EDITORIAL

Perspectives on Chocolate Consumption and Risk of Cardiovascular Diseases and Cognitive Function

Krassimira Hristova[1], Takashi Nakaoka[2], Kuniaki Otsuka[2], Jan Fedacko[3], Reema Singh[4], RB Singh[5,*], Fabien De Meester[5], Agnieszka Wilczynska[5] and DW Wilson[6]

[1]*University National Heart Hospital, Department of Noninvasive Functional Diagnostic and Imaging, Sofia , Bulgaria*

[2]*Department of Medicine, Tokyo Women's Medical University, Tokyo, Japan*

[3]*Faculty of Medicine, PJ Safaric University, Kosice, Slovakia*

[4]*Reema Singh's 'The Chocolate Factory (Rim chocolatier), Mumbai, India*

[5]*The Tsim Tsoum Institute, Krakow, Poland*

[6]*School of Medicine, Pharmacy, and Health, Durham University, Stockton-on-Tees, UK*

Abstract: Flavonoid deficiency in the diet is a risk factor for cardiovascular diseases (CVDs) and other chronic diseases. Recent studies indicate that increased consumption of chocolates may be associated with decreased risk of CVDs and insulin resistance, inflammation and hyperlipidemia. In the present editorial, we have sought supporting evidence for such claims. It is possible that cocoa consumption (30-1000mg/day) in the form of dark chocolates can protect against hypertension, stroke, atherosclerosis, insulin resistance and memory dysfunction. Further research is necessary to prove this finding.

Keywords: Flavonoids, flavonols, antioxidants, diet, nutrition, hypertension, stroke, dementia, cognitive function.

Cocoa which has polyphenolic flavonoid constituents was consumed as an unsweetened drink of raw, dried cocoa powder, traditionally by native Indians [1]. Sugar was added, after it was brought to Europe, and other processing steps became common in order to reduce bitterness and to provide European taste and flavour. These modifications resulted in reduction in flavanol content, the likely polyphenolic having potential antioxidant effects. Cocoa appears to be beneficial against the risk of insulin resistance, hypertension, stroke, coronary artery disease (CAD), metabolic syndrome, cognitive function and dementia [2-10]. It seems that, all chocolates are not equal and the protective effect of high cocoa consumption by native Indians may not be achievable with Western chocolate products unless the products are duly fortified and more research is needed on its (plant) epidemiology and manufacturing processes and interactions with co-ingredients and subsequent consumption.

Epidemiological studies of human consumption, in particular observations in native Kuna Indians living on Central American islands, suggest that cocoa-rich products reduce cardiovascular mortality [3-9]; a diminished trait upon migration. Further, flavanol-rich cocoa drinks (8 weeks) can decrease blood pressure as well as improve cognitive function in elderly subjects with mild cognitive impairment. The memory dysfunction, a condition thought to be associated with (micro-)vascular dysfunction [1]. Thus, the health benefits of chocolate, similar to those of red wine, may be multifactorial, and we should be concerned with only such effect without bothering about the disappointing antihypertensive effect. The potential benefits of chocolate's should be explored in an outcome study looking at dementia, heart attack, stroke, and death [2-9].

CARDIOMETABOLIC DISORDERS

Epidemiological evidence suggest a blood pressure-lowering effects of cocoa and tea [3]. A meta-analysis of randomized controlled trials was conducted to determine changes in systolic and diastolic blood pressure due to the intake of cocoa products or black and green tea. Five randomized controlled studies of cocoa administration involving a total of 173 subjects with a median duration of 2 weeks were included. After the cocoa diets, the pooled mean systolic and diastolic blood pressure were -4.7 mm Hg (95% confidence interval [CI], -7.6 to -1.8 mm Hg; P = .002) and -2.8 mm Hg (95% CI, -4.8 to -0.8 mm Hg; P = .006) lower, respectively, compared with the cocoa-free controls. Five stud-

*Address correspondence to this author at the Halberg Hospital and Research Institute, Civil Lines, Moradabad-10(UP) 244001, India; Tel/Fax: 00915912417437; E-mails: rbs@tsimtsoum.net, drkk@dataone.in

1876-3960/12

ies of tea consumption involving a total of 343 subjects with a median duration of 4 weeks were selected. The tea intake had no significant effects on blood pressure. It seems that current randomized dietary studies indicate that consumption of foods rich in cocoa may reduce blood pressure, while tea intake appears to have no effect.'

Another study reported that flavanol-rich cocoa products; dark chocolates may be an alternative treatment option for hypertension, which is a risk factor for cardiovascular disease (CVDs) [4]. Previous meta-analyses concluded that cocoa-rich foods may reduce blood pressure but the results remained conflicting, despite other trials. Only fifteen trial arms of 13 assessed studies met the inclusion criteria. Nine trials used chocolate containing 50% to 70% cocoa compared with white chocolate or other cocoa-free controls, while six trials compared high- with low-flavanol cocoa products. Daily flavanol dosages ranged from 30 mg to 1000 mg in the active treatment groups, and interventions ran for 2 to 18 weeks. Pooled meta-analysis of all trials revealed a significant blood pressure-reducing effect of cocoa-chocolate compared with control (mean BP change ±SE: SBP: -3.2 ±1.9 mmHg, P = 0.001; DBP: -2.0 ± 1.3 mmHg, P = 0.003). However, subgroup meta-analysis was significant only for the hypertensive or pre-hypertensive subgroups (SBP: -5.0 ± 3.0 mmHg; P = 0.0009; DBP: -2.7 ± 2.2 mm Hg, P = 0.01), while BP was not significantly reduced in the normotensive subgroups (SBP: -1.6 ± 2.3 mmHg, P = 0.17; DBP: -1.3 ± 1.6 mmHg, P = 0.12). It is possible that dark chocolate is superior to placebo in reducing systolic hypertension or diastolic prehypertension. However, flavanol-rich chocolate did not significantly reduce mean blood pressure below 140 mmHg systolic or 80 mmHg diastolic indicating that it could be a supplement to other treatments of hypertension. Desch *et al* [5] also supports previous claims that flavanol-rich chocolate and cocoa products have a small and acute antihypertensive effect, both in individuals with manifested and pre-hypertension. It remains open whether this effect persists long-term and is associated with improved patient-relevant cardiovascular outcomes i.e. lowered mortality, similar to the lower incidence of cardiovascular diseases observed in Kuna Indians in Panama. The risk of regularly eating energy-dense versions of cocoa such as chocolate may cause weight gain and counteract any benefit from lowering bloodpressure.

A meta-analysis of randomized controlled trials assessing the antihypertensive effects of flavanol-rich cocoa products was conducted [5]. In total, 10 randomized controlled trials comprising 297 individuals were included in the analysis. The populations studied were either healthy normotensive adults or patients with pre-hypertension/stage 1 hypertension. Treatment duration ranged from 2 to 18 weeks. The mean BP change in the active treatment arms across all trials was -4.5 mm Hg (95% confidence interval (CI), -5.9 to -3.2, P < 0.001) for systolic BP and -2.5 mm Hg (95% CI, -3.9 to -1.2, P < 0.001) for diastolic BP. This meta-analysis confirms the BP-lowering capacity of flavanol-rich cocoa products in a larger set of trials than previously reported. Dark chocolate contains saturated fat and is a source of dietary calories; consequently, it is important to determine whether consumption of dark chocolate adversely affects the blood lipid profile.Cocoa products, are rich sources of flavonoids, can reduce blood pressure as well as the risk of cardiovascular disease [6]. In all, 10 clinical trials consisting of 320 participants with treatment duration of 2-12 weeks were included in this analysis. Intervention with dark chocolate/cocoa products significantly reduced serum low-density lipoprotein (LDL) and total cholesterol (TC) levels (differences in means (95% CI) were -5.90 mg/dl (-10.47, -1.32 mg/dl) and -6.23 mg/dl (-11.60, -0.85 mg/dl), respectively). No statistically significant effects were observed for high-density lipoprotein (HDL) (difference in means (95% CI): -0.76 mg/dl (-3.02 to 1.51 mg/dl)) and triglyceride (TG) (-5.06 mg/dl (-13.45 to 3.32 mg/dl)).

A meta analysis by Hooper *et al* [7] included 42 acute or short-term chronic (≤18 wk) randomized trials that comprised 1297 participants. Insulin resistance (HOMA-IR: -0.67; 95% CI: -0.98, -0.36) was improved by chocolate or cocoa due to significant reductions in serum insulin. Flow-mediated dilatation (FMD) improved after chronic (1.34%; 95% CI: 1.00%, 1.68%) and acute (3.19%; 95% CI: 2.04%, 4.33%) intakes. Effects on HOMA-IR and FMD remained stable to sensitivity analyses. The investigators observed reductions in diastolic blood pressure (BP; -1.60 mm Hg; 95% CI: -2.77, -0.43 mm Hg) and mean arterial pressure (-1.64 mm Hg; 95% CI: -3.27, -0.01 mm Hg) and marginally significant effects on LDL (-0.07 mmol/L; 95% CI: -0.13, 0.00 mmol/L) and HDL (0.03 mmol/L; 95% CI: 0.00, 0.06 mmol/L) cholesterol. Chocolate or cocoa improved FMD regardless of the dose consumed, whereas doses >50 mg epicatechin/d resulted in greater effects on systolic and diastolic BP. There was a consistent acute and chronic benefit of chocolate or cocoa on FMD and previously unreported promising effects on insulin and HOMA-IR.

STROKE

The association between chocolate consumption and risk of stroke in men was assessed in a meta-analysis including a cohort study [8]. The authors prospectively followed 37,103 men in the Cohort of Swedish Men. Chocolate consumption was assessed at baseline using a food-frequency questionnaire. Study-specific results were combined using a random-effects model. The investigators ascertained 1,995 incident stroke cases, including 1,511 cerebral infarctions, 321 hemorrhagic strokes, and 163 unspecified strokes during 10.2 years of follow up. High chocolate consumption was associated with a lower risk of stroke. The multivariable relative risk of stroke comparing the highest quartile of chocolate consumption (median 62.9 g/week) with the lowest quartile (median 0 g/week) was 0.83 (95 % CI 0.70-0.99). The association did not differ by stroke subtypes. In a meta-analysis of 5 studies, with a total of 4,260 stroke cases, the overall relative risk of stroke for the highest vs. lowest category of chocolate consumption was 0.81 (95% CI 0.73-0.90), without heterogeneity among studies (p = 0.47).These findings suggest that moderate chocolate consumption may lower the risk of stroke. However, further studies are needed to reduce fat and sugar content of chocolates to improve the efficacy and long term safety in the prevention of obesity and metabolic syndrome and vacular diseases [8-11].

In a recent meta analysis [12] randomized trials and cohort, case-control, and cross sectional studies carried out in human adults, were included, in which the association be-

tween chocolate consumption and the risk of outcomes related to cardiometabolic disorders were reported. Only seven studies met the inclusion criteria comprising of 114 009 participants. None of the studies was a randomised trial, six were cohort studies, and one a cross sectional study. Five of the seven studies reported a beneficial association between higher levels of chocolate consumption and the risk of cardio-metabolic disorders. The highest levels of chocolate consumption were associated with a 37% reduction in cardiovascular disease (relative risk 0.63 (95% confidence interval 0.44 to 0.90)) and a 29% reduction in stroke compared with the lowest levels (Fig. **1**).

Further studies show endothelial function is impaired during hyperglycemia which may be due to decreased nitric oxide release [13]. Dark chocolate increases flow-mediated dilation in healthy and hypertensive subjects with and without glucose intolerance; however, the effect of pretreatment with dark chocolate on endothelial function and other vascular responses to hyperglycemia has not been examined. The authors 'investigated the effects of flavanol-rich dark chocolate administration on; flow-mediated dilation and wave reflections as well as on blood pressure,endothelin-1 and oxidative stress, before and after oral glucose tolerance test (OGTT) [13]. Healthy volunteers(n=12) (5 males, aged 28.2-2.7 years) randomly received either 100 g/d dark chocolate or flavanol-free white chocolate for 3 days. After 7 days washout period, volunteers were switched to the other treatment. Flow-mediated dilation, stiffness index, reflection index, peak-to–peak time, blood pressure, endothelin-1 and 8-iso-PGF2_ were evaluated after each treatment phase and OGTT. Compared with white chocolate, dark chocolate ingestion improved flow-mediated dilation (P=0.03), wave reflections, endothelin-1 and 8-iso-PGF2 (P=0.05). After white chocolate ingestion, flow-mediated dilation was reduced after OGTT from 7.88_0.68 to 6.07-0.76 (P=0.027), 6.74-0.51 (P=0.046) at 1 and 2 h after the glucose load, respectively. Similarly, after white chocolate but not after dark chocolate, wave reflections, blood pressure, and endothelin-1 and 8-iso-PGF2- increased after OGTT. OGTT causes acute, transient impairment of endothelial function and oxidative stress, which is attenuated by flavanol-rich dark chocolate. These results suggest that cocoa flavanols may contribute to vascular health by reducing the postprandial impairment of arterial function associated with the pathogenesis of atherosclerosis' and cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans.

In brief, these outcomes in CVDs and hyperglycemia may be related to an antioxidant, anti-inflammatory and anti-hypertensive effect of cocoa, which had been claimed earlier by a number of clinical trials, reviews and meta-analyses [2-7, 11-13]. The blood-pressure lowering effect is small (2-3mmHg) but significant. However, blood pressure-independent effects, as mentioned above, improved insulin sensitivity, also have been suggested for cocoa. Possible side effects of long-term daily chocolate consumption such as obesity and type 2 diabetes should be assessed. Such studies should then also clarify both dose-response relationships and address the optimal processing method of raw cocoa beans to optimise anti-hypertensive actions and other actions causing beneficial effects on blood lipids, hypertension and insulin resistance. Interestingly, fat content and thus energy density of chocolate may be reduced by incorporation of fruit juice or water acidified with ascorbic acid without impacting mouthfeel [9]. Cocoa has been suggested to increase

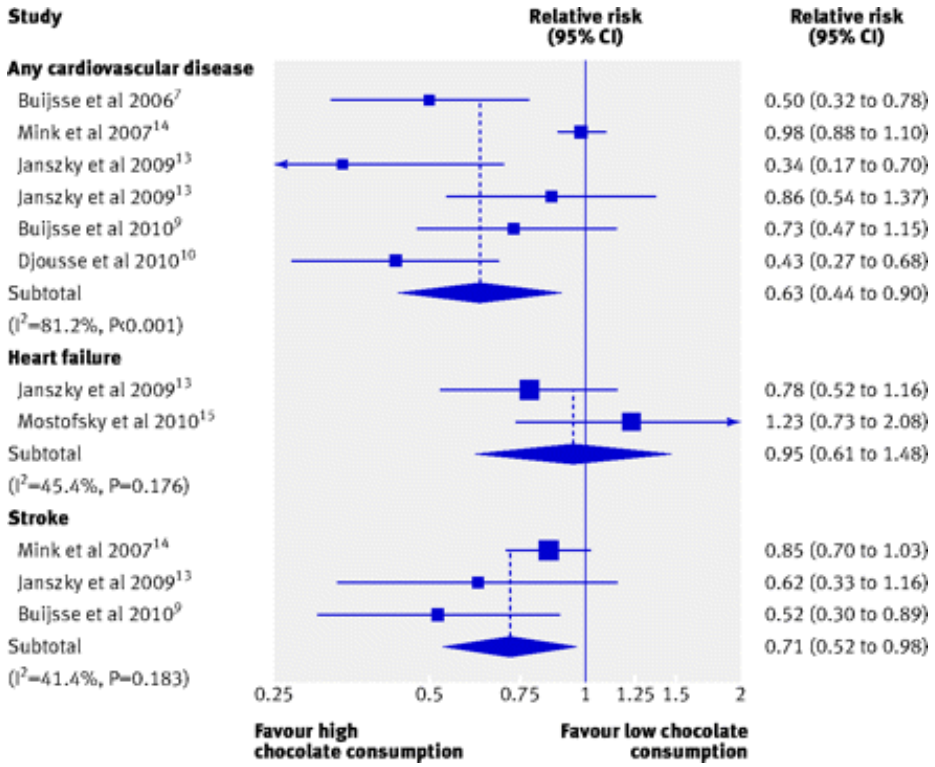

Fig. (1). Relative risks for cardiovascular disease, heart failure, and stroke in adults with higher levels of chocolate consumption com-pared with lower levels. Buitrago-Lpez *et al*, BMJ 2011. With per-mission? Red

endothe-lial nitric oxide (NO) formation. Flavanols may also up-regulate endogenous antioxidant enzymes and thereby lower reactive oxygen species (ROS) levels. Since ROS interfere with NO's bioavailability[10], this may indirectly increase NO levels and its actions. Another natural product, nitrate-rich vegetables such as beetroot, also reduce blood pressure in hypertensives in a NO-dependent manner [11]. It may even be beneficial to combine beetroot or dietary nitrate (generating NO) with cocoa (increasing NO's bioavailability), and thus move from adverse effect feeling fat containing chocolate to nitric oxide containing chocolate. Cerebral ischemia is a common, morbid condition accompanied by cognitive decline. Recent reports on the vascular health benefits of flavanol-containing foods signify a promising approach to the treatment of cerebral ischemia. This study was designed to investigate the effects of flavanol-rich cocoa (FRC) consumption on cerebral blood flow in older healthy volunteers [14]. 'Transcranial Doppler (TCD) ultrasound was used to measure mean blood flow velocity (MFV) in the middle cerebral artery (MCA) in thirty-four healthy elderly volunteers (72 to 76 years) in response to the regular intake of FRC or flavanol-poor cocoa (FPC).In response to two weeks of FRC intake, MFV increased by 8% and 4% at one week ($p = 0.01$) and 10% and 4% ($p = 0.04$) at two weeks. In response to one week of cocoa, significantly more subjects in the FRC as compared with the FPC group had an increase in their MFV ($p = 0.05$). It seems that dietary intake of FRC is associated with a significant increase in cerebral blood flow velocity in the MCA as measured by TCD. The data and other studies suggest a promising role for regular cocoa flavanol consumption in the treatment of cerebrovascular ischemic syndromes and stroke including dementias and cognitive function [14-18].

COGNITIVE FUNCTION

Desideri *et al* tested the hypothesis that dietary flavanols might improve cognitive function in subjects with mild cognitive impairment [15]. A double-blind, parallel arm study was conducted in 90 elderly individuals with mild cognitive impairment randomized to consume once daily for 8 weeks a drink containing ≈990 mg (high flavanols), ≈520 mg (intermediate flavanols), or ≈45 mg (low flavanols) of cocoa flavanols per day. Cognitive function was assessed by Mini Mental State Examination, Trail Making Test A and B, and verbal fluency test. At the end of the follow-up period, Mini Mental State Examination was similar in the 3 treatment groups ($P=0.13$). The time required to complete Trail Making Test A and Trail Making Test B was significantly ($P<0.05$) lower in subjects assigned to high flavanols (38.10±10.94 and 104.10±28.73 seconds, respectively) and intermediate flavanols (40.20±11.35 and 115.97±28.35 seconds, respectively) in comparison with those assigned to low flavanols (52.60±17.97 and 139.23±43.02 seconds, respectively). Similarly, verbal fluency test score was significantly ($P<0.05$) better in subjects assigned to high flavanols in comparison with those assigned to low flavanols (27.50±6.75 versus 22.30±8.09 words per 60 seconds). Insulin resistance, blood pressure, and lipid peroxidation also decreased among subjects in the high-flavanol and intermediate-flavanol groups. Changes of insulin resistance explained ≈40% of composite z score variability through the study period (partial $r(2)=0.4013$; $P<0.0001$)'. It is possible that regular consumption of cocoa flavanols might be effective in improving cognitive function in elderly subjects with mild cognitive impairment. This effect appears to be mediated in part by an improvement in insulin sensitivity.

In a cross-sectional survey among 2031 subjects aged 70-74 years, (55% women) from Norway [16], Nurk *et al* examined the relation between intake of 3 common foodstuffs that contain flavonoids (chocolate, wine, and tea) and cognitive performance. A cognitive test battery included the Kendrick Object Learning Test, Trail Making Test, part A (TMT-A), modified versions of the Digit Symbol Test, Block Design, Mini-Mental State Examination, and Controlled Oral Word Association Test. Participants who consumed chocolate, wine, or tea had significantly better mean test scores and lower prevalence of poor cognitive performance than those who did not. Participants who consumed all 3 studied items had the best test scores and the lowest risks for poor test performance. The associations between intake of these foodstuffs and cognition were dose dependent, with maximum effect at intakes of approximately 10 g/d for chocolate and approximately 75-100 mL/d for wine, but approximately linear for tea. Most cognitive functions tested were influenced by intake of these 3 foodstuffs. The effect was most pronounced for wine and modestly weaker for chocolate intake. Thus, in the elderly, a diet high in some flavonoid-rich foods is associated with better performance in several cognitive abilities in a dose-dependent manner. In recent studies [14-18] dietary flavonoids, abundant in plant-based foods, have been shown to improve cognitive function particularly a reduction in the risk of dementia, enhanced performance on some cognitive tests, and improved cognitive function in elderly patients with mild impairment have been associated with a regular intake of flavonoids. A subclass of flavonoids called flavanols, which are widely present in cocoa, green tea, red wine, and some fruits, seems to be effective in slowing down or even reversing the reductions in cognitive performance that occur with aging. Improved cognitive performance with the administration of a cocoa polyphenolic extract has even been reported in aged Wistar–Unilever rats [19].

Since chocolate consumption could hypothetically improve cognitive function not only in individuals but also in whole populations, it is possible that there would be a correlation between a country's level of chocolate consumption and its population's cognitive function. The total number of Nobel laureates per capita could serve as a surrogate end point reflecting the proportion with superior cognitive function and thereby give us some measure of the overall cognitive function of a given country showing association of chocolate consumption and number of Nobel laureates in a country [17]. There was a close, significant linear correlation ($r=0.791$, $P<0.0001$) between chocolate consumption per capita and the number of Nobel laureates per 10 million persons in a total of 23 countries (Fig. **2**). Messerli noted a correlation between Countries' Annual Per Capita Chocolate consumption and the number of Nobel Laureates per 10 Million population was analysed. Calculation with the exclusion of Sweden revealed that the correlation coefficient increased to 0.862. Switzerland was the top performer in terms of both the number of Nobel laureates and chocolate consumption.

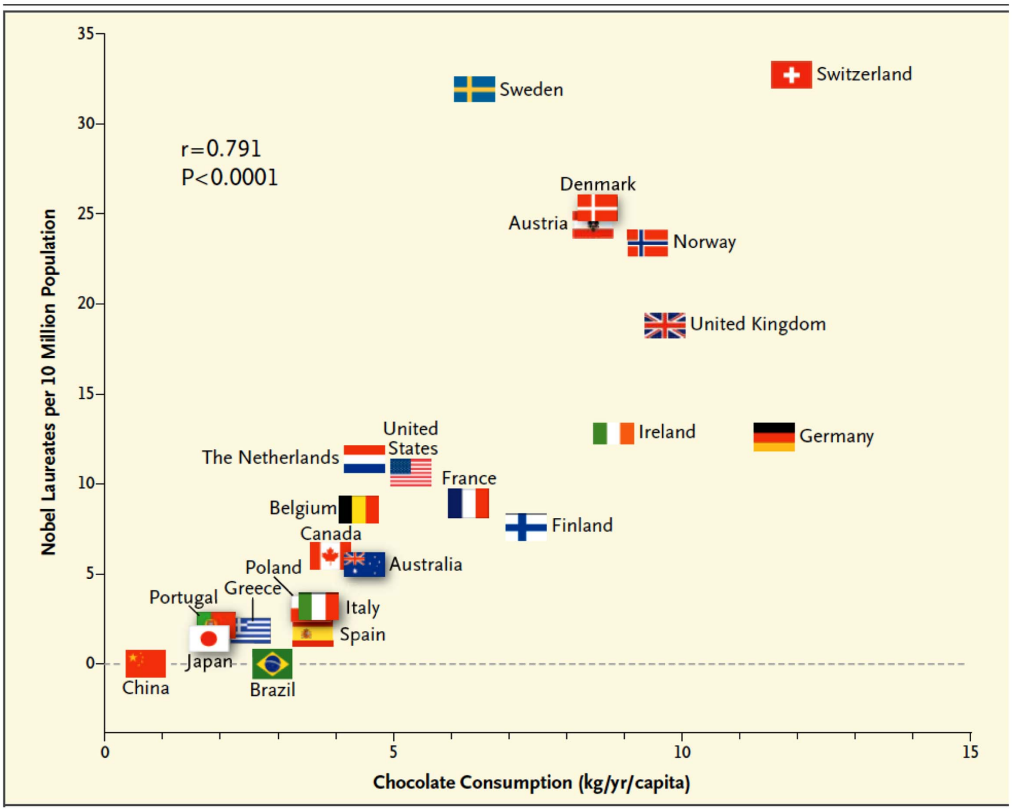

Fig. (2). Correlation between Countries' Annaual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

The slope of the regression line allows us to estimate that it would take about 0.4 kg of chocolate per capita per year to increase the number of Nobel laureates in a given country by 1. For the United States, that would amount to 125 million kg per year. The minimally effective chocolate dose seems to hover around 2 kg per year, and the dose–response curve reveals no apparent ceiling on the number of Nobel laureates at the highest chocolate-dose level of 11 kg per year. However, a much more rigorous association between chocolate consumption per capita and cognitive function needs to be undertaken, possibly with migrant or community based studies.

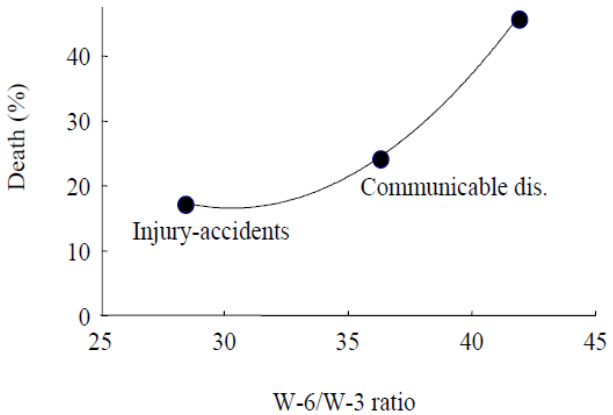

Fig. (3). Association of w-6/w-3ratio of fatty acids with mortality due to injury- accidents, communicable diseases and non-communicable diseases.

Seven of nine of the published studies that have examined the effects of cocoa- and chocolate-related products on neurocognitive processes have found that the compounds are associated with significantly improved and/or preserved aspects of cognitive functioning [18]. Further evidence suggests that dietary flavonoids and methylxanthines, such as those commonly found in cocoa and chocolate products, may possess neuroprotective, neuroenhancing, and neurostimulating and cardioprotective effects [20]. Addition of w-3 fatty acids to dark chocolates can enhance its capability in the prevention of CVDs and other chronic diseases [21], (Fig. **3**).

Cocoa-rich chocolate has been known not only for its good taste but also for its proposed health effects [1-20]. Several supposed health effects of cocoa have been considered, including improved cardiac function and relief of angina pectoris, stimulation of the nervous system, facilitated digestion, and improved kidney and bowel function. In addition, cocoa has been used to treat anemia, mental fatigue, tuberculosis, fever, gout, kidney stones, and even poor sexual appetite. The Incas considered it the drink of gods, an association that gave rise to the scientific name of the cocoa tree, Theobroma cacao, from the Greek words theo (god) and broma (drink) [22]. In Honduras, archeologists uncovered elaborately designed bowls of this period that are believed to have been used by the Aztecs to drink liquid cocoa thousands of years ago [22]. In the 16th century, Aztec Emperor Montezuma was a keen admirer of cocoa, calling it a divine drink, which builds up resistance and fights fatigue. A cup of this precious drink permits a man to walk for a whole day without food.

In brief, this paper, albeit perspectives which has drawn on the results of other nutrition experts, indicate that increased consumption of dark chocolates or cocoa (30-1000mg/day) can protect against CVDs and other chronic diseases including insulin resistance and memory dysfunction.

CONFLICT OF INTERESTS

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Acknowledgements are due to International College of Nutrition, International College of Cardiology and the Tsim Tsoum Institute for logistic support to write this article.

REFERENCES

[1] Grivetti LE, Howard-Yana S. Chocolate: history, culture, and heritage. John Wiley and Sons 2009; ISBN 9780470121658.

[2] Henderson JS, Joyce RA, Hall GR, Hurst WJ, McGovern PE. Chemical and archaeological evidence for the earliest cacao beverages. Proc Natl Acad Sci U S A 2007; 104: 18937-40.

[3] Taubert D, Roesen R, Schömig E. Effect of cocoa and tea intake on blood pressure: a meta-analysis. Arch Intern Med 2007; 167(7): 626-34.

[4] Ried K, Sullivan T, Fakler P, Frank OR, Stocks NP. Does chocolate reduce blood pressure? A meta-analysis. BMC Med 2010; 8: 39.

[5] Desch S, Schmidt J, Kobler D, *et al*. Effect of cocoa products on blood pressure: systematic review and meta-analysis. Am J Hypertens 2010; 23(1): 97-103.

[6] Tokede OA, Gaziano JM, Djoussé L. Effects of cocoa products/dark chocolate on serum lipids: a meta-analysis. Eur J Clin Nutr 2011; 65(8): 879-86.

[7] Hooper L, Kay C, Abdelhamid A, *et al*. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr 2012; 95(3): 740-51.

[8] Larsson SC, Virtamo J, Wolk A. Chocolate consumption and risk of stroke A prospective cohort of men and meta-analysis. Neurology 2012; 79: 1223-9.

[9] Skelhon T, Grossiord N, Morgan A, Bon S. Quiescent water-in-oil Pickering emulsions as a route toward healthier fruit juice infused chocolate confectionary. J Mater Chem 2012; 22: 19289-95.

[10] Armitage ME, Wingler K, Schmidt HH, La M. Translating the oxidative stress hypothesis into the clinic: NOX versus NOS. J Mol Med (Berl) 2009; 87(11): 1071-6.

[11] Webb AJ, Patel N, Loukogeorgakis S, *et al*. Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate *via* bioconversion to nitrite. Hypertension 2008; 51(3): 784-90.

[12] Buitrago-Lopez A, Sanderson J, Johnson L, *et al*. Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis. BMJ 2011; 343: d4488.

[13] Grassi D, Desideri G, Necozione S, *et al*. Protective Effects of Flavanol-Rich Dark chocolate on endothelial function and wave reflection during acute hyperglycemia. Hypertension 2012; 60: 827-32.

[14] Sorond FA, Lipsitz LA, Hollenberg NK, Fisher ND. Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. Neuropsychiatr Dis Treat 2008; 4(2): 433-40.

[15] Desideri G, Kwik-Uribe C, Grassi D, *et al*. Benefits in cognitive function, blood pressure, and insulin resistance through cocoa flavanol consumption in elderly subjects with mild cognitive impairment: the Cocoa, Cognition, and Aging (CoCoA) Study. Hypertension 2012; 60: 794-801.

[16] Nurk E, Refsum H, Drevon CA, *et al*. Intake of flavonoid-rich wine, tea, and chocolate by elderly men and women is associated with better cognitive test performance. J Nutr 2009; 139: 120-7.

[17] Messerli FH. Chocolates consumption, cognitive function and Nobel laureates. N Engl J Med 2012; 367(16): 1562-4.

[18] David WC, Harrison DW, Kim P, *et al*. The effects of cocoa- and chocolate-related products on neurocognitive functioning. Nutr Health 2012; 7: 369-79.

[19] Bisson JF, Nejdi A, Rozan P, Hidalgo S, Lalonde R, Messaoudi M. Effects of long-term administration of a cocoa polyphenolic extract (Acticoa powder) on cognitive performances in aged rats. Br J Nutr 2008; 100: 94-101.

[20] Corti R, Flammer AJ, Hollenberg NK, Luscher TF. Cocoa and cardiovascular health. Circulation 2009; 119: 1433-41.

[21] Fedacko J, Vargova V, Singh RB, *et al*. Association of high w-6/w-3 fatty acid ratio diet with causes of death due to noncommunicable diseases among urban decedents in North India. Open Nutra J 2012; 5: 113-23.

[22] Dillinger TL, Barriga P, Escarcega S, Jimenez M, Salazar Lowe D, Grivetti LE. Food of the gods: cure for humanity? A cultural history of the medicinal and ritual use of chocolate. J Nutr 2000; 130: 2057S-72.

Received: November 23, 2012 Revised: November 29, 2012 Accepted: November 29, 2012