions raised by this study left me pondering if we should rethink how we dose not just chocolate, but many natural substances. Let me retrace my path here.

The study that left me pondering is by Baynham and colleagues, published in March 2021, and reminds me of JK Rowling's Harry Potter books and how her characters used chocolate as an antidote to terror.[2]

Let's start with a simple question we've been pondering. How much chocolate should people eat? In a 2019 meta-analysis by Ren et al of 23 studies on chocolate consumption and risk of cardiovascular disease, (that included 405,304 participants and 35,093 cases of CVD), the authors reported observing a "A non-linear dose-response ... [that] indicated that the most appropriate dose of chocolate consumption for reducing risk of CVD was 45 g/week."[3] That's only one chocolate bar a week.

The caveat, mentioned in Ren et al, is that the dose response to chocolate is non-linear. More may not be better. The dose response appears as an inverted U-shaped curve. This phenomenon was elaborated in a 2019 meta-analysis of cocoa flavanols and human endothelial function by Sun et al. Combining data from 15 published studies with 18 intervention arms, Sun et al calculated that endothelial function could be improved by 1.17%. The benefit peaked and then decreased with increasing daily flavanol intake. Participants in these intervention groups received 80 to 1248 mg (mean: 704 mg) per day more flavanols than control groups. The dose mattered and the most improvement was seen with 710 mg total flavanols, 95 mg (-)-epicatechin or 25 mg (+)-catechin. These numbers help us to a limited degree as there is no easy way to know how many flavanols are in specific chocolates.[4]

Cocoa solids, which are often reported on chocolate packages, have no correlation with flavanol content. On average, based on a current USDA analysis, milk chocolate contains about 0.703 mg/gm total flavanols compared to dark chocolate at 1.156 mg/gm.[5] If the goal is 700 mg/day of flavanols that would calculate out to be about 600 grams or 21 ounces per day or about a pound and quarter of chocolate and obviously this goal will not work for most people.

In contrast to these meta-analyses of studies that have tested intense high flavanol chocolates, past retrospective studies that have examined chocolate consumption suggest just 1-2 servings per week for women[6] and from 3-6 servings per week for men would have the greatest benefit at lowering heart disease.[7]

This is confusing, at least to me, and I have alternated between encouraging patients to eat chocolate a few times a week to purchasing the specific high flavanol cocoa powders used in the clinical trials.

With all of this rather confusing information in mind, we should consider the study by Baynham et al.[8] I've begun to refer to this as the Harry Potter study. This was a randomized, placebo controlled, double-blind, cross-over intervention study. Thirty males between 18 and 45 years old were enrolled and consumed a single cup of cocoa between 7:30 an 9:00 AM made with either high flavanol or low flavanol cocoa. Both cocoas were manufactured by Barry Callebaut of Zurich, Switzerland. The high flavanol cocoa delivered 681.4 mg flavanols per serving, while the low-flavanol powder delivered only 4.1 mg of total flavanols.

Once they had drank their morning cocoa, the participants took part in a mental exercise guaranteed to cause a significant stress response, something called Paced-Auditory-SerialAddition-Task (PASAT), for eight minutes. This process incorporates elements of increasing difficulty, social evaluation, punishment, competition, and reward that reliably raise stress markers. Before and at intervals after this stress inducing episode, endothelial function was assessed by brachial flow mediated dilation (FMD) and brachial blood pressure.

The basic cardiovascular responses exhibited by the study participants to stress did not differ between high vs. low flavanol cocoa. The difference was seen in the flow mediated dilation (FMD) measurements. While FMD was impaired 30 min post-stress in both groups, the high-flavanol cocoa attenuated this decline so that readings remained significantly higher compared to low-flavanol cocoa. These improvements persisted to the 90-minute post-stress results.

High-flavanol cocoa increased forearm blood flow (FBF) at rest and during stress. Flavanols are effective at counteracting mental stress induced endothelial dysfunction and improving peripheral blood flow during stress.

FMD is a technique developed in 1992 by Celermajer and colleagues to measure the impact of stress on cardiac function. Blood flow in the arm is first occluded, using a blood pressure cuff, then quickly released. Immediately on the cuff's release, endothelial cells produce nitric oxide and the vessels dilate increasing blood flow causing a surge of blood in the vessels, a reaction called hyperemia. The increase in arterial diameter is measured by ultrasound and is compared to the baseline diameter and expressed simply as a percentage of the baseline diameter (% FMD).

Although performed on the forearm, these measurements correlate well with functionality within the coronary arteries.[9] Alterations in FMD are considered the first sign of cardiovascular disease. FMD is inversely associated with risk of future cardiovascular events.[10,11] Meta-analyses suggest CVD risk drops 13% with a 1% increase in FMD.[12] Plenty of past studies tell us that chocolate consumption, in particular flavanols, increase FMD.[13] Baynham et al are probably the first to closely examine how chocolate affects the acute response of FMD after stress.

Mental stress triggers immediate increases in heart rate and blood pressure with peripheral arterial vasodilation. Baynham et al observed these reactions in their test subjects after drinking both the low and high flavanol cocoa mixtures. Mental stress also leads to post-stress impairment of endothelial function as measured by FMD. The blood vessels don't dilate as well.

Stress reduces the compensatory blood flow that delivers oxygen and removes metabolic wastes. Endothelial function as measured by FMD typically declines 15 to 90 minutes after stress in young healthy adults,[14] older adults, and especially those with depression, diabetes, and high cholesterol,[15] or metabolic syndrome.[16,17]

Reductions in FMD after mental stress (1-3% FMD) are significant because they are so predictive of future cardiovascular disease (CVD) risk. Remember, a 1% FMD reduction, which doesn't sound like much, is associated with a 13% increase in CVD risk.[18] The current theories why this occurs suggest nitric oxide (NO), inflammation, and cortisol play major roles.[19]

A 2005 trial that put obese children on low-calorie diets and exercise training is often cited because the intervention increased their peripheral vasodilation after mental stress[20] and suggests that diet and exercise can protect against stress damage. This thinking is congruent with our belief that diets rich in fruits and vegetables reduce risk of CVD, myocardial infarction, cardiovascular mortality and all-cause mortality.[21]

Credit for this dietary protection has focused on flavonoids, a group of molecules found in most fruits and vegetables; and epidemiological evidence shows significant associations between high intake of flavonoids and lower CVD mortality and morbidity.[22,23] Flavanols, a sub-group of the flavonoids, are found in cocoa, berries, grapes, apples, and tea, and are reported to improve

human endothelial function within a few hours of consumption.[24,25] Acute improvements in endothelial function translate into chronic benefits.[26]

Other high flavanol foods that improve endothelial function exhibit similar U-shaped dose/benefit curves as chocolate. Freeze dried blueberry powder's effect peaks at 766 mg of polyphenols; higher doses, 1278 or 1791 mg of polyphenols do not have a higher impact on FMD.[27] Same story with cranberry extracts, FMD peaks at 1238 mg polyphenols.[28]

This study by Baynham et al, might change the way we view chocolate's benefits. Up until now chocolate has been considered as something that might be 'good for you' over the long term, a habit that people might cultivate and indulge in regularly. These new results suggest that we reconsider how we consume chocolate and that it could be advantageous to eat it purposefully during and after exposure to acute stress.

Using chocolate in this way reminds me of how J.K. Rowling employs it in her Harry Potter books, as an antidote for the acute experience of despair and hopelessness triggered by exposure to dementors. Perhaps it is only in those situations when chocolate has the greatest benefit? Maybe there isn't a daily dose of flavanols that we need but just a PRN dose that are required from time to time, in particular when under stress?

It must also be considered that chocolate may work better in some people than others. Children of hypertensive parents are at greater risk of abnormal FMD results, suggesting an inherent propensity toward cardiovascular problems.[29] Maybe these kids are the ones who should eat the most chocolate?

What if chocolate only helps people who are susceptible to endothelial dysfunction? If so, chocolate might help those people a tremendous amount and not others but still average out and seem to help average people.

If chocolate encourages NO release, it really may work better with infrequent dosing. The classic cardiac drug isosorbide mononitrate (Imdur), which is used because it creates a surge in nitric oxide and relieves angina, is ineffective if used constantly. Endothelial tissue quickly develops a tolerance to nitric oxide so the drug can only be used effectively for a portion of the day. If used too long, it becomes ineffective. Could chocolate create a similar tolerance and eating too much chocolate too often weaken benefit?

Our conception of appropriate supplement dosing has descended from vitamin requirements. For example, vitamin C isn't stored long in the body so needs to be consumed daily. Not all vitamins or minerals need daily consumption, but this is often forgotten. It is assumed everything needs to be

taken in regularly to work. Chocolate isn't a vitamin so why assume there is a recommended daily allowance?

Once one starts to ponder this idea of benefits situational, other examples come to mind. We wouldn't think of taking antibiotics daily for long periods—their benefit is also situational; they may be useful against specific infections. Something similar occurs with immunotherapy inducing mushrooms. Go back to Eliza et al's 2012 meta-analysis on *Coriolus versicolor* for cancer. Patients who took Coriolus in the 13 trials considered had a mean 9% reduction in five-year mortality. The detail that stands out even a decade later is that 5-year survival was not associated with length of treatment; whether the patient took mushrooms for only a month or for three years, duration didn't affect that benefit.[30] What if chocolate were similar?

Once one starts wondering about this, it's hard to stop. How many things have we suggested to patients that they take two or three times per day for the rest of their lives? How many things might be like chocolate and exhibit a hormetic dose response where more doesn't necessarily work better? Our routine of bigger doses, stronger extractions, and longer periods of treatment may benefit the vendors who sell our supplements more than our patients.

More of a good thing isn't always a better plan.

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