Tea Expert Newsletter

Issue five

Scientific update on tea, flavonoids and blood pressure

Unilever

SCIENTIFIC UPDATE ON TEA, FLAVONOIDS AND BLOOD PRESSURE

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"From the editors"

The worldwide epidemic of cardiovascular disease (CVD) is of epic proportions. Being responsible for an estimated 17.3 million deaths in 2008 (30% of the overall total), it is the number one cause of mortality globally and will remain so, with the WHO predicting that by 2030 approximately 24 million people will die from CVD[1].

Elevated blood pressure or hypertension* is a major risk factor for CVD, specifically coronary heart disease (CHD) and stroke. On its own it is estimated to cause 7.5 million (about 13% of the global total) deaths annually. Almost 30% of all adults aged 25 and older suffer from hypertension[2]. This means that the potential impact of even small reductions in blood pressure, typically achievable through changes in diet and lifestyle, across the population is significant. The scale increases even further when one considers that there is a linear relationship between blood pressure and cardiovascular disease risk which starts as low as 115/70 mmHg[3]. This means that almost anyone will gain benefit from lowering their blood pressure or even better from preventing the age-related increase in blood pressure.

A variety of dietary and lifestyle modifications that would lower blood pressure or reduce CVD risk have been identified. These include smoking cessation, weight loss, increased physical activity, moderation of alcohol intake, reduced salt intake, increased fruit and vegetable intake and decreased saturated and total fat intake. It is advocated that these diet and lifestyle measures are applied in all people, including those that require drug treatment[4]. Next to these established measures, there is an emerging body of evidence suggesting a role for dietary flavonoids in reducing hypertension and CVD risk, which we will cover in more detail in this newsletter.

After water, tea is the most widely consumed beverage in the world[5, 6]. It is a rich source of flavonoids - polyphenolic compounds synthesized by plants thought to have beneficial effects on health. A cup of tea generally provides 150 to 200mg of flavonoids, which makes tea a significant contributor to the daily flavonoid intake for the population across the world. A substantial body of research has been produced on the possible health benefits of tea and its flavonoids. Human intervention studies have demonstrated that tea can improve vascular function and bring about small but relevant reductions in blood pressure.
Because of the potential positive effects of tea on blood pressure, the impact thereof on public health could be substantial[7-9]. Indeed, population studies suggest a decreased risk of developing CVD with higher tea consumption, which has been found to be associated with the high flavonoid content of tea.

*Systolic blood pressure ≥140mmHg or Diastolic blood pressure ≥90mmHg.

CONTENT

CONTENT OF THE NEWSLETTER

For this newsletter we have selected and set in context recent scientific papers published in the past year which have looked into the effects of tea and flavonoids on CVD and blood pressure.

We start with a look at recent observational data from three new publications: a large prospective cohort study which examined the association between flavonoid intake and CVD mortality; a prospective study among 69,622 women from the Nurses' Health Study which examined associations between a range of flavonoid subclasses and risk of stroke and lastly a new meta-analysis of prospective cohort studies which examined the impact of black and green tea consumption on the risk of stroke.

We also share with you the outcomes of two intervention studies done in collaboration with Unilever experts on tea and health. One investigated the effects of longer term black tea consumption on blood pressure whilst the other demonstrated the shorter term beneficial effects of black tea on blood pressure and vascular function. This is followed by an intervention study that investigated the blood pressure lowering effects of green tea and lastly, we discuss an interesting meta-analysis which combined data on a large number of intervention studies on flavonoid rich foods, blood pressure and vascular function.

1 INTRODUCTION 4

1.1 Black and green tea are rich sources of flavonoids in the diet

2. TEA, FLAVONOIDS, BLOOD PRESSURE AND CARDIOVASCULAR DISEASE: RECENT DEVELOPMENTS 5

2.1 Tea, flavonoids, cardiovascular disease and stroke – recent observational data

2.2 Tea and blood pressure – evidence from recent human intervention studies

3. CONCLUDING REMARKS 19

4. REFERENCES 20

1. Introduction

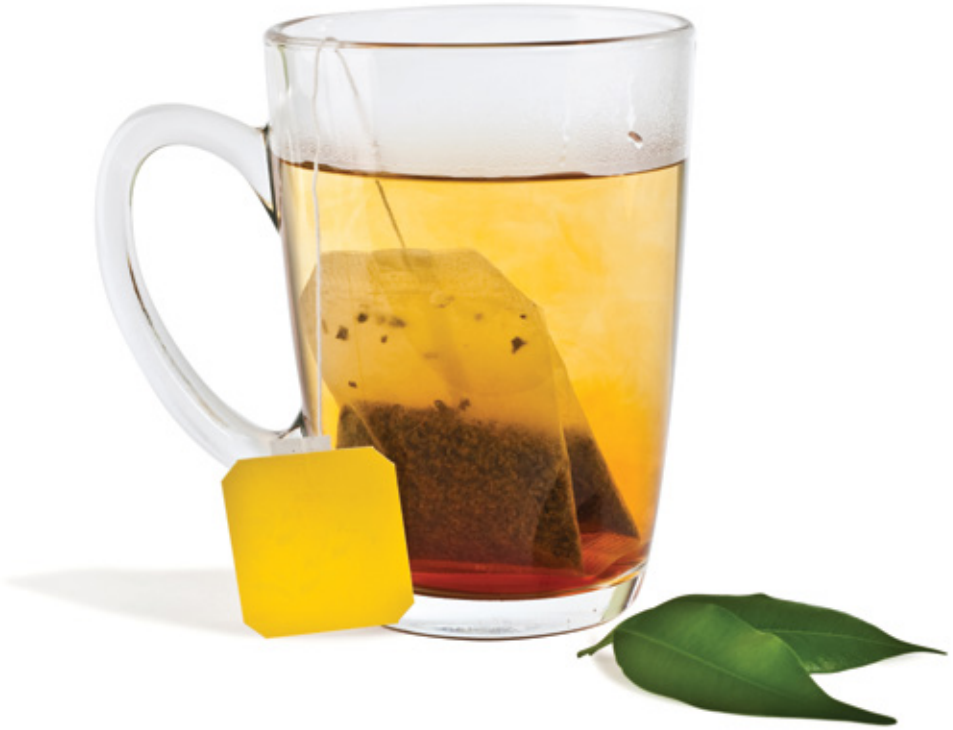
1.1 Black and green tea are rich sources of flavonoids in the diet

Flavonoids are a diverse range of polyphenolic compounds synthesized by plants. They are present in significant amounts in many commonly consumed foods such as fruits, vegetables, cocoa, tea and wine[10]. More than 6000 flavonoid compounds have been identified to date and due to their structural complexity they have been grouped into a number of different sub-classes, the six major ones being flavonols, flavones, flavanones, flavan-3-ols, isoflavones and anthocyanidins.

Both green and black tea, brewed from the leaves of *Camellia sinensis* naturally contain a high concentration of flavonoids. The flavan-3-ol subclass accounts for more than 90% of the total flavonoid content in tea with the remaining made up of the flavonol subclass.

A cup of tea generally provides 150 to 200mg of flavonoids[11]. Given that total flavonoid intake from all sources is usually less than 1000mg/day, in tea-drinking populations, the beverage (as little as 2–3 cups per day) will usually contribute well over half of all flavonoids consumed in the diet[12]. In fact, tea is the major source of dietary flavonoids in most Western countries and in the Far and Middle East[13, 14].

The interest in possible health benefits of black and green tea is increasing[5, 12] and a specific role for the flavonoids contained in tea has been suggested to explain its potential health properties[15, 16].



2. TEA, FLAVONOIDS, BLOOD PRESSURE AND CARDIOVASCULAR DISEASE: RECENT DEVELOPMENTS

2.1 TEA, FLAVONOIDS, CARDIOVASCULAR DISEASE AND STROKE – RECENT OBSERVATIONAL DATA

McCullough ML, Peterson JJ, Patel R, Jacques PF, Shah R, Dwyer JT. Flavonoid intake and cardiovascular disease mortality in a prospective cohort of US adults. Am J Clin Nutr. 2012 Feb; 95(2): 454-64.

ABSTRACT

BACKGROUND: *Flavonoids are plant-based phytochemicals with cardiovascular protective properties. Few studies have comprehensively examined flavonoid classes in relation to cardiovascular disease mortality.*

OBJECTIVE: *We examined the association between flavonoid intake and cardiovascular disease (CVD) mortality among participants in a large, prospective US cohort.*

DESIGN: *In 1999, a total of 38,180 men and 60,289 women in the Cancer Prevention Study II Nutrition Cohort with a mean age of 70 and 69 y, respectively, completed questionnaires on medical history and lifestyle behaviours, including a 152-item food-frequency questionnaire. Cox proportional hazards modeling was used to calculate multivariate-adjusted hazard RRs and 95% CIs for associations between total flavonoids, 7 flavonoid classes, and CVD mortality.*

RESULTS: *During 7 y of follow-up, 1589 CVD deaths in men and 1182 CVD deaths in women occurred. Men and women with total flavonoid intakes in the top (compared with the bottom) quintile had a lower risk of fatal CVD (RR: 0.82; 95% CI: 0.73, 0.92; P-trend = 0.01). Five flavonoid classes-anthocyanidins, flavan-3-ols, flavones, flavonols, and proanthocyanidins-were individually associated with lower risk of fatal CVD (all P-trend < 0.05). In men, total flavonoid intakes were more strongly associated with stroke mortality (RR: 0.63; 95% CI: 0.44, 0.89; P-trend = 0.04) than with ischemic heart disease (RR: 0.90; 95% CI: 0.72, 1.13). Many associations appeared to be nonlinear, with lower risk at intakes above the referent category.*

CONCLUSIONS: *Flavonoid consumption was associated with lower risk of death from CVD. Most inverse associations appeared with intermediate intakes, suggesting that even relatively small amounts of flavonoid-rich foods may be beneficial.*

SUMMARY

In this prospective cohort study, the relation between total flavonoid intake, as well as intake of individual flavonoid classes, and deaths from CVD, ischemic heart disease (IHD), and stroke was investigated in a large US cohort of men and women from the American Cancer Society's CPS-II Nutrition Cohort. The scientists used a validated semi-quantitative food frequency questionnaire (FFQ) to quantify the total flavonoid intake and that of 7 flavonoid classes (anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, proanthocyanidins and isoflavones) in a selection of 38,180 men and 60,289 women. The subjects were followed for 7 years, and during this period, a total of 2,771 deaths occurred due to CVD, 1,286 deaths due to IHD and 573 deaths due to stroke. Flavonoid intakes were grouped into quintile categories to examine CVD and IHD endpoints. Due to the smaller number of events, flavonoid intakes were grouped into quartile categories to examine stroke endpoints.

2.1

In this population, energy-adjusted total flavonoid intakes for men ranged from 99–498 mg/d (10th–90th percentile) with a mean of 268 mg/d; and for women, it ranged from 92–522 mg/d with a mean of 268 mg/d. Subjects with higher total flavonoid intakes were more educated, less likely to have a history of hypertension, exercised more, had a slightly lower BMI, and were less likely to smoke, although oddly enough were more likely to have a history of high cholesterol. These participants also ate more fruit and vegetables as well as less trans- and saturated fats. They were also more likely to be regular users of vitamin supplements.

After adjustment for confounders, men and women with total flavonoid intakes in the highest (compared with lowest) quintile had an 18% lower risk of fatal CVD. For the individual flavonoid classes, statistically significant inverse associations were observed for anthocyanidins, flavan-3-ols, flavones, flavonols, and proanthocyanidins with risk reductions ranging from 14% to 18%. For fatal IHD, only flavone consumption was associated with lower risk in men and women combined (25% risk reduction for the highest versus the lowest quintile). For fatal stroke total flavonoid intake was associated with 37% reduction in risk, but only in men (quartile 4 compared with quartile 1). Interestingly, many of the relations between flavonoid intakes and outcomes were non-linear, meaning that risk reduction already appeared at the second quintile.

INTERPRETATION:

The findings from this large prospective cohort study make an important contribution to the existing body of evidence for a role of flavonoids in lowering the risk of fatal CVD. What is very interesting is that the observed associations between CVD risk and flavonoid intake (as well as those for several flavonoid classes) were non-linear, which suggests that consumption of relatively small amounts flavonoid-rich foods could already have a beneficial effect on CVD risk. For fatal stroke though, only total flavonoid intake was associated with a reduced risk and only in men whilst no reduction in risk was seen for any of the sub-classes. By contrast, a recent meta-analysis of 6 prospective cohort studies by Hollman *et al.* demonstrated a 20% reduction in stroke risk for the flavonol sub-class[17]. It has to be mentioned though that the meta-analysis looked at the combined incidence of both fatal- and non-fatal stroke whereas the current study only investigated the effect on fatal outcomes.

The authors noted possible limitations of the study: flavonoid intake may have been misclassified and risk estimates attenuated as FFQs cannot capture all possible sources of flavonoids in the diet. In spite of this the authors believe that the majority of important flavonoid sources in the US diet were captured as their intake data are in agreement with other studies in this population. It also has to be considered that due to the multiple associations examined that some of the findings could be due to chance – as such the authors' state that their findings should be seen as suggestions for hypotheses generation and further testing, and not as evidence of cause and effect. Nevertheless, it can be concluded that total flavonoid intake and that of several flavonoid classes are associated with a reduced risk of death from CVD and if these findings could be replicated, recommendations for food sources rich in specific flavonoids should be considered for CVD risk reduction in the population.

2.1

Cassidy A, Rimm EB, O'Reilly EJ, Logroscino G, Kay C, Chiuve SE, Rexrode KM. Dietary flavonoids and risk of stroke in women. Stroke. 2012 Apr;43(4):946-51.

ABSTRACT

BACKGROUND AND PURPOSE: *To date, few studies have examined associations between the wide range of flavonoid subclasses and risk of ischemic, hemorrhagic, and total stroke.*

METHODS: *We conducted a prospective study among 69 622 women from the Nurses' Health Study. Total flavonoid and subclass intakes were calculated from semiquantitative food frequency questionnaires collected every 4 years using an updated and extended US Department of Agriculture flavonoid database.*

RESULTS: *During 14 years of follow-up, 1803 incident strokes were confirmed. After adjusting for potential confounders, women in the highest compared with the lowest quintile of flavanone intake had a relative risk of ischemic stroke of 0.81 (95% CI, 0.66-0.99; P=0.04). Citrus fruits/juices, the main dietary source of flavanones, tended to be associated with a reduced risk for ischemic stroke (relative risk, 0.90; 95% CI, 0.77-1.05) comparing extreme quintiles.*

CONCLUSIONS: *Total flavonoid intake was not inversely associated with risk of stroke; however, increased intake of the flavanone subclass was associated with a reduction in the risk of ischemic stroke. Citrus fruit consumption may be associated with a reduction in stroke risk, and experimental data support these epidemiological associations that the flavanone content of citrus fruits may potentially be cardioprotective. Further prospective studies are needed to confirm these associations.*

SUMMARY:

For this paper, Cassidy et *al.* examined the relationship of the 6 main flavonoid subclasses (flavanones, anthocyanins, flavan-3-ols, polymers, flavonols and flavones) commonly consumed in the US diet with the risk of ischemic, hemorrhagic and total stroke. For this purpose they conducted a prospective study among women taking part in the Nurses' Health Study (NHS), a cohort of 121 700 female US nurses followed since 1976. Dietary intake data was collected by means of semiquantative FFQs sent to the participants every 4 years. Data from 1990 was chosen as the baseline since the FFQs administered at that time contained a sufficient number of fruits and vegetables to more accurately estimate intake of the various flavonoid subclasses. After exclusion of subjects with unsuitable FFQ data and those who reported a history of cancer or cerebrovascular disease prior to 1990, a total of 69 622 women were available for analysis. The participants provided person-time of follow-up from the date of return of 1990 FFQ up until the date of stroke diagnosis, death or end of the follow-up period. The authors used Cox proportional hazard modelling to assess the associations between the different flavonoid classes and stroke risk.

2.1

The total flavonoid intake in this population ranged from 96.8 to 761 mg/d (lowest to highest quintile) with a median of 232 mg/d. Tea was the main contributor to flavonoid intake with oranges and orange juice along with apples also providing significant contributions. As was the case with the cohort in the paper of McCullough *et al.*, subjects with higher total flavonoid intake tended to have a healthier diet and lifestyle. Follow-up lasted for 14 years and during this period 1803 cases of stroke were documented (943 ischemic, 253 hemorrhagic and 607 unknown).

When comparing the lowest with the highest quintiles of intake, none of the flavonoid subclasses were associated with a reduced risk of hemorrhagic stroke. For ischemic stroke, only the flavanone subclass was associated with a statistically significant reduction in risk (19% reduction for the highest versus the lowest quintile of intake). Flavanones are derived mainly from citrus fruits and juices which also contain vitamin C and potassium which may also reduce the risk of stroke. Adjusting for these components in the statistical model did not appreciably alter the effect though (20 and 17% risk reduction when adding vitamin C and potassium respectively).

INTERPRETATION:

This study demonstrated an impressive association between flavanone intake and a reduction in stoke risk in women. The findings are supported by existing data associating citrus fruit with a reduced risk of stroke, given that 95% of flavanone intake was derived from citrus consumption. Neither total flavonoid intake nor any of the other flavonoid subclasses were associated with a reduced stroke risk though. As mentioned above, Hollman *et al.* did find an association between a higher intake of the flavonol sub-class and a reduced risk of stroke. The authors suggest that a possible explanation for this difference might be the fact that flavonol intake in this cohort was quite low (median of 14.5 mg/day) whereas the intake of flavanones was much higher (30.4 mg/day). In a Letter to the Editor, Olié *et al.* commented that recent data they produced from the SU.VI.MAX study (a prospective cohort study of 6101 French men and women followed for 13 years) showed flavonol intakes more than 3-fold higher and total flavonoid intakes nearly twice as high as those in the NHS cohort[18]. In keeping with the findings of Hollman *et al.*, a higher flavonol intake was also associated with a reduced risk of stroke. The same association was found for total flavonoid intake and that of several of the other individual sub-classes as well. Oddly though, flavanone intake was not associated with a reduced stroke risk.

This highlights an important shortcoming in current flavonoid and health epidemiological research. Different studies on the health effects of flavonoids have often used different databases of analytical data to calculate intakes of the various flavonoid classes which makes direct comparison between studies difficult. For instance Olié *et al.* used the recent phenol-explorer database which combines a relatively large number of individual components to make up the individual flavonoid sub-classes; e.g. 22 for flavanones, 49 for flavones, 34 for flavonols and 74 for anthocyanins. Cassidy *et al.* constructed their database before the availability of phenol-explorer and used much less components to define the individual sub-classes – only 3 to 6 components in most cases. Such fundamental differences in the tools used would obviously result in differences in the calculated flavonoid intakes. This could also result in differences in the observed associations with clinical endpoints. Both Cassidy and Olié *et al.* agreed that there is a definite need for harmonization of the databases used in different studies to allow for proper comparison of results between studies.

2.1

Shen L, Song LG, Ma H, Jin CN, Wang JA, Xiang MX. Tea consumption and risk of stroke: a dose-response meta-analysis of prospective studies. J Zhejiang Univ Sci B. 2012 Aug;13(8):652-62.

ABSTRACT

OBJECTIVE: *To determine the association between tea consumption and the risk of stroke.*

METHODS: *We searched the PubMed database from January 1966 to March 2012 and reviewed reference lists of retrieved articles to identify relevant studies. Studies were included if they reported relative risks (RRs) and corresponding 95% confidence intervals (CIs) of stroke with respect to three or more categories of tea consumption. A random-effects model was used to combine the study-specific risk estimates.*

RESULTS: *Fourteen studies, consisting of 513804 participants with a median follow-up of 11.5 years, were included in this meta-analysis. We observed a modest but statistically significant inverse association between tea consumption and risk of stroke. An increase of three cups/d in tea consumption was associated with a 13% decreased risk of stroke (RR 0.87; 95% CI, 0.81-0.94). The decreased risk of stroke with tea consumption was consistent among most subgroups. Based on the three studies that provided results for stroke subtypes, tea consumption was also inversely associated with the risk of ischemic stroke (RR 0.76; 95% CI, 0.69-0.84), but not cerebral haemorrhage (RR 0.96; 95% CI, 0.82-1.11) or subarachnoid haemorrhage (RR 0.81; 95% CI, 0.57-1.16).*

CONCLUSIONS: *Tea consumption is associated with a decreased risk of stroke, particularly ischemic stroke. More well-designed, rigorously conducted studies are needed in order to make confident conclusions about the association between tea consumption and stroke subtypes.*

SUMMARY:

In 2009 Arab *et al.* published a meta-analysis in which they demonstrated a strong inverse association between tea consumption and the risk of stroke[19]. Since that time a number of new cohort studies investigating the same association have been published. This prompted Shen *et al.* to perform an updated meta-analysis of prospective cohort studies to re-assess the association between tea consumption and the risk of stroke and its subtypes.

The authors searched the PubMed database for prospective cohort studies published from January 1966 to March 2012. Reference lists of obtained papers were also reviewed to search for additional studies. The search produced 14 studies from the USA, Japan, the Netherlands and Finland which provided data from 513 804 individuals which were followed for 4 to 20.8 years. In all but two studies (which were not clearly defined) subjects were free from cardiovascular disease and stroke at baseline.

Overall, 10,192 cases of stroke were reported during the median follow up of 11.5 years. The authors reported a reduction in risk for total stroke of 13% for every 3 cups per day increase in tea consumption. For stroke subtypes, a 24% reduction in ischemic stroke risk was seen for every 3 cups per day increment. The inverse association with hemorrhagic stroke did not reach statistical significance however. The authors noted that there was moderate heterogeneity between the studies but their analysis showed little evidence of possible publication bias.

2.1

INTERPRETATION:

These results provide compelling evidence supporting the association of tea intake with a reduced risk of stroke and are in agreement with those of the previous meta-analysis by Arab *et al*. This analysis however had more than double the number of subjects and cases of stroke, which allowed for a more precise estimation of risk. An important caveat needs to be taken into account though; the authors used statistical assumptions to combine the data from various studies and calculated continuous risk for every 3 cups of tea. They therefore also assumed that there is a linear dose-response relationship between tea consumption and risk of stroke. Arab *et al*. found a similar reduction in stroke risk, but only compared consumption of < 1 cup of tea per day to ≥ 3 cups of tea per day. Given the data from McCullough *et al*. discussed above, it is highly unlikely that the reduction in risk of stroke would double for every additional 3 cups of tea.

Another important point that needs to be taken into account is the fact that observational studies are prone to influence from a wide variety of confounding factors and results should always be interpreted with caution. The authors noted that one cannot completely rule out the possibility that the associations they observed were due to residual confounding. It has been found in some cases, that individuals with a high consumption of tea lead a generally healthier lifestyle, which in itself can also have an impact on the risk of stroke. It was also mentioned that there was an insufficient number of studies investigating the association between tea consumption and hemorrhagic stroke (only 3 of the studies also provided data on stroke subtypes) and therefore the non-significant association observed could be due to insufficient statistical power. In the end the authors conclude that their meta-analysis of prospective cohort studies provides strong support for an inverse association between tea consumption and the risk of stroke, although more research is warranted into the associations with different stroke subtypes.

OBSERVATIONAL DATA – CONCLUSION:

The publications discussed above provide interesting population-based data that add to the existing body of evidence of flavonoids' (and tea as a major source of flavonoids) beneficial cardiovascular effects. The meta-analysis of Shen *et al*. is especially interesting since it reaffirms link between tea and a reduced risk of stroke demonstrated by Arab *et al*. a few years ago.

The three studies that investigated the associations between the different sub-classes of flavonoids are of note since only one previous study has attempted this[20] – most previous studies have investigated a specific sub-class or individual flavonoid. Even though McCullogh-, Cassidy- and Olié *et al*. all found some form of association between flavonoid intake and a reduced risk of stroke, inconsistencies between their results indicate that much work still needs to be done in this field, especially with regard to harmonization of the various flavonoid databases used to calculate intakes, in order to make comparisons between these kinds of studies more meaningful.

As mentioned before, due to their inherent shortcomings, findings from epidemiological studies like those above should be interpreted with caution and not seen as evidence of cause and effect. However "conclusive proof" for a protective effect of flavonoids (and flavonoid-rich foods like tea) on cardiovascular disease in the form of long-term intervention studies with hard clinical outcomes is simply out of reach due to the massive scope and staggering costs involved. Studies like those discussed above therefore provide interesting suggestions for hypotheses generation and further testing; testing which could be done on surrogate endpoints of cardiovascular disease such as blood pressure and endothelial function in human intervention studies which in combination with epidemiological data do provide compelling evidence to support a cause and effect relationship.

2.2

2.2. TEA AND BLOOD PRESSURE – EVIDENCE FROM RECENT HUMAN INTERVENTION STUDIES

Bogdanski P, Suliburska J, Szulinska M, Stepien M, Pupek-Musialik D, Jablecka A. Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. Nutr Res. 2012 Jun;32(6):421-7. Epub 2012 Jun 20.Epub 2012 Jun 20.

ABSTRACT

Green tea (GT) consumption is known to be associated with enhanced cardiovascular and metabolic health. The purpose of this study is to examine the hypothesis that supplementation with GT alters insulin resistance and associated cardiovascular risk factors in obese, hypertensive patients. In a double-blind, placebo-controlled trial, 56 obese, hypertensive subjects were randomized to receive a daily supplement of 1 capsule that contained either 379 mg of GT extract (GTE) or a matching placebo, for 3 months. At baseline and after 3 months of treatment, the anthropometric parameters, blood pressure, plasma lipid levels, glucose levels, creatinine levels, tumour necrosis factor α levels (TNF-α), C-reactive protein levels, total antioxidant status, and insulin levels were assessed. Insulin resistance was evaluated according to the homeostasis model assessment-insulin resistance protocol. After 3 months of supplementation, both systolic and diastolic blood pressures had significantly decreased in the GTE group as compared with the placebo group ($P < .01$). Considerable ($P < .01$) reductions in fasting serum glucose and insulin levels and insulin resistance were observed in the GTE group when compared with the placebo group. Serum tumour necrosis factor α and C-reactive protein were significantly lower, whereas total antioxidant status increased in the GTE group compared with the placebo ($P < .05$). Supplementation also contributed to significant ($P < .05$) decreases in the total and low-density lipoprotein cholesterol and triglycerides, but an increase in high-density lipoprotein cholesterol. In conclusion, daily supplementation with 379 mg of GTE favourably influences blood pressure, insulin resistance, inflammation and oxidative stress, and lipid profile in patients with obesity-related hypertension.

SUMMARY:

Obesity, hypertension and low-grade inflammation are a set of conditions that often co-exist and significantly increase the risk of CVD through a set of common pathological mechanisms involving insulin resistance and endothelial dysfunction. Available evidence suggests that green tea and its most abundant catechin, epigallocatechin-3-gallate (EGCG), could have beneficial effects on different markers of cardiovascular health. Therefore Bogdanski *et al.* set out to determine the effects of a green tea extract on blood pressure, insulin resistance and markers of inflammation and oxidative stress in obese hypertensive individuals.

The authors recruited 56 obese hypertensive patients from their outpatient clinic into a randomised, double blind, placebo controlled parallel trial. Subjects were randomised to receive either 379 mg GTE (containing 208 mg EGCG) or a cellulose placebo for a period of 3 months. Subjects returned to the study centre every 14 days to return their test product packaging and to receive a new supply. Compliance was checked by means of pill counting. During these visits, the investigators also collected dietary records by means of 24 hour recalls in order to ensure that nutrient and caffeine intake remained constant for the duration of the study.

2.2

After 3 months of intervention, the authors found statistically significant reductions in systolic- and diastolic blood pressure of approximately 4 mmHg when comparing the intervention and placebo groups. Statistically significant reductions were also seen in plasma lipids, insulin and insulin resistance as well as in the inflammatory markers TNF-α and CRP.

INTERPRETATION:

This study provides interesting additional data that the green tea flavonoid EGCG could have beneficial effects on blood pressure in human subjects. These findings are in line with a number of previous studies that have demonstrated blood pressure lowering effects in subjects supplemented with catechins[21-23]. Conversely, two others could not demonstrate any blood pressure lowering effects[24, 25]. Several differences between these studies such as the type of product given, the dose and composition of catechins, the way the test product was administered, the length of the intervention period and the nature of the study population could however explain the discrepancy in findings between them.

There are a few limitations of this study that need to be taken into account, chief of which is the fact that only office blood pressure was measured. Ideally 24-hour ambulatory blood pressure measurement would provide a more accurate and relevant measure of any effect of an intervention on blood pressure. The study was also quite small, with only 28 subjects per study arm. The authors also state that future studies on a larger scale and with a longer follow-up are needed to support the current data, although with the rising epidemics of obesity and hypertension across the world, such potential blood pressure lowering effects hold great promise for public health.

2.2

Grassi D, Draijer R, Desideri G, Mulder T, Ferri C. Blood pressure lowering and other vascular effects of black tea in mildly hypertensive subjects. Journal of Hypertension, Vol 30, e-Supplement A, April 2012, e477.

ABSTRACT

Hypertension is the leading risk factor for cardiovascular morbidity and mortality. Black tea consumption improved flow-mediated vasodilation (FMD) in previous studies and we hypothesized this may positively affect blood pressure (BP) and digital volume pulse (DVP), also protecting from fat-challenged vascular alterations. We assessed black tea effects with and without a fat load on office BP, FMD and DVP in never treated grade 1 hypertensives without additional cardiovascular risk factors. According to a randomized, double-blind, controlled, cross-over design, 19 patients were assigned to consume black tea (150 mg polyphenols) or placebo drink matched for caffeine, color and taste, twice a day for 8 days (13 day wash-out period). On day 7 measurements were in a fasted state, while on day 8 subjects consumed whipping cream (1 g fat/kg) 30 min after consuming test products. FMD, DVP and BP were measured at baseline and 1, 2, 3 and 4 h after consumption of the test products. Compared to placebo, baseline systolic (–3.3 mmHg) and diastolic (–2.6 mmHg) BP decreased and FMD improved after tea consumption (+1.3%; $p < 0.0001$). An additional cup of tea further increased FMD at 1, 2, 3 and 4 h after consumption ($p < 0.0001$). Fat challenge significantly increased BP ($p < 0.0001$) and decreased FMD ($p < 0.0001$). This was counteracted by tea consumption. Tea improved reflection index (small vessel tone; $p < 0.0001$) and stiffness index (large arterial stiffness; $p < 0.0001$) with additional effects after acute tea consumption with and without fat load. This study confirms positive effects of tea on endothelial function, also suggesting black tea protects against fat load-induced arterial dysfunctions in hypertensive subjects. The vascular benefits of tea are also reflected in BP lowering and peripheral arterial protection under fasted and postprandial conditions. Our findings are of clinical relevance and interest from a population-based point of view, because of the consumer-relevant black tea dose used in this study, and tea being globally the most consumed beverage after water.

SUMMARY:

Previous research by this group and others has demonstrated that consumption of black tea has positive effects on endothelial function. In contrast, a meal rich in fat has been reported to have detrimental effects on endothelial function[26, 27]. Although both the positive effects after tea dinking and the negative effects after a fatty meal could be transient in nature, they may nevertheless be of major interest since lipemia following a fatty meal occurs several times per day and tea drinkers usually consume a number of cups of tea during the day. Therefore the investigators set out to examine the effect of treatment with black tea on endothelial function and blood pressure before and after consumption of a fat load.

2.2

Nineteen newly diagnosed hypertensive subjects that had never been treated before were recruited into a randomised, double blind, placebo-controlled cross-over trial. After a 7-day run-in period, the subjects were randomly assigned to consume 2 cups of either the tea or placebo interventions per day. The tea was provided in the form of a powder reconstituted in hot water to ensure that the same dose taken every time. The placebo was also matched for colour, taste and caffeine content. On the 7th intervention day, blood pressure, endothelial function and vascular stiffness was measured in a fasted state and after consumption of the test beverage. The same procedure was followed on the 8th intervention day with the addition of an oral fat load (1 gram per kilogram bodyweight) 30 minutes after consumption of the test beverage. On both days, measurements were also repeated at 1, 2, 3 and 4 hours after consumption of the test beverages.

Compared with placebo, one week's black tea ingestion led to a statistically significant decrease in baseline systolic blood pressure (- 3.3 mmHg on day 7 and -3.9 mmHg day 8) and diastolic blood pressure (- 2.6 mmHg on day 7 and -3.5 mmHg day 8). Acute black tea administration led to additional decreases over the 4-hour measurement period. Administration of the fat load led to statistically significant increases in blood pressure values over the 4-hour measurement period; whereas after black tea ingestion, blood pressure was not significantly different in response to the fat load. Similar patterns were also demonstrated for the measures of endothelial function and vascular stiffness.

INTERPRETATION:

The investigators demonstrated that flavonoid-rich black tea attenuated, or completely prevented, the abnormalities in endothelial function and peripheral arterial hemodynamics that were caused by an acute oral fat load in never-treated hypertensive patients.

An acute fat load administered orally or intravenously significantly increases blood pressure, alters endothelial function, and activates the sympathetic nervous system[27]. This could at least be partly due to fat loading causing an increase in the production of oxygen-derived free radicals which rapidly combines with NO, leading to a transient loss of NO bioavailability and an increase vascular damage, resulting in endothelial dysfunction, impaired peripheral vascular tone and arterial stiffness[28].

The results of this study confirm the abovementioned observations, and also show for the first time that the fat-induced changes in blood pressure, endothelial function and arterial stiffness could be prevented by flavonoid-rich black tea administration. Flavonoids may protect from stress-induced fat load by increasing the bioavailability of NO and decreasing the formation of reactive oxygen and nitrogen species. In keeping to this, the effect of black tea observed on endothelial function, is consistent with previous studies by this group and several others[28, 29].

It is important to note that while the study design was rigorous, it was also short-term and included only a small number of subjects. However, epidemiological- and mechanistic studies suggest that flavonoids may have beneficial effects on the cardiovascular system and protect against the risk of CVD[6]. Several lines of clinical and experimental evidence also indicate that tea flavonoids may protect against CVD by improving endothelial function, increasing NO bioavailability, and decreasing blood pressure, which support these findings. Similar studies with larger numbers of subjects and longer durations are still warranted though.

2.2

Hodgson JM, Puddey IB, Woodman RJ, Mulder TP, Fuchs D, Scott K, Croft KD. Effects of black tea on blood pressure: a randomized controlled trial. Arch Intern Med. 2012 Jan 23;172(2):186-8; Hodgson JM, Woodman RJ, Puddey IB, Mulder T, Fuchs D, Croft KD. Short-term effects of polyphenol-rich black tea on blood pressure in men and women. Food Funct. 2012 Oct 5. [Epub ahead of print].

ABSTRACT

There is increasing evidence that black tea polyphenols contribute to vascular health. We have recently shown that regular ingestion of polyphenol-rich black tea over 6 months results in lower systolic and diastolic blood pressure. However, the time course of these effects remains unclear. Therefore, our objective was to determine if short-term effects of tea on blood pressure could contribute to longer-term benefits of regular tea consumption on blood pressure. Men and women (n=111) were recruited to a randomised placebo-controlled double-blind parallel designed trial. During a 4-wk run-in, all participants consumed 3 cups/d of black tea. Participants then consumed 3 cups over 1 d of either powdered black tea solids containing 429 mg of polyphenols (tea), or a control product matched in flavour and caffeine content, containing no tea solids. The 24 h ambulatory blood pressure and heart rate was measured at the end of the 4-week run-in (baseline) and again during the 24 h intervention period. The 24 h, day-time and night-time blood pressures were not significantly different between tea and control (P>0.05). Baseline-adjusted net effects on mean 24 h ambulatory blood pressure for systolic and diastolic blood pressure were -0.2 mm Hg (95% CI, -1.5 to 1.0), P=0.72, and 0.0 mm Hg (95% CI, -1.0 to 0.9), P=0.95, respectively. Heart rate was significantly lower for tea compared to control during the night-time and early-morning periods (-2.0 (95% CI, -3.2,-0.8) bpm; and -1.9 (95% CI, -3.7,-0.2) bpm, respectively, P<0.05 for both), but not during the day-time. These results suggest that the longer-term benefits of black tea on blood pressure are unlikely to be due to short-term changes.

SUMMARY:

Even though consumption of black and green tea is associated with lower blood pressure and a lower incidence of cardiovascular disease and stroke, there is still limited clinical evidence on the effects on the long-term effects of tea on blood pressure. The group of Hodgson *et al*. therefore set out to assess the effects of regular black tea consumption for 6 months on 24-hour ambulatory blood pressure as described in a Letter to the Editor in the Archives of Internal Medicine followed by a second publication where the authors looked specifically at the effect that tea consumed over the course of a day at the beginning of the study had on 24-hour ambulatory blood pressure.

Healthy regular tea drinkers were recruited from the general population to take part in this randomised, placebo controlled double-blind parallel trial. A total of 111 subjects entered the study and were randomly divided into either the tea or placebo intervention groups. A 4-week run-in period followed during which all subjects were instructed to drink 3 cups of regular leaf tea.

2.2

At the end of the run-in, subjects ceased consumption of their regular leaf tea and entered the intervention phase of the study. During this period, subjects were provided with sachets containing a standardised black tea powder. Each sachet was equivalent to one cup of tea and contained approximately 500 mg black tea solids, which provided 120 mg flavonoids and 30 mg caffeine. The tea was reconstituted by adding hot water and the subjects were instructed to drink 3 cups per day. Subjects in the control group received a placebo tea which was matched in colour, flavour and caffeine content. Measures of 24-hour ambulatory blood pressure were taken at the end of the run-in period (baseline), during the first intervention day to assess the acute effects, and after 3 and 6 months to assess the longer-term effects.

For the long-term effects, ninety-five subjects with complete baseline data were eventually included in the final statistical analysis. The investigators found that compared with placebo, regular consumption of 3 cups of black tea per day resulted in statistically significant reductions of systolic- and diastolic blood pressure of between 2 and 3 mmHg at both 3 and 6 months. For the acute effects, complete ambulatory blood pressure data of the first intervention day were available for 84 participants. Compared with placebo, it was found that black tea did not alter mean ambulatory blood pressure during the first 24-hour period. In addition, black tea did not significantly alter blood pressure during pre-specified early morning-, night- and day-time periods during the 24 hours.

INTERPRETATION:

This was the first study to demonstrate that long-term regular consumption of black tea can lead to statistically significant reductions in blood pressure. A previous study of the same duration and design by Mukamal *et al*[30]. found no effect of black tea; however this was a pilot study with only 14 subjects per study group and was therefore not sufficiently powered to detect small changes in blood pressure. The combination of acute and long-term blood pressure measurements in the current study provide interesting information and indicate that any benefits on blood pressure with long term regular black tea intake are unlikely to be due to short-term blood pressure changes. If the data of Grassi *et al*. are considered, any blood pressure lowering effects probably take at least a week to manifest.

A number of previous studies have investigated the acute blood pressure effects of a single dose of tea after an overnight fast. In most cases a short-lived transient increase in blood pressure was found which has been attributed to the caffeine present in the tea[31-33]. The relevance of such effects to the impact of regular tea consumption on ambulatory blood pressure and ultimately to the risk of hypertension and cardiovascular disease is uncertain however. Also, considering the current data, whatever effect of caffeine may occur it has minimal impact on ambulatory blood pressures in the short-term.

It has to be mentioned that this study assessed the effects of black tea against a background of regular tea consumption. Therefore there is a possibility that effects of black tea could be different if participants were not consuming tea during the run-in period.

2.2

Kay CD, Hooper L, Kroon PA, Rimm EB, Cassidy A. Relative impact of flavonoid composition, dose and structure on vascular function: A systematic review of randomised controlled trials of flavonoid-rich food products. Mol Nutr Food Res. 2012 Sep 19. [Epub ahead of print]

ABSTRACT

SCOPE: *Previous systematic reviews suggest beneficial effects of flavonoids on biomarkers of cardiovascular disease (CVD) risk, but have overlooked the impact of dose response or food complexity. The aim of the present study was to examine the relative impact of composition, flavonoid structure and dose.*

METHODS AND RESULTS: *MEDLINE, EMBASE and Cochrane were searched for randomised controlled trials (RCTs) of flavonoids or flavonoid-rich foods/extracts. Flavonoid composition was established using United States Department of Agriculture (USDA) and Phenol-Explorer databases. Effects of six flavonoid subgroups on endothelial function (flow-mediated dilation; FMD), and systolic and diastolic blood pressures were assessed by random effects meta-analyses and regression analyses. Meta-analyses of combined flavonoid subclasses showed significant improvements in FMD (chronic, 0.73% (0.17, 1.30) 14 RCTs; acute, 2.33% (1.58, 3.08) 18 RCTs) and blood pressures (systolic, -1.46 mmHg (-2.38, -0.53) 63 RCTs; diastolic, -1.25 mmHg (-1.82, -0.67) 63 RCTs). Similar benefits were observed for the flavan-3-ol, catechol flavonoids (catechins, quercetin, cyanidin etc.), procyanidins, epicatechin and catechin subgroups. Dose-response relationships were non-linear for FMD ($R(2) \leq 0.30$), with greater associations observed when applying polynomial regression analyses ($R(2) \leq 0.72$); there was no indication of a dose response for blood pressure.*

CONCLUSION: *The present analysis suggests that flavonoid bioactivity does not follow a classical linear dose-response association and this may have important biological implications.*

SUMMARY:

During the past decade the interest in the possible health benefits of flavonoids have grown significantly. As such, a large number of intervention studies investigating possible vascular function or blood pressure benefits of the various flavonoid classes, single flavonoids or flavonoid-rich foods have been published. Summarizing the data of many intervention studies in a meta-analysis is a robust way to indicate whether the effects of an intervention are consistent. To that end, Kay *et al.* took the interesting approach of combining data of various randomised controlled trials on flavonoids and flavonoid rich foods to investigate the relative impact of composition, flavonoid structure and dose on blood pressure and endothelial function as measured by flow mediated dilation (FMD).

The authors conducted a systematic search which produced 77 studies that reported data on blood pressure, FMD or both with interventions that varied between chocolate, green or black tea, red wine, berries or grapes and extracts containing single flavonoids or flavonoid classes. The compositions of the various interventions were extracted from each manuscript if reported and in cases where no compositional information was present estimations were made using the USDA and phenol-explorer databases. This enabled the authors to conduct individual meta-analyses for the effects of total flavonoids, as well as a number of classes and individual flavonoids.

2.2

When all flavonoid interventions were pooled, statistically significant reductions in both systolic and diastolic blood pressure were observed (–1.46 mmHg and –1.25 mmHg respectively). Similar effects were noted when the flavan-3-ol subclass or catechol flavonoids were grouped together as well as slightly larger effects for epicatechin, procyanidins and quercetin analysed alone. Similar statistically significant improvements were also noted when studies that reported data on FMD were pooled. Interestingly, no indication of a dose-response relationship could be found in the available data for effects on blood pressure. For effects on FMD, non-linear dose-response relationships were found for total flavonoids as well as the different classes, often indicating stronger effects at lower doses.

INTERPRETATION:

The data from this systematic review and meta-analysis provide additional evidence to support the potential blood pressure and vascular function benefits of flavonoids and flavonoid-rich foods. The absence of a dose-response relationship between flavonoid intake and blood pressure is intriguing though. Equally so are the non-linear dose-response relationships found for FMD, which in some cases indicated that the size of the effect decreased as the dose went up. The authors however state that the dose-response data should be interpreted with caution since few of the studies included in their meta-analysis provided high doses of flavonoids, leaving them with a preponderance of lower-dose studies thus rendering the present interpretation of the dose-response somewhat incomplete. However, one should consider that the association with flavonoid intakes and CVD outcomes in the study of McCullough *et al.* (discussed above) was also non-linear with reduced risk of CVD death already becoming apparent at low levels of intake. Such a suggestion that a dose-threshold might exist hold the important implication that systematic reviews combining high- and low-dose interventions without accounting for dose response, may overlook potentially important physiological effects of flavonoids.

The approach of combining different flavonoid intervention studies together in order to investigate the effects of their common flavonoid denominators provides interesting new data. An important limitation however are the assumptions that it is valid to pool data from the different interventions and that individual flavonoids or classes would elicit similar effects when administered in isolation. From the current data it is not possible to tell what effect possible interactions with the food matrix in which the various flavonoids exist has. Therefore investigations into the cardiovascular health effects of individual flavonoid-rich foods are still relevant. Although the results of the meta-analyses of Kay *et al.* are in agreement with previous meta-analyses on the FMD effects of both cocoa and tea[29, 34] (major sources of the flavonoids studies here), only meta-analyses of cocoa have demonstrated blood pressure lowering effects[35] – one on studies on tea found no such effects[36]. Since the publication of this meta-analysis in 2007 a number of new studies including those discussed earlier in this newsletter have been published providing good reason for an update.

HUMAN INTERVENTION DATA – CONCLUSION:

The papers by Bogdanski-, Grassi-, and Hodgson *et al.* discussed above demonstrated that regular consumption of flavonoid-rich tea may have beneficial effects on blood pressure and vascular function. This notion is supported by the meta-analysis of Kay *et al.* that found similar effects on blood pressure and vascular function when pooling data from a large number of flavonoid interventions. The blood pressure lowering effects found ranged from roughly 1.5 to 4 mmHg between the studies, which might be construed as quite modest at an individual level. It has to be noted that at a population level, the effects of even small reductions in blood pressure can deliver substantial gains. As such, reductions of 2 to 3 mmHg in blood pressure are associated with a 10% reduction in the prevalence of hypertension and a 7 to 10% reduction in the risk of cardiovascular disease[3]. Because tea is globally the most consumed beverage after water, these findings may have important public health implications.

3. Concluding remarks

FROM THIS SCIENCE OVERVIEW THE TAKE AWAY MESSAGES FOR THE ROLE OF TEA AND FLAVONOIDS IN CARDIOVASCULAR HEALTH ARE:

- Dietary and lifestyle modifications, such as reduced salt intake and increased physical activity amongst others, have been shown to lower blood pressure or reduce CVD risk. Next to these modifications, there is an emerging body of evidence suggesting a protective role for dietary flavonoids as well.
- Tea is a rich source of flavonoids in the diet. It has been shown that in tea drinking populations, the beverage provides a significant contribution to the daily flavonoid intake.
- Flavonoids may play a role in cardiovascular health. Epidemiological studies have explored the relationships between dietary flavonoids and cardiovascular diseases and their intake has been associated with a lower risk of death from heart disease and stroke.
- Tea, one of the major sources flavonoids in the diet, can play a role in cardiovascular health. Population studies suggest a decreased risk of stroke with higher tea consumption. Human intervention studies have found effects on blood pressure and vascular function, which support the observations from population studies.
- Although more well controlled longer term studies are needed, current evidence suggests that tea and flavonoids contribute to a healthy cardiovascular system by lowering blood pressure.

To conclude, there is a large body of evidence suggesting that flavonoids and tea as a major source thereof may have beneficial effects on cardiovascular health. Since tea is the second most consumed beverage in the world after water, the findings of the studies discussed above, and of those preceding them, are of particular interest for the potential impact that tea can have on public health.

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