Tea Expert Newsletter

Issue one

A scientific update on tea, flavonoids and cardiovascular health

Unilever

SCIENTIFIC UPDATE ON TEA, FLAVONOIDS AND CARDIOVASCULAR HEALTH

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"From the editor"

Tea is the most widely consumed beverage in the world after water [1, 2]. In its long history, tea has always been perceived as healthy beverage. Research into the possible health benefits of tea only took off in the last two decades. Nevertheless a significant body of research has been produced, from population studies all the way through human intervention studies and down to mechanistic, animal and in-vitro research – each providing a piece to a larger puzzle that suggests possible positive effects of tea on blood vessel function and even cardiovascular health as a whole.

The global burden of cardiovascular disease is massive – having claimed an estimated 17 million lives worldwide in 2004, it is still the number one cause of death and the WHO estimates that this number will increase to almost 24 million by 2030 [3]. The developing world will bear an increasing portion of this burden, for example in countries like China and India factors like westernisation, urbanization, increasing affluence and rapid population growth are causing rates of cardiovascular disease incidence to reach epic proportions [4].

Population studies strongly suggest a decreased risk of CVD with higher tea consumption, which has been found to be associated with the high flavonoid content of tea. A cup of tea generally provides 150 to 200 mg of flavonoids, which makes tea a significant contributor to the daily flavonoid intake.

Because of the potential role of tea in cardiovascular health – most likely via an effect of tea flavonoids in improving blood vessel functioning – the impact of tea consumption on public health could be substantial [5-7].

CONTENT

For this newsletter we have selected and put in context recent scientific papers which have looked into the role of tea and flavonoids in cardiovascular health

We start with a new meta-analysis which combined data from case-control- and prospective cohort studies on the impact of black and green tea consumption on coronary artery disease. It is followed by recent large prospective cohort study on the effects of coffee and tea consumption on cardiovascular morbidity and mortality which corroborates some of the meta-analysis' findings.

The potential role of flavonols, a specific class of tea flavonoids, in relation to a reduction in stroke risk is discussed, linked to a meta-analysis of 6 prospective cohort studies and a well-written narrative review by two experts in the field of tea and cardiovascular health.

We also share with you a recent meta-analysis by our Unilever R&D experts on tea and cardiovascular health, on the effects of tea on blood vessel function. Lastly we discuss a paper indicating the importance of blood vessel function as a surrogate marker for cardiovascular risk.

1. INTRODUCTION

1.1. TEA - MADE OF THE LEAVES OF CAMELLIA SINENSIS, IS A RICH SOURCE OF FLAVONOIDS IN THE DIET

The interest in possible health benefits of tea is increasing [1, 2] and a specific role for certain flavonoids has been suggested [8, 9] to explain the potential health properties of tea .

Flavonoids are polyphenolic compounds synthesized by plants. Their structure (C6-C3-C6) consists of two aromatic rings linked by a 3-carbon chain that forms an oxygenated heterocyclic ring (C ring) as illustrated in Figure 1. Flavonoids are generally classified into a number of different subgroups, the six major subclasses being flavonols, flavones, flavanones, flavan-3-ols, isoflavones and anthocyanidins. More than 6000 flavonoid compounds have been identified, many of which are present in fruits, vegetables, cocoa, tea and wine [10].
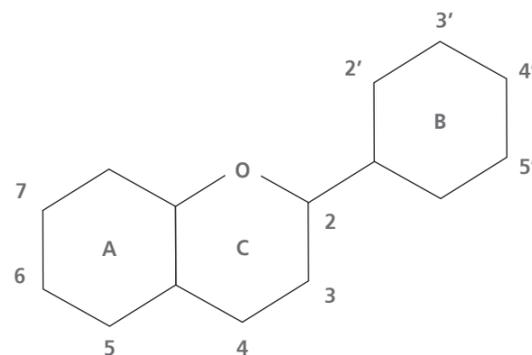
The main flavonoids found in tea are flavan-3-ols, accounting for more than 90% of the total flavonoid content in tea, the remaining flavonoids being flavonols. The level and type of flavonoids in tea varies greatly depending on the type of tea (green or black), variety, growing condition, manufacture process, amount of tea in the bag, size of the leaves, and tea preparation habits (e.g. brewing time) though [11].

Both green and black teas naturally contain a high amount of flavonoids. In fact, tea is the major source of dietary flavonoids in most Western countries and in the Far and Middle East [12, 13]. A cup of tea generally provides 150 to 200 mg of flavonoids [14]. Considering that total flavonoid intake from all sources is usually less than 1000 mg/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 [2].

Figure 1: The basic structure of a flavonoid

2. SOME RECENT DEVELOPMENTS IN THE AREA OF TEA, TEA FLAVONOIDS AND CARDIOVASCULAR HEALTH

2.1. TEA, TEA FLAVONOIDS AND CARDIOVASCULAR HEALTH – OBSERVATIONAL DATA

ABSTRACT
BACKGROUND: Epidemiologic studies are inconsistent regarding the association between tea consumption and the risk of coronary artery disease (CAD).

OBJECTIVE: The objective was to perform a meta-analysis to determine whether an association exists between tea consumption and total CAD endpoints in observational studies.

DESIGN: We searched PUBMED and EMBASE databases for studies conducted from 1966 through November 2009. Study-specific risk estimates were combined by using a random-effects model.

RESULTS: A total of 18 studies were included in the meta-analysis: 13 studies on black tea and 5 studies on green tea. For black tea, no significant association was found through the meta-analysis [highest compared with lowest, summary relative risk (RR): 0.92; 95% CI: 0.82, 1.04; an increment of 1 cup/d, summary RR: 0.98; 95% CI: 0.94, 1.02]. For green tea, the summary RR indicated a significant association between the highest green tea consumption and reduced risk of CAD (summary RR: 0.72; 95% CI: 0.58, 0.89). Furthermore, an increase in green tea consumption of 1 cup/d was associated with a 10% decrease in the risk of developing CAD (summary RR: 0.90; 95% CI: 0.82, 0.99).

CONCLUSIONS: Our data do not support a protective role of black tea against CAD. The limited data available on green tea support a tentative association of green tea consumption with a reduced risk of CAD. However, additional studies are needed to make a convincing case for this association.

SUMMARY:
The objective of the authors was to perform a meta-analysis to determine whether an association exists between tea consumption and total coronary artery disease endpoints in observational studies. Of the 18 studies identified from the authors' search (from 1966 through November 2009) and included in the meta-analysis, 13 studies were on black tea and 5 studies on green tea. A random-effects model allowed combination of study-specific risk estimates.

The meta-analysis showed no significant association between black tea intake and the risk for coronary artery disease. However for green tea, the summary relative risk showed a significant association between the highest intake of green tea and a lower risk for coronary artery disease (summary RR, 0.72; 95% CI, 0.58 - 0.89). Increased green tea intake by 1 cup per day was associated with a 10% reduction in the risk for the development of coronary artery disease (summary RR, 0.90; 95% CI, 0.82 - 0.99).

INTERPRETATION:

This meta-analysis found a tentative association between consumption of green tea and a reduced risk for coronary artery disease which adds to the available body of evidence on beneficial effects of the beverage on cardiovascular health. The association between black tea consumption and coronary artery disease did not reach statistical significance however.

These results are similar to, but not completely in line with those from a previous meta-analysis by Peters et al., which included many of the same studies as in Wang's analysis. That study found that the incidence rate of myocardial infarction decreased by 11% with an increase in tea consumption of three cups per day [15]. No distinction was made between green and black tea in Peter's meta-analysis however. Unfortunately, Wang et al. did not analyse what the effects on coronary artery disease risk would be if all studies (i.e. both green and black tea) were combined. It would have been interesting to see whether combining the data would have produced similar results between the two meta-analyses. An important note has to be made in this regard however. A large number of the studies included in the black tea group of Wang's meta-analysis simply referred to "tea" and did not make distinctions between green and black. This imprecision of exposure measurement is an important limitation since "tea" comprises a heterogeneous group of beverages. This includes fermented black tea, half fermented oolongs, unfermented green tea, and sweetened or unsweetened ice tea, and it might even be understood to include fruit tea or herbal teas. Although most of the tea consumed in these populations is generally black, it cannot be said with certainty that black tea exposure was accurately measured in these studies.

It also has to be kept in mind that heterogeneity of the underlying cardiovascular disease problem may be another reason for not finding a clear relationship between black tea intake and coronary artery disease events. "Coronary artery-" or "coronary heart disease" are blanket terms which are used interchangeably (and in the opinion of some, wrongly16) to describe all diseases, and manifestations thereof, involving the heart and its supplying blood vessels. Therefore it could be that Wang et al. simply pooled too many diseases in their "coronary artery disease" categorization to get at potential meaningful mechanistic effects, as evidenced by the analysis of Peters et al. whose narrower focus (only myocardial infarction) did produce a meaningful association.

The findings of this study do however confirm previous research in the sense that tea has a promising protective role against coronary artery disease. This study did not find a significant association for black tea though, but this may be due to the influence of the myriad of confounding factors mentioned above.

ABSTRACT

OBJECTIVE: To examine the associations of coffee and tea consumption with risk of morbidity and mortality of stroke and coronary heart disease (CHD) and with all-cause mortality.

METHODS AND RESULTS: Coffee and tea consumption were assessed with a validated food-frequency questionnaire, and 37 514 participants were observed for 13 years for the occurrence of cardiovascular morbidity and mortality. A U-shaped association between coffee and CHD was found, with the lowest hazard ratio (HR [95% CI]) for 2.1 to 3.0 cups per day (0.79 [0.65 to 0.96]; P(trend)=0.01). Tea was inversely associated with CHD, with the lowest HR (95% CI) for more than 6.0 cups per day (0.64 [0.46 to 0.90]; P(trend)=0.02). No associations between tea or coffee and stroke were found (P(trend)=0.63 and P(trend)=0.32, respectively). Although not significant, coffee slightly reduced the risk for CHD mortality.

(HR, 0.64; 95% CI, 0.37 to 1.11; P(trend)=0.12) for 3.1 to 6.0 cups per day. A U-shaped association between tea and CHD mortality was observed, with an HR of 0.55 (95% CI, 0.31 to 0.97; P(trend)=0.03) for 3.1 to 6.0 cups per day. Neither coffee nor tea was associated with stroke (P(trend)=0.22 and P(trend)=0.74, respectively) and all-cause mortality (P(trend)=0.33 and P(trend)=0.43, respectively).

CONCLUSIONS: High tea consumption is associated with a reduced risk of CHD mortality. Our results suggest a slight risk reduction for CHD mortality with moderate coffee consumption and strengthen the evidence on the lower risk of CHD with coffee and tea consumption.

SUMMARY:

In this prospective cohort study the relation between tea and coffee consumption and cardiovascular diseases was investigated in a large Dutch cohort of healthy men and women in the European Prospective Investigation into Cancer and Nutrition (EPIC-NL). The scientists used a questionnaire to quantify the consumption of tea and coffee in 17,357 women aged 50 to 69 years who participated in a breast cancer screening program and 22,564 men and women aged 20 to 65 years who were recruited through random population sampling. The subjects were followed for 13 years, and during this period, 1,950 cardiovascular events were documented, with 563 cases of stroke and 1,387 cases of coronary heart disease. Seventy deaths from stroke were documented and 123 from coronary heart disease.

In this population high coffee consumption was associated with a lower educational level, the prevalence of diabetes and smoking, a higher waist circumference, hypercholesterolemia, and a less healthy diet. Conversely, high tea consumption was associated with a higher educational level, higher physical activity, a healthier diet, lower waist circumference, and a lower prevalence of smoking, hypercholesterolemia, and diabetes.

It was observed that drinking more than 6 cups of tea per day was associated with a 36% reduction in risk of having a coronary heart disease event, whilst the risk of dying from coronary heart disease was reduced by 45% with consumption of between 3 and 6 cups per day. Drinking between 2 and 3 cups of coffee per day was also associated with a 21% reduction in the risk of having a coronary heart disease event. No statistically significant associations were however found between coffee consumption and stroke morbidity or coronary heart disease-, stroke- or all-cause mortality. Also, no statistically significant associations were found between tea consumption and a reduced risk of stroke morbidity, mortality or all-cause mortality.

INTERPRETATION:

This recently published study provides compelling evidence to support the association of regular tea consumption with a reduced risk of coronary heart disease, and that tea seems to have a stronger association than coffee. The findings on stroke are however in contrast to earlier data by Dr. Lenore Arab that demonstrated a reduction in stroke risk of 21% associated with drinking more than three cups of tea per day[17].

Certain aspects of de Koning's study need to be taken into account though. First, relatively few patients died of coronary heart disease (123) or stroke (70) and thus the findings on mortality from these causes should be viewed with caution. The study also provided no specific information on the type of tea that the participants consumed, but as 78 % of tea consumed in the Netherlands is black tea, the authors assume that their findings are mainly relevant for black tea, but as previously mentioned, care needs to be taken with such assumptions as well.

Nevertheless, whilst the meta-analysis of Wang is mostly inconclusive (for black tea at least), this large prospective cohort study adds to the available evidence that tea consumption is in fact associated with a lower risk of coronary heart disease.

ABSTRACT

Flavonols are strong antioxidants in plant foods and tea is a major dietary source. There is evidence from prospective cohort studies that tea and flavonols are inversely related to stroke incidence. We conducted a metaanalysis of prospective cohort studies to assess quantitatively the strength of the association between flavonol intake and stroke incidence. Prospective cohort studies with data from individuals free of cardiovascular diseases (CVD) or stroke at baseline were included in the metaanalysis. Persons were followed for between 6 and 28 y. Data from 6 cohorts involving 111,067 persons with at least 2155 nonfatal and fatal cases were pooled. A random effects model was used. In all studies included, adjustments were made for major CVD risk factors except for 2 that did not adjust for alcohol and energy intake. A high intake of flavonols compared with a low intake was inversely associated with nonfatal and fatal stroke with a pooled relative risk of 0.80 (95% CI: 0.65, 0.98). Visual inspection of Begg's funnel plot and Egger's test (P = 0.01) indicated potential publication bias. We conclude that flavonols may reduce stroke risk.

SUMMARY:

Tea is a major dietary source of flavonols, a specific class of flavonoids also found in wine, cocoa and a variety of fruit and vegetables. These components contribute significantly to taste and colour of tea and have a range of biochemical properties such as vasodilatory, antithrombotic and anti-inflammatory effects and thereby possibly offer health benefits.

The authors searched the PubMed database for prospective cohort studies published in English from March 1996, the date of the first cohort study on flavonol intake and stroke[18], to August 2009. The search produced six studies from the Netherlands, Finland and the US that provided data from 111,067 individuals free of cardiovascular disease or stroke which were followed for 6 to 28 years.

In order to determine exposure to flavonols, dietary intake was assessed at baseline in each of the studies. Food frequency questionnaires were applied in 3 studies whilst in the other studies, more extensive dietary survey methods were used, such as cross-check dietary history and 4-day food records. The authors found that flavonol intakes were quite similar amongst the different cohorts, with the exception of the Finnish cohorts where intakes were at least 50% lower.

Overall, 2,155 fatal and non-fatal cases of stroke were reported. After adjustments were made for age, gender, body mass index, smoking, blood pressure, blood lipids and dietary factors, mostly energy and alcohol, it was observed that a high intake of flavonols compared to low intake was associated with a 20% lower risk of stroke. The authors noted that there was moderate heterogeneity between the studies and their analysis also showed evidence of a possible publication bias.

INTERPRETATION:

These results provide compelling evidence supporting the association of flavonoid intake with a reduced risk of stroke and are in agreement with those of the meta-analysis by Arab et al. on tea consumption and the risk of stroke [17].

The authors used the Dutch and USDA flavonoid data-bases to estimate the dietary exposure to flavonols from the data available from the included studies and assumed that tea probably was the major flavonol source in all cohorts, but its contribution differed among countries. In a typical tea-drinking country like The Netherlands, tea contributed 70% of the flavonol intake but in the US, tea contributed only approximately 30%. There were other important sources of flavonols though, such as onions and apples, with contributions between 25 and 8%.

An important caveat needs to be taken into account though. Observational studies are prone to influence from a wide variety of confounding factors and results should always be interpreted with caution. In this case, the authors acknowledge that the intake of flavonols has been positively associated with a healthy lifestyle and that this has wider implications: it can be presumed that those people with a higher flavonol intake have a healthier lifestyle, and thus are more likely to be non-smokers and have lower intakes of total saturated fat and lower a BMI. Additionally they also make a remark about the contribution of onions to the flavonol intake which may have been underestimated in this research, because it tends to be a hidden ingredient in soups and sauces.

In the end though, the authors conclude "that evidence is accumulating that flavonol intake is inversely related to different cardiovascular disease outcomes".

OBSERVATIONAL DATA – CONCLUSION:

The three publications discussed above provide interesting population-based data that add to the existing body of evidence of tea's beneficial cardiovascular effects. The meta-analysis of Hollman is especially interesting since it provides a link between tea and flavonoids - a third of the studies included in a previous meta-analysis on tea and stroke were also included in Hollman's analysis on flavonoids and stroke, which suggests that flavonols might play an important role in the protective effects seen for tea.

In the end as, previously suggested by experts in the field, the best approach to the question of whether tea has a beneficial effect on cardiovascular disease would be a randomized study comparing tea consumption to placebo against a background of minimal flavonoid consumption [19]. However since intervention studies that have morbidity and mortality endpoints (e.g. from coronary artery disease) are typically massive undertakings requiring large numbers of subjects and many years of intervention, it remains to be seen if someone within the scientific community would be up to the challenge.

2.2. TEA, TEA FLAVONOIDS AND CARDIOVASCULAR HEALTH – MECHANISTIC INSIGHTS

ABSTRACT

The two main types of tea are green and black. Both green and black teas are rich dietary sources of flavonoids. Available evidence suggests that regular tea consumption may reduce the risk of cardiovascular disease. The cardiovascular health benefits of drinking tea are thought to be largely due to flavonoids. Tea intake and intake of flavonoids found in tea have been associated with reduced risk of cardiovascular disease in cross-sectional and prospective population studies. Isolated flavonoids found in tea have also been consistently shown to inhibit the development of atherosclerosis in animal models. A number of possible pathways and mechanisms have been investigated. There is now consistent data indicating that tea and tea flavonoids can enhance nitric oxide status and improve endothelial function, which may be at least partly responsible for benefits on cardiovascular health. There is also evidence, although limited, to suggest benefits of green tea (flavonoids) on body weight and body fatness. Data supporting reduced oxidative damage, inflammation, platelet activation, blood pressure, and risk of type 2 diabetes with tea (flavonoids) remains inadequate to draw any conclusions.

SUMMARY:

A recent review by researchers from University of Western Australia suggests that regular tea consumption may reduce the risk of cardiovascular diseases, due to its flavonoid content.

The researchers reviewed and summarised 63 studies on the effects of green and black tea. Apart from examining data from epidemiological studies, the authors also reviewed a large number of human and animal studies examining possible mechanisms for the cardioprotective effects of tea flavonoids like atherosclerosis, endothelial function, blood pressure, oxidative stress, cholesterol reduction, inflammation, platelet function, levels of homocysteine, body weight- and composition, and type 2 diabetes.

MAIN FINDINGS WERE:

- Population studies suggest that tea consumption may reduce cardiovascular disease risk;
- Animal studies suggest that tea can inhibit development of atherosclerosis although further human studies are needed to confirm the effects;
- Several well-designed human studies have shown that tea can enhance nitric oxide levels and improve endothelial function (which has a role in cardiovascular disease);
- There is promising evidence in Asian populations on the potential benefits of green tea and its flavonoids on body weight and body fatness, but further studies in Caucasian populations are required;
- At this time there is inadequate evidence to draw conclusions about the effects of tea on blood pressure, cholesterol lowering, inflammation, oxidative stress, platelet activation, type 2 diabetes.

INTERPRETATION:

A significant number of human intervention, animal and in-vitro studies have been conducted in order to ascertain mechanistic explanations for the associations seen in population studies like those described above. In this review, the authors provide an overview of earlier epidemiological work on tea, tea flavonoids and cardiovascular disease after which they provide a comprehensive overview of data from human intervention, animal and in vitro studies that have investigated the effects of tea flavonoids on cardiovascular health-related endpoints.

It has to be kept in mind that this is a narrative review – the authors did not state how they identified and selected the studies to be included and did not systematically examine the quality of those that were included.

Nevertheless, this paper gives an excellent overview of the current scientific evidence linking tea and tea flavonoids with cardiovascular health benefits. The authors state that population studies strongly suggests a decreased risk of cardiovascular diseases with higher tea consumption and that the available data also suggest that the magnitude of the benefit of green and black tea is similar. Results of studies using animal models clearly show that flavonoids present in tea can inhibit the development of atherosclerosis and consistent evidence from human randomized controlled trials show that consumption of black and green tea, and specific flavonoids present in tea, can improve endothelial function. Lastly, there is some support from population studies for the idea that tea and tea flavonoids can attenuate the development of hypertension. However, further trials are needed to establish the effect of tea on blood pressure.

ABSTRACT

BACKGROUND: Tea consumption is associated with a lower risk of cardiovascular disease including stroke. Direct effects of tea components on the vasculature, particularly the endothelium, may partly explain this association.
Objective: We performed a meta-analysis of controlled human intervention studies on the effect of tea on flow-mediated dilation (FMD) of the brachial artery, a measurement of endothelial function, which is suggested to be associated with cardiovascular risk.

METHODS - Human intervention studies were identified by systematic search of the databases Medline, Embase, Chemical Abstracts and Biosis through March 2009 and by hand-searching related articles. Studies were selected based on predefined criteria: intervention with tea as the sole experimental variable, placebo-controlled design, and no missing data on FMD outcome or its variability. A random effects model was used to calculate the pooled overall effect on FMD due to the intake of tea. The impact of various subject and treatment characteristics was investigated in the presence of heterogeneity.

RESULTS: In total, 9 studies from different research groups were included with 15 relevant study arms. The overall absolute increase in FMD of tea vs. placebo was 2.6% of the arterial diameter (95% CI: 1.8-3.3%; P-value <0.001) for a median daily dose of 500 mL of tea (2-3 cups). This is a relative increase of approximately 40% compared to the average FMD of 6.3% measured under placebo or baseline conditions. There was significant heterogeneity between studies (P-value <0.001) that might partly be explained by the cuff position either distal or proximal to the area of FMD measurement. No indication for publication bias was found.

CONCLUSION: Moderate consumption of tea substantially enhances endothelial-dependent vasodilation. This may provide a mechanistic explanation for the reduced risk of cardiovascular events and stroke observed among tea drinkers.

SUMMARY:

Ras et al. recently conducted a meta-analysis on a number of studies investigating the effect of tea on vascular function and concluded that consumption of two to three cups of tea per day could have profound effects on vascular health.

The authors identified potentially relevant publications by searching the databases Medline, Embase, Chemical Abstracts and Biosis (from the starting date of the databases until March 2009). Of the 478 potentially relevant publications identified, 9 studies (totalling 213 participants) investigating the effects of tea on vascular function were included in the meta-analysis. Seven of the studies investigated the effects of black tea whilst the effects of green tea were investigated in only 3. Most of the studies investigated acute effects but a small number also looked at longer term (4 week) effects. Dose varied from 120 to 1250 mL per day.

In each of the individual studies, except for one, tea showed a statistically significant effect on FMD. Combining all the studies showed that tea consumption at a median dose of 500 mL (2 to 3 cups) per day produced a relative increase in FMD of approximately 40% compared to placebo.

INTERPRETATION:

The function of blood vessels can be evaluated by observing and measuring the phenomenon known as flow-mediated vasodilation (FMD) (see the following section for a more in-depth discussion on FMD). Since changes in FMD can be induced via pharmaceutical and dietary interventions, it is an attractive means by which to investigate whether certain compounds have an effect on vascular health. Indeed, in the past decade several investigators have employed this technique to determine whether the reduced risk for cardiovascular diseases associated with tea consumption in observational studies could be explained via possible effects on vascular health.

The results in the publication of Ras et al. are in line with findings from an earlier meta-analysis on flavonoids/flavonoid-rich foods and cardiovascular risk factors [20], which included two studies on tea and FMD published at that time. The effect of tea on FMD revealed in this new meta-analysis seems robust because the estimated overall effect is large and the effect was observed in 8 of the 9 studies including different study populations and varying black and green tea types. The authors also state that they could not detect indications of systematic publication bias which lends a bit more credence to the results.

The authors did mention some limitations that need to be kept in mind. Firstly, reproducibility of a functional marker such as FMD is low as compared to most biochemical markers. Secondly, the majority of included studies measured FMD acutely, i.e. about 2 hours after ingestion of a defined dose of tea. The clinical relevance of this acute improvement in FMD is still unclear. Having said that, an improvement in FMD by tea was also seen in three studies after longer-term (4 weeks) regular tea consumption and an overnight fast. ,

In conclusion, the findings of this meta-analysis indicate that tea consumption results in substantial effects on vascular function as indicated by an improved endothelial-dependent vasodilation shortly after intake, and also after longer-term regular consumption of tea. This effect may partly explain the relationship between tea consumption and reduction in cardiovascular disease risk seen in population studies.

ABSTRACT

BACKGROUND: We conducted a meta-analysis of observational studies which examined the association between flow-mediated dilatation (FMD) of brachial artery, a noninvasive measure of endothelial function, and future cardiovascular events.

METHODS: Electronic databases were searched using a predefined search strategy. Data was independently abstracted on study characteristics, study quality, and outcomes by two reviewers. The multivariate relative risks, adjusted for confounding factors, were calculated from individual studies and then pooled using random-effects models. Statistical heterogeneity was evaluated using I2 statistics. Subgroup analyses and meta-regression analyses were conducted to assess the robustness of the meta-analysis. Publication bias was examined with funnel plot analysis and Egger's test.

RESULTS: Four population-based cohort studies and ten convenience-cohort studies, involving 5,547 participants, were included in the meta-analysis. The pooled relative risks of cardiovascular events per 1% increase in brachial FMD, adjusted for confounding risk factors, was 0.87 (95% CI, 0.83- 0.91). The significant associations between brachial FMD and cardiovascular events were consistent among all subgroups evaluated, suggesting the robustness of the meta-analysis. However, the presence of heterogeneity in study quality, the remaining confounding factors, and publication bias in the available literature prevent a definitive evaluation of the additional predictive value of brachial FMD beyond traditional cardiovascular risk factors.

CONCLUSIONS: The meta-analysis of heterogeneous studies with moderate methodological quality suggested that impairment of brachial FMD is significantly associated with future cardiovascular events. Further prospective randomized trials are warranted to confirm the efficacy of the usage of brachial FMD in the management of cardiovascular diseases.

3. CONCLUDING REMARKS

SUMMARY:

Endothelial dysfunction is thought to be an important factor in the development of atherosclerosis, hypertension, and heart failure [21].

The capacity of blood vessels to respond to stimuli present in their lumen grants them the ability to self-regulate their tone and to adjust the distribution of blood flow in response to local changes. Many blood vessels respond to the shear stress brought on by an increase in flow by dilating. This phenomenon is called FMD. A principal mediator of FMD is endothelium derived nitric oxide [22].

The purpose of the meta-analysis by Inaba et al was to examine the association between FMD and future cardiovascular events. To this end the authors looked for longitudinal studies, or nested case–control studies, which measured brachial FMD at baseline, reported a cardiovascular event outcome and adjusted results for possible confounding factors. From the search 14 studies (13 prospective and 1 retrospective) were included in the meta-analysis. Collectively the studies involved 5547 subjects and had a follow-up duration that ranged between 6 months and 7.8 years.

The pooled multivariate relative risks of cardiovascular events per 1% increase in FMD was 0.872 (95% CI, 0.832–0.914). This suggests that 1% decrease in FMD was associated with 13% increase in risk of future cardiovascular events. The authors did notice possible presence of publication bias though – after adjusting for it the association was smaller (8%) but still significant.

INTERPRETATION:

For the past two decades FMD has been used by numerous investigators to evaluate endothelial function in humans and also to assess effects of therapeutic interventions on endothelial function. The relevance of FMD for predicting CVD risk independent of other well-established risk factors is crucial in this respect.

The present meta-analysis shows that impairment of brachial artery FMD is significantly associated with future cardiovascular events beyond conventional cardiovascular risk factors. A similar meta-analysis published by Green et al. shortly after this one found similar results [23]. Both authors noted however that the presence of heterogeneity in study quality, confounding factors, and publication bias in the available literature, prevent a definitive evaluation of the additional predictive value of brachial FMD beyond traditional cardiovascular risk factors.

Nevertheless, the currently analysed literature, which contained a large number of high methodological quality studies, showed that the impairment of brachial FMD is significantly associated with future cardiovascular events. The consistent results across a broad range of populations provide strong evidence that the vascular endothelium plays a critical role in various phases of the atherosclerotic disease process.

MECHANISTIC INSIGHTS – CONCLUSION:

In the review of Hodgson and Croft, tea's beneficial effects on blood vessel function were highlighted as an important possible mechanism, responsible for the reduced cardiovascular disease risk seen in epidemiological studies. The meta-analysis of Ras et al. provides compelling evidence to support this notion, finding an impressive 40% improvement in blood vessel function as measured by FMD.

There are strong indications from epidemiological data that blood vessel function is an important surrogate marker for cardiovascular risk. It therefore seems very likely that the short term beneficial effects that consumption of tea (and likely tea flavonoids) has on FMD, could eventually confer a protective effect on cardiovascular risk in the longer term.

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

- Tea is a rich source of flavonoids in the diet. Although large variations in content can occur due to source, preparation methods etc, a cup of tea generally provides 150 to 200 mg of flavonoids. It has been shown that in tea drinking populations, the beverage provides a significant contribution to the daily flavonoid intake.
- Tea can play a role in cardiovascular health. Population studies suggest a decreased risk of CVD with higher tea consumption. Human intervention studies in intermediate endpoint as well as mechanistic data from in-vitro and animal studies provide evidence that supports the observations from population studies.
- Flavonoids can play a role in cardiovascular health. Epidemiological studies have explored the relationships between dietary flavonoids and cardiovascular diseases and their intake has been related to lower risk of heart disease, stroke and total mortality.
- Current evidence suggests that tea and flavonoids contribute to a healthy cardiovascular system by improving blood vessels function. There is strong evidence suggesting that improvements in blood vessel function, as measured by FMD, favourably relates to cardiovascular disease risk. Data from intervention studies indicates that tea consumption can improve FMD by up to 40%.

To conclude, there is a large body of evidence suggesting that tea and its flavonoids 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.

4. REFERENCES

1. Gardner EJ, Ruxton CH, Leeds AR. Black tea--helpful or harmful? A review of the evidence. Eur J Clin Nutr 2007 January;61(1):3-18.

2. Hodgson JM, Croft KD. Tea flavonoids and cardiovascular health. Mol Aspects Med 2010 December; 31(6):495-502.

3. World Health Organization. Cardiovascular diseases (CVDs). Fact sheet No. 317. WHO, Geneva, Switzerland 2011 January;Available at: URL: http://www.who.int/mediacentre/factsheets/fs317/en/index.html. Accessed March 1, 2011.

4. Gaziano TA. Reducing the growing burden of cardiovascular disease in the developing world. Health Aff (Millwood) 2007 January; 26(1):13-24.

5. Cooney MT, Dudina A, Whincup P et al. Re-evaluating the Rose approach: comparative benefits of the population and high-risk preventive strategies. Eur J Cardiovasc Prev Rehabil 2009 September 19.

6. Rodgers A, Ezzati M, Vander HS, Lopez AD, Lin RB, Murray CJ. Distribution of major health risks: findings from the Global Burden of Disease study. PLoS Med 2004 October; 1(1):e27.

7. Rose G. Strategy of prevention: lessons from cardiovascular disease. Br Med J (Clin Res Ed) 1981 June 6; 282(6279):1847-51.

8. Loke WM, Hodgson JM, Proudfoot JM, McKinley AJ, Puddey IB, Croft KD. Pure dietary flavonoids quercetin and (-)-epicatechin augment nitric oxide products and reduce endothelin-1 acutely in healthy men. Am J Clin Nutr 2008 October; 88(4):1018-25.

9. Widlansky ME, Hamburg NM, Anter E et al. Acute EGCG supplementation reverses endothelial dysfunction in patients with coronary artery disease. J Am Coll Nutr 2007 April; 26(2):95-102.

10. Erdman JW, Jr., Balentine D, Arab L et al. Flavonoids and heart health: proceedings of the ILSI North America Flavonoids Workshop, May 31-June 1, 2005, Washington, DC. J Nutr 2007 March; 137(3 Suppl 1):718S-37S.

11. Astill C, Birch MR, Dacombe C, Humphrey PG, Martin PT. Factors affecting the caffeine and polyphenol contents of black and green tea infusions. J Agric Food Chem 2001 November; 49(11):5340-7.

12. Geleijnse JM, Launer LJ, Van der Kuip DA, Hofman A, Witteman JC. Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam Study. Am J Clin Nutr 2002 May;75(5):880-6.

13. McKay DL, Blumberg JB. The role of tea in human health: an update. J Am Coll Nutr 2002 February; 21(1):1-13.

14. U.S.Department of Agriculture. USDA database for the flavonoid content of selected foods. USDA 2003 March; Available at: URL: http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/flav.pdf.

15. Peters U, Poole C, Arab L. Does tea affect cardiovascular disease? A meta-analysis. Am J Epidemiol 2001 September 15; 154(6):495-503.

16. Stehbens WE. Misuse of "coronary heart disease". Heart 1999 July; 82(1):1-2.

17. Arab L, Liu W, Elashoff D. Green and black tea consumption and risk of stroke: a meta-analysis. Stroke 2009 May; 40(5):1786-92.

18. Keli SO, Hertog MG, Feskens EJ, Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. Arch Intern Med 1996 March 25; 156(6):637-42.

19. Vita JA. Tea consumption and cardiovascular disease: effects on endothelial function. J Nutr 2003 October; 133(10):3293S-7S.

20. Hooper L, Kroon PA, Rimm EB et al. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2008 July; 88(1):38-50.

21. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003 February 1; 23(2):168-75.

22. Corretti MC, Anderson TJ, Benjamin EJ et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002 January 16; 39(2):257-65.

23. Green DJ, Jones H, Thijssen D, Cable NT, Atkinson G. Flow-mediated dilation and cardiovascular event prediction: does nitric oxide matter? Hypertension 2011 March; 57(3):363-9.

5. NOTES

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