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Issue ten

Scientific update on effects of tea and flavonoids on glycaemic control and diabetes

Unilever

Scientific Update On Effects Of Tea and Flavonoids On Glycaemic Control and Diabetes

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"From the editor"

Tea is the most consumed beverage in the world after water and consumption of unsweetened tea (green or black) fits well into a healthy dietary pattern as it is a refreshing beverage containing zero calories. It has been suggested that tea has the potential to directly influence insulin sensitivity and glucose homeostasis and to reduce risk of diabetes.[1]

It is currently estimated that 382 million people globally have diabetes[2] and this is projected to reach 600 million in less than 25 years, placing a huge burden on health care systems and economies. Type 2 diabetes mellitus (T2DM) is the most common form of the disease, accounting for more than 90% of all cases globally.

Cohort studies, prospective studies, and randomized clinical trials, are beginning to build evidence for a potential beneficial role of tea on the risk of developing T2DM. In the context of this developing evidence base, the aim of this expert newsletter is to review the latest relevant science, to indicate the strength of the evidence for a role of tea and/or tea flavonoids in glycaemic control and to determine current relevance of tea consumption to diabetes risk.

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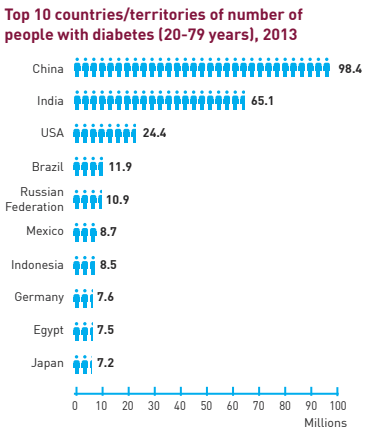
1. Introduction

Diabetes mellitus is a chronic syndrome of disordered metabolism characterised by high levels of glucose in the bloodstream (hyperglycaemia). Diabetes occurs when the body's cells either resist the effects of insulin, the hormone that regulates movement of glucose into cells (Type 2 diabetes) or does not produce enough insulin to maintain a normal glucose level (Type 1 diabetes). It is currently estimated that 8.3% of adults globally - 382 million people - have diabetes[2] and the number of people with the disease is projected to approach 600 million in less than 25 years, placing a huge burden on health care systems and economies.

Type 2 diabetes mellitus (T2DM) is the most common form of the disease, accounting for more than 90% of all cases globally. The prevalence of this disease is increasing rapidly and is associated with economic development, ageing populations, increasing urbanisation, dietary changes (increased intake of energy, sugars, refined grains and fat) and physical inactivity. The co-morbidities associated with T2DM, including cardiovascular disease, stroke, and kidney disease, contributed to more than 5 million deaths worldwide in 2013 - meaning that every six seconds someone dies from diabetes.[2] Historically, T2DM has been a problem of developed, prosperous societies, but it is becoming clear that this is no longer the case, with 80% of people with diabetes living in low and middle income countries (see below data from IDF Atlas, 6th edition 2013[2]).



People who develop T2DM gradually become less responsive to the effects of insulin, the pancreatic hormone which regulates the uptake of glucose into most tissues. In this "pre-diabetic" phase, muscle, liver and fat cells become relatively insensitive to insulin and do not take up glucose as they would normally. Additionally, liver cells are not inhibited in their own glucose production and excess glucose is not stored as it would normally be in the form of glycogen. This insulin-resistance leads to a state referred to as pre-diabetes, defined by impaired glucose tolerance (as measured by the response to a standard oral glucose load) and/or elevated fasting blood glucose. In this pre-diabetic stage there is still potential to return to normal insulin sensitivity or to delay diabetes onset through intensive diet and lifestyle interventions including weight loss, increasing physical activity and improving diet (in particular increasing fibre and reducing saturated fat intake). Very often however, pre-diabetes remains undiagnosed and the necessary lifestyle changes are not implemented, with the resulting escalation of the disease process to T2DM.

Tea is the most consumed beverage in the world after water and consumption of unsweetened tea (green or black), with reduced-fat milk if preferred, fits well into a healthy dietary pattern as it is a refreshing beverage containing zero or few calories. In addition to its potential to contribute to weight maintenance through its low calorie content, tea is a hydrating beverage which contributes to daily fluid requirements. It has been suggested for many years that tea has the potential to directly influence insulin sensitivity and glucose homeostasis and to reduce risk of diabetes.[1] In particular, the flavonoids in infusions of Camellia sinensis have been postulated as the active anti-diabetic components, with proposed mechanisms of action including inhibition of intestinal glucose uptake via the sodium-dependent glucose transporter (SGLT1), inhibition of small intestinal carbohydrate-hydrolyzing enzymes (e.g. amylase) and stimulation of insulin production from pancreatic beta-cells.[3] In 2009, the first meta-analyses of cohort studies on the relationship between tea consumption and risk of T2DM were published and both reported significantly reduced risk of diabetes associated with higher tea consumption.[4,5] More recently, prospective studies have reported on the association between tea and/or tea flavonoid consumption and T2DM risk and a growing number of randomized clinical trials studying the effects of both green and black tea on glycaemic control are being reported, particularly in at-risk populations.

In the context of this developing evidence base, the aim of this expert newsletter is to review the latest relevant science, to indicate the strength of the evidence for a role of tea and/or tea flavonoids in glycaemic control and to determine current relevance of tea consumption to diabetes risk.

2. EVIDENCE FROM EPIDEMIOLOGICAL DATA TESTING EFFECTS OF TEA AND FLAVONOIDS ON DIABETES RISK AND BIOMARKERS OF GLUCOSE CONTROL

2.1 ASSOCIATION BETWEEN DIETARY FLAVONOID AND LIGNAN INTAKES

Zamora-Ros, R., N. G. Forouhi, S. J. Sharp, C. A. Gonzalez, B. Buijsse, M. Guevara, Y. T. van der Schouw, P. Amiano, H. Boeing, L. Bredsdorff, F. Clavel-Chapelon, G. Fagherazzi, E. J. Feskens, P. W. Franks, S. Grioni, V. Katzke, T. J. Key, K. T. Khaw, T. Kuhn, G. Masala, A. Mattiello, E. Molina-Montes, P. M. Nilsson, K. Overvad, F. Perquier, J. R. Quiros, I. Romieu, C. Sacerdote, A. Scalbert, M. Schulze, N. Slimani, A. M. Spijkerman, A. Tjonneland, M. J. Tormo, R. Tumino, A. Dl van der, C. Langenberg, E. Riboli and N. J. Wareham.
The Association between Dietary Flavonoid and Lignan Intakes and Incident Type 2 Diabetes in European Populations: The Epic-Interact Study. Diabetes Care 2013; 36: 3961-70.

ABSTRACT

Objective: *To study the association between dietary flavonoid and lignan intakes, and the risk of development of type 2 diabetes among European populations.*

Research Design and Methods: *The European Prospective Investigation into Cancer and Nutrition-InterAct case-cohort study included 12,403 incident type 2 diabetes cases and a stratified subcohort of 16,154 participants from among 340,234 participants with 3.99 million person-years of follow-up in eight European countries. At baseline, country-specific validated dietary questionnaires were used. A flavonoid and lignan food composition database was developed from the Phenol-Explorer, the U.K. Food Standards Agency, and the U.S. Department of Agriculture databases. Hazard ratios (HRs) from country-specific Prentice-weighted Cox regression models were pooled using random-effects meta-analysis.*

Results: *In multivariable models, a trend for an inverse association between total flavonoid intake and type 2 diabetes was observed (HR for the highest vs. the lowest quintile, 0.90 [95%CI 0.77–1.04]; P value trend = 0.040), but not with lignans (HR 0.88 [95% CI 0.72–1.07]; P value trend = 0.119). Among flavonoid subclasses, flavonols (HR 0.81 [95% CI 0.69–0.95]; P value trend = 0.020) and flavanols (HR 0.82 [95% CI 0.68–0.99]; P value trend = 0.012), including flavan-3-ol monomers (HR 0.73 [95% CI 0.57–0.93]; P value trend = 0.029), were associated with a significantly reduced hazard of diabetes.*

Authors Conclusions: *Prospective findings in this large European cohort demonstrate inverse associations between flavonoids, particularly flavanols and flavonols, and incident type 2 diabetes. This suggests a potential protective role of eating a diet rich in flavonoids, a dietary pattern based on plant-based foods, in the prevention of type 2 diabetes.*

SUMMARY

The EPIC-InterAct is a large prospective T2DM case-cohort study nested within the well-known EPIC (European Prospective Investigation into Cancer and Nutrition) study which includes more than 500,000 adult participants from 10 EU countries.[6] With the exception of Greece and Norway, all EPIC countries participated in the EPIC-Interact study. After exclusion of individuals without stored blood or with prevalent diabetes at baseline, 340,234 participants with 3.99 million years of follow-up were included into the InterAct study. From this subject pool, after following the exclusion protocol, 11,559 cases and 15,258 non-case participants were included in the analysis, with 729 case subjects emerging from the non-case group during follow-up. Habitual diet during the 12 months prior to recruitment was recorded using country-specific, validated food frequency questionnaires (FFQ's) or diet histories. Flavonoid intakes were derived from foods included in the dietary questionnaires using a comprehensive food database based on the USDA, Phenol Explorer and the UK Food Standards Agency databases. Total flavonoid intake varied markedly across the 10 EPIC countries, with median intakes ranging from 201.7 mg/day in Sweden to 850.6 mg/day in the UK. The main food sources of total flavonoid intake were fruits (36.4%), tea (33.1%), wine (8.6%) chocolate products (4.2%), fruit juices (3.9%), beer (2.5%), vegetables (2.3%) and legumes (2.3%). After adjustment for potential confounders, an inverse trend between total dietary flavonoid intake and incidence of T2DM was observed, with flavanols, including flavan-3-ol monomers, and flavonols identified as the flavonoid sub-classes which were significantly associated with a lower risk of T2DM.

2.1

INTERPRETATION

This study, in an important European cohort, adds to the body of epidemiological data on the association between flavonoid intake and diabetes risk. The EPIC-Interact study carries significant weight within the hierarchy of epidemiological studies due to its prospective nature, the multi-center design and the large sample size at recruitment, from which a large number of verified cases of T2DM accrued during follow-up. Two large US prospective studies have previously reported on the association between flavonoid intake and incident T2DM. A study in the Nurses Health cohort using the 2007 USDA database release 2.1 (as also used in the EPIC study) observed a consistent inverse association only between anthocyanidin intake and T2DM risk, not with total flavonoid intake.[7] Song *et al*. (2005) reported no statistically significant associations of diabetes with flavonoid intake using an earlier version of the same database, but did find that tea consumption was inversely associated with diabetes risk, with a borderline significant trend (> or =4 cups/d vs. none: RR 0.73, 95% CI: 0.52-1.01; p for trend = 0.06).[8] A Finnish study from 2002 reported the same inverse significant trends for flavonols as seen in the EPIC-InterAct study but not for flavanols.[9]

Of note in the InterAct study is that associations between flavonoid intake and the risk of T2DM remained significant after adjustment for compounds co-occurring in flavonoid-rich foods such as fibre, vitamin C, magnesium and alcohol. There was also a wide variation in flavonoid intakes among participants from eight European countries with highest intakes of flavanols and flavan-3-ol monomers associated with an 18 and 27% lower risk, respectively, of T2DM. Tea was the major source of both flavanols (39.1%) and flavan-3-ol monomers (81%) in this study, indicating a potential protective effect of tea consumption on T2DM risk. In agreement with the current flavonoid analysis in this cohort, an earlier report from the same EPIC-InterAct cohort (and therefore not an independent observation) had reported a linear inverse association between tea consumption and incidence of T2DM.[10] A 16% reduction in risk of developing T2DM was observed in people who drank at least 4 cups of tea per day compared to non-tea drinkers – and risk already tended to be lower with 1 - <4 cups per day. At the time of dietary data collection (1990s), consumption of green and herbal teas was not as popular as black tea in most included countries and it can be reasonably concluded that the effect observed in both EPIC-Interact studies is related to black tea.

A further very recent analysis from the EPIC-Interact cohort supports a protective role against T2DM for all individual flavan-3-ol monomers (with epigallocatechin gallate showing the strongest association), proanthocyanidins of low polymerization degree and the flavonol myricetin.[11] As these results are highly related to those already published in this cohort, more studies in different populations are needed to strengthen these potential inverse associations.

2.2

2.2 BIOMARKERS OF INSULIN RESISTANCE AND INFLAMMATION

Jennings, A., A. A. Welch, T. Spector, A. Macgregor and A. Cassidy. Intakes of Anthocyanins and Flavones Are Associated with Biomarkers of Insulin Resistance and Inflammation in Women. J Nutr 2014; 144: 202-8.

ABSTRACT

Although laboratory data suggest that several flavonoid subclasses are involved in glucose metabolism, limited clinical and epidemiologic data are available. The current study examined associations between habitual intake of flavonoid subclasses, insulin resistance, and related inflammatory biomarkers.

In a cross-sectional study of 1997 females aged 18–76 y, intakes of total flavonoids and their subclasses (flavanones, anthocyanins, flavan-3-ols, polymeric flavonoids, flavonols, flavones) were calculated from food frequency questionnaires using an extended USDA database. Fasting serum glucose, insulin, high-sensitivity C-reactive protein (hs-CRP; n = 1432), plasminogen activator inhibitor-1 (n = 843), and adiponectin (n = 1452) concentrations were measured. In multivariable analyses, higher anthocyanin and flavone intake were associated with significantly lower peripheral insulin resistance (homeostasis model assessment of insulin resistance, HOMA-IR); quintile 5 (Q5) to Q1 = -0.1, P-trend = 0.04 for anthocyanins and flavones] as a result of a decrease in insulin concentrations (Q5–Q1 = -0.7 μU/mL, P-trend = 0.02 anthocyanins; Q5–Q1 = -0.5 mU/mL, P-trend = 0.02 flavones). Higher anthocyanin intake was also associated with lower hs-CRP concentrations (Q5–Q1 = -0.3 mg/L, P-trend = 0.04), whereas those in the highest quintile of flavone intake had improved adiponectin concentrations (Q5–Q1 = 0.7 μg/L, P-trend = 0.01). Anthocyanin-rich foods were also associated with lower insulin and inflammation levels. No significant associations were observed for total or other flavonoid subclasses. Higher intakes of both anthocyanins and flavones were associated with improvements in insulin resistance and hs-CRP. These associations were found with intakes readily achieved in the diet. The observed reduction in insulin concentrations was similar to that reported previously for other lifestyle factors. Dose–response trials are needed to ascertain optimal intakes for the potential reduction of type 2 diabetes risk.

SUMMARY

This very recently reported cross-sectional study has investigated the association between intake of flavonoid subclasses and biomarkers of insulin resistance and inflammation.[12] The study cohort was derived from the TwinsUK registry, consisting of 1,997 adult twin volunteers recruited from the general UK population. Study participants were female, aged 18-76 y, and were a sample of the total population group who completed food frequency questionnaires (FFQs) and clinically assessed between 1996 and 2000. A UK validated 131 item FFQ was used to assess dietary intake, and flavonoid intakes were calculated using the updated USDA database. Mean flavonoid intake was 1.2g/d. Polymeric flavonoids (including proanthocyanidins, theaflavins and thearubigins) made the greatest contribution to total flavonoid intake (73%), followed by the flavan-3-ol subclass (20%). Overall, tea (presumably black in this UK population) was the main source of total flavonoid (81%), flavan-3-ol (91%), flavonol (63%) and polymeric flavonoid (theaflavins and thearubigins) intake (83%). Mean anthocyanin intake was significantly lower than flavan-3-ol intake (17.8 ± 14.3 mg/d (1.48% of total flavonoid intake versus 233±144 mg/d), as was mean flavone intake (2.0 ± 1.4 mg/d (0.17% of total flavonoid intake)). In this cohort, higher intake of anthocyanins (anthocyanin-rich foods include, blackberries, blueberries, plums and red grapes) was associated with significantly lower insulin resistance and inflammation status (as measured by hs-CRP). Flavone intake was also associated with lower insulin resistance plus reduced insulin and adiponectin concentrations. No statistically significant biomarker associations were observed with other flavonoid fractions.

2.2

INTERPRETATION

This study found no association between higher intakes of flavan-3-ols and markers of insulin resistance or inflammation, an observation which is in line with results from the Nurses Health Study which also showed associations with anthocyanin and not flavan-3-ol intake.[7] These results are however not in line with those observed in the EPIC-Interact study, where flavanols and flavonols were found to be associated with decreased diabetes risk.[6,11] Total anthocyanin consumption in the EPIC-Interact study was only associated with decreased risk in the unadjusted model – as were all other flavonoid classes except flavanones, isoflavones and lignans, but in the most recent EPIC-Interact analysis,11 proanthocyanidin dimers were associated with reduced T2DM risk in the fully adjusted model, possibly reflecting the better bioavailability of dimers compared to more polymerized forms.

Flavan-3-ol intake in the study of Jennings *et al*. ranged from 30.1 mg/d in Q1 to 429 mg/d in Q5 (means), which compared reasonably with < 19.1 mg/d and > 211.8 mg/d (medians) in the EPIC-Interact study.[6] Jennings *et al*. refer to the lack of beneficial associations with flavan-3-ol intake as the result in this study was in contrast to earlier results from their research group which had observed an association with lower insulin resistance (HOMA-IR).[12] Differences in flavan-3-ol intakes between these studies was proposed as an explanation for differing results, with lower epicatechin intakes observed in the current study.

There may be other reasons for the somewhat contrasting results observed in the two epidemiological studies reviewed in this newsletter. Firstly the studies had different designs: one was prospective[6] and this one cross-sectional.[13] While both studies confirm findings of previous studies they do not concur with each other and it may be that in cross-sectional studies the cases may have changed dietary habits due to the knowledge of current illness. In the EPIC-Interact study, dietary intake was assessed at the start of the study in a supposedly healthy population and consumption patterns compared between those who eventually developed diabetes and those who did not. This makes the prospective design somewhat less susceptible to bias.

However, due to the observational nature of both study designs, no conclusions can be made on cause and effect, which requires results from randomized, controlled trials. These are reviewed in the following chapter.

3. EVIDENCE FROM INTERVENTION STUDIES TESTING EFFECTS OF GREEN TEA ON GLYCAEMIC CONTROL

3.1 EFFECTS ON INSULIN SENSITIVITY AND GLYCAEMIC CONTROL

Wang, X., J. Tian, J. Jiang, L. Li, X. Ying, H. Tian and M. Nie.
Effects of Green Tea or Green Tea Extract on Insulin Sensitivity and Glycaemic Control in Populations at Risk of Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. J Hum Nutr Diet 2013; doi:10.1111/jhn.12181.

ABSTRACT

Background: *Although the regular consumption of green tea or green tea extract has been considered to improve insulin sensitivity, the reported results are inconsistent. Therefore, we conducted a meta-analysis to evaluate the effect of green tea or green tea extract on insulin sensitivity and glycaemic control in populations at risk of type 2 diabetes mellitus (T2DM).*

Method: *Electronic databases, including PUBMED, The Cochrane Library, EMBASE, ISI Web of Knowledge, Chinese Biomedical Literature Database and Chinese Scientific Journals Fulltext Database, were systematically searched to identify randomised controlled trials (RCTs) up to December 2011, supplemented by the Clinicaltrials.gov websites and the reference lists of identified studies. Two reviewers independently selected trials, extracted data, and evaluated the methodological qualities and evidence levels.*

Results: *Seven RCTs involving 510 participants were identified. There was no statistically significant difference between green tea or green tea extract group and placebo group with regard to fasting plasma glucose [standardised mean difference (SMD) 0.04; 95% confidence interval (CI) -0.15 to 0.24], fasting serum insulin (SMD -0.09; 95% CI -0.30 to 0.11), 2-h plasma glucose in the oral glucose tolerance test (OGTT-2 h) (SMD -0.14; 95% CI -0.63 to 0.34), haemoglobin A1c (SMD 0.10; 95% CI -0.13 to 0.33) and homeostasis model of insulin resistance (HOMA-IR) index (SMD -0.06; 95% CI -0.35 to 0.23) in participants at risk of T2DM.*

Conclusions: *The consumption of green tea did not decrease the levels of fasting plasma glucose, fasting serum insulin, OGTT-2 h glucose, haemoglobin A1c and HOMA-IR in populations at risk of T2DM. Larger, longer term and high-quality RCTs are needed to further definitely determine the effect of green tea or green tea extract on insulin sensitivity and glycaemic control in populations at risk of T2DM.*

SUMMARY

This meta-analysis identified 7 RCTs (performed in the period 2006 - 2011) involving 510 participants who were purported to be at risk of developing T2DM - subjects either already had T2DM or could be classified as high risk through the presence of obesity or metabolic syndrome.[14] Of the 7 trials, 4 were performed in Asia and 2 trials enrolled only women. The median length of intervention ranged from 4 weeks to 6 months. The interventions were green tea, green tea extract or epigallocatechin gallate (EGCG) and studies were included regardless of green tea (extract) dose. Included papers reported at least one of the outcomes: fasting plasma glucose, fasting serum insulin, 2-h plasma glucose following the oral GTT, HbA1c and HOMA-IR. Fixed effects models were used for all data analyses and for all outcomes no statistically significant effects of green tea consumption were observed. Sub-group analyses did also not reveal significant differences.

3.2

3.2 EFFECTS ON GLUCOSE CONTROL AND INSULIN SENSITIVITY

Liu, K., R. Zhou, B. Wang, K. Chen, L. Y. Shi, J. D. Zhu and M. T. Mi. Effect of Green Tea on Glucose Control and Insulin Sensitivity: A Meta-Analysis of 17 Randomized Controlled Trials. Am J Clin Nutr 2013; 98: 340-8.

ABSTRACT

Background: *The results of studies investigating the effect of green tea on glucose control and insulin sensitivity in humans are inconsistent.*

Objective: *We aimed to quantitatively evaluate the effect of green tea on glucose control and insulin sensitivity.*

Design: *We performed a strategic literature search of PubMed, EMBASE, and the Cochrane Library (updated to January 2013) for randomized controlled trials that evaluated the effects of green tea and green tea extract on glucose control and insulin sensitivity. Study quality was assessed by using the Jadad scale. Weighted mean differences were calculated for net changes in glycaemic measures by using fixed-effects or random-effects models. We conducted prespecified subgroup and sensitivity analyses to explore potential heterogeneity. Meta-regression analyses were conducted to investigate dose effects of green tea on fasting glucose and insulin concentrations.*

Results: *Seventeen trials comprising a total of 1133 subjects were included in the current meta-analysis. Green tea consumption significantly reduced the fasting glucose and hemoglobin A1c (Hb A1c) concentrations by -0.09 mmol/L (95% CI: -0.15, -0.03 mmol/L; P< 0.01) and -0.30% (95% CI: -0.37, -0.22%; P< 0.01), respectively. Further stratified analyses from high Jadad score studies showed that green tea significantly reduced fasting insulin concentrations (-1.16 mIU/mL; 95% CI: -1.91, -0.40 mIU/mL; P = 0.03).*

Conclusions: *This meta-analysis suggested that green tea had favorable effects, ie, decreased fasting glucose and HbA1c concentrations. Subgroup analyses showed a significant reduction in fasting insulin concentrations in trials with high Jadad scores.*

SUMMARY

This meta-analysis by Liu *et al.* identified 17 RCTs (reported in the period 2005 - 2012) in 1,133 subjects.[15] Of these, 9 trials focused on overweight or obese subjects, 4 on patients with type 2 diabetes, 2 included subjects with borderline diabetes and 2 included "healthy", presumably normal body mass index, subjects. Seven trials were estimated as high quality (by Jadad score[16]) and all these trials reported adequate allocation concealment. The total number of subjects included in each study ranged from 34 – 240, study durations varied from 2 weeks to 6 months and green tea catechin content ranged from 208 – 1207 mg/d (approximating to 1 – 5 cups based on data from the USDA flavonoid database[17]) This meta-analysis demonstrated that green tea significantly, but modestly, lowered fasting blood glucose (FBG) concentrations (by 0.09 mmol/L [1.6 mg/dl]) and HbA1c (by 0.3%), but did not affect fasting insulin, 2-hour glucose concentration or HOMA-IR values. Sub-group analyses indicated that green tea had a lowering effect on fasting insulin only in studies with a high quality rating and on fasting glucose in subjects at risk of the metabolic syndrome (15 studies), but not in "healthy" subjects (2 studies). The effects of green tea on FBG were only observed in parallel, not cross-over designed studies, but this may be related to the higher number of parallel trials included (14 v 3) and to the low quality scores of the cross-over studies. Also in sub-group analyses, higher catechin intakes (> 457 mg/day) were associated with significant FBG lowering effects but not length of study duration.

3.3

3.3 EFFECTS WITH OR WITHOUT CAFFEINE ON GLYCAEMIC CONTROL

Zheng, X. X., Y. L. Xu, S. H. Li, R. Hui, Y. J. Wu and X. H. Huang. Effects of Green Tea Catechins with or without Caffeine on Glycemic Control in Adults: A Meta-Analysis of Randomized Controlled Trials. Am J Clin Nutr 2013; 97: 750-62.

ABSTRACT

Background: *The effect of green tea catechins (GTCs) with or without caffeine on glycaemic control is controversial.*

Objective: *We aimed to identify and quantify the effects of GTCs or GTC-caffeine mixtures on glucose metabolism in adults.*

Design: *A comprehensive literature search was conducted to identify relevant trials of GTCs with or without caffeine on markers of glycemic control [fasting blood glucose (FBG), fasting blood insulin (FBI), glycated hemoglobin (Hb A1c), and homeostatic model assessment of insulin resistance (HOMA-IR)]. Weighted mean differences were calculated for net changes by using fixed-effects models. Prespecified subgroup analyses were performed to explore the influence of covariates on net changes in FBG and FBI concentrations.*

Results: *Twenty-two eligible randomized controlled trials with 1584 subjects were identified. Pooled analyses showed that FBG (-1.48 mg/dL; 95% CI: -2.57, -0.40 mg/dL) decreased significantly with GTCs with or without caffeine, whereas FBI (0.04 mU/mL;95% CI: -0.36, 0.45 μU/mL), Hb A1c (-0.04%; 95% CI: -0.15, 0.08%), and HOMA-IR (-0.05; 95% CI: -0.37, 0.26) did not. Subgroup analyses indicated that the glucose-lowering effect was apparent when the duration of follow-up was over a median of 12 wk. Overall, no significant heterogeneity was detected for FBG, FBI, Hb A1c, or HOMA-IR.*

Conclusions: *The meta-analysis showed that the administration of GTCs with or without caffeine resulted in a significant reduction in FBG. The limited data available on GTCs did not support a positive effect on FBI, HbA1c, or HOMA-IR. Thus, more large and well-designed trials are needed in the future.*

SUMMARY

In this meta-analysis (which was also reviewed in issue 7 of our Tea Expert Newsletter series [Scientific update on green tea and weight management, July 2013, focusing on green tea and weight management], Zheng *et al.* identified 22 relevant randomized, controlled studies (reported in the period 2002 – 2011) which had looked at the effects of green tea on FBG and insulin and insulin resistance in 1,584 subjects.[18] The included studies investigated different doses of green tea, mostly in the range of regular conditions of use (260 – 661 mg green tea catechins/day, equivalent to 1 - 3 cups[17]) but also included studies with higher green tea doses (> 800 mg catechins/day). Length of intervention ranged from 3 – 24 weeks, with most studies conducted for 8 – 12 weeks. Of the 22 studies included, 25 observations could be used to evaluate the effects on FBG as some studies provided information on subjects with high and low habitual caffeine intake. The available evidence for an effect of green tea on glycated haemoglobin (HbA1c) and evaluation of insulin sensitivity (HOMA-IR) was more limited (6 studies). This analysis found that consumption of green tea (catechins), with or without caffeine, significantly reduced FBG, but did not affect HbA1c or HOMA-IR.

3.

INTERPRETATION OF RESULTS FROM META-ANALYSES

During 2013, three meta-analyses reported on the effects of green tea or green tea extracts on glycaemic control in randomised, controlled, intervention trials.[14,15,18] The fact that these meta-analyses appeared almost simultaneously, indicates that a significant number of trials on this topic have been reported in recent years and that it was feasible to perform systematic reviews which potentially enable more robust conclusions on the role of green tea to be established.

Two meta-analyses of randomised, controlled intervention trials demonstrated that green tea consumption significantly, but modestly, reduces FBG levels[15,18] while a third meta-analysis found no statistically significant effects of green tea consumption on any markers of glycaemic control.[14] The reduction in FBG levels with green tea consumption observed in the two larger meta-analyses was of a similar, albeit relatively small magnitude: 0.09[15] and 0.08 mmol/L[18]. A normal FBG is in the range 3.9 – 5.6 mmol/L, so a reduction of 0.09 mmol/L represents a reduction from the mean normal value (4.75 mmol/L) of 1.9%.

The analysis by Liu *et al.* additionally found that green tea significantly reduced HbA1c levels, a marker of glucose exposure over the preceding 3 months, and sub-group analysis in this study revealed that green tea also reduced fasting insulin levels when low quality studies were excluded. These small but significant reductions in key markers of glycaemia were observed in analyses which included both Asian and Caucasian populations and FBG was reduced in sub-groups consuming green tea for both long (≥ 12 weeks) or short (≤ 12 weeks) duration. In addition, green tea consumption significantly lowered fasting glucose concentrations in subgroups with higher catechin intakes (≥ 457 mg/d) but no effect was found at lower catechin intakes – this result being in line with a recent meta-analysis of prospective studies which indicated that participants who drank ≥ 4 cups tea/day had a 20% lower risk of T2DM than those who drank less or none.[19] In the analysis of Zheng *et al.*, it appeared that the duration of the green tea intervention was critical, with significant effects only seen > 12 weeks but green tea dosage did not significantly modify the effect.

In sub-group analyses, Liu *et al.*, showed that the beneficial effects of green tea consumption on fasting glucose could only be observed in studies using decaffeinated interventions. This may be a chance finding related to study quality, because all 7 studies that used caffeinated green tea as a supplement showed a lower Jadad quality score. The role of caffeine remains unclear as the analysis of Zheng *et al.* showed an effect of green tea with and without caffeine while a report from the Nurses' Health Study indicated that only caffeinated tea was associated with lower risk of T2DM.[20]

The meta-analyses by Liu *et al.* (17 studies) and Zheng *et al.* (22 studies) used similar search strategies to identify relevant studies for inclusion but only 13 studies were common to both. The study by Wang *et al.* (7 studies) had most overlap with the study by Zheng *et al.* (6/7) but Wang *et al.* only included studies in subjects with T2DM or with insulin resistance. The other meta-analyses also included studies in (apparently) healthy subjects. A limitation of all three meta-analyses is the fact that measures for glucose control or insulin sensitivity were not the primary outcome measures in most of the trials selected. Wang *et al.* acknowledged the fact that the methodological qualities of the studies included in their meta-analysis was poor, that the sample sizes of the included RCTs was small, as was the overall number of subjects included (n=510). The question of study quality was also raised in the study by Liu *et al.*, in which 7 trials were classified as high quality and the remainder as low quality, on the basis of a Jadad score greater or less than 4. Similarly Zheng *et al.* classified 9 trials as high quality (Jadad score > 4) and 13 trials as low quality. Liu *et al.* noted that the included studies were generally of short duration (2 weeks – 6 months) and inconsistent results in the sub-group analyses where effects were seen on some glycaemic parameters but not others, were probably related to the limited number of high quality studies.

CURRENT CONCLUSIONS ON GREEN TEA AND GLYCAEMIC CONTROL

Taken together these meta-analyses indicate a potential for green tea to exert at least a small-modest benefit in glycaemic control. The studies included in these meta-analyses were however quite heterogeneous in relation to various aspects of their designs (e.g. subject characteristics, green tea dose, study duration) and in most cases glycaemic parameters were not the primary outcomes of the study, so the modest effects seen could be reflective of a true effect. If this is the case then most of the individual studies will have been underpowered to identify the "expected" effect as statistically significant and "negative" results from small studies should not be over-interpreted as the risk of Type 2 error (false negative result) is high. Indeed, all three meta-analyses concluded that larger, longer duration and high-quality RCTs are needed to conclusively establish the effect of green tea on glycaemic control.

4. EVIDENCE FROM INTERVENTION STUDIES TESTING EFFECTS OF BLACK TEA ON GLYCAEMIC CONTROL

4.1 EFFECTS ON RISK FACTORS OF CARDIOVASCULAR DISEASE

Bahorun, T., A. Luximon-Ramma, V. S. Neergheen-Bhujun, T. K. Gunness, K. Googoolye, C. Auger, A. Crozier and O. I. Aruoma. The Effect of Black Tea on Risk Factors of Cardiovascular Disease in a Normal Population. Prev Med 2012; 54: S98-102.

ABSTRACT

Objective: *A prospective randomized controlled clinical trial determined the effect of Mauritian black tea consumption on fasting blood plasma levels of glucose, lipid profiles and antioxidant status in a normal population.*

Method: *The study group (71%) consumed 3 x 200 ml of black tea infusate/day for 12 weeks without additives followed by a 3 week wash-out. The control group (29%) consumed equivalent volume of hot water for same intervention period.*

Results: *The tea used had high levels of gallic acid derivatives (50±0.4 mg/L), flavan-3-ols (42±2 mg/L), flavonols (32±1 mg/L) and theaflavins (90±1 mg/L). Daily 9 g supplementation of black tea infusate induced, in a normal population, a highly significant decrease of fasting serum glucose (18.4%; p<0.001) and triglyceride levels (35.8%; p<0.01), a significant decrease in LDL/HDL plasma cholesterol ratio (16.6%; p<0.05) and a non significant increase in HDL plasma cholesterol levels (20.3%), while a highly significant rise in plasma antioxidant propensity (FRAP: 418%; p<0.001) was noted.*

Conclusions: *Black tea consumed within a normal diet contributes to a decrease of independent cardiovascular risk factors and improves the overall antioxidant status in humans.*

SUMMARY

This study was a randomized, controlled clinical trial in a Mauritian population of males and females in which the treatment group consumed 3 x 200 ml of black tea infusate/day (3 standard cups of 200 ml hot water each containing 3 g of black tea (infused for 5 minutes)) for 12 weeks without additives (milk or sugar), followed by a 3 week wash-out period in which the same volume of hot water was consumed per day.[21] The control group consumed the equivalent volume of hot water for the same intervention period. Subjects were maintained on their normal diet and were required to fill a diet survey form over the study period. The mean fasting blood glucose level, recorded at baseline, was 134±66 mg/dL (7.44±3.66 mmol/L) for males and 111±38 mg/dl (6.16±2.11 mmol/L) for female subjects. In the statistical analysis performed by the authors, these levels were greatly influenced by tea consumption with a significant drop of 20.3% and 14.8% (p<0.001) respectively after 12 weeks. However, the comparison was pre- and post-intervention and not a comparison of FBG difference in the tea groups versus differences in the control group. Non-significant, but substantial decreases in FBG (12.6% and 22%) were observed in the control groups which raises questions about the true significance of the tea effect proposed.

INTERPRETATION

It is noteworthy in this study that the baseline blood glucose levels in these presumably healthy study subjects were above normal values, indicating the presence of prediabetes and even diabetes in the majority of these Mauritian subjects. It is however disappointing that the statistical approach used by the authors to determine the effects of the black tea intervention on FBG levels did not focus on comparing differences between outcomes in the treatment versus the control group. This precludes any firm conclusions about the relative effect of the tea intervention. The authors instead focused on changes from baseline values measured after 12 weeks of intervention. It is well-known that subjects enrolled into nutrition intervention studies can start to pay more attention to their dietary and other health-related habits and this could be a likely explanation for the reduced blood glucose levels observed in both groups in this study.

4.2

4.2 EFFECTS ON STRESS BIOMARKERS AND SERUM C-REACTIVE PROTEIN LEVELS

Neyestani, T. R., N. Shariatzade, A. Kalayi, A. Gharavi, N. Khalaji, M. Dadkhah, T. Zowghi, H. Haidari and S. Shab-bidar.
Regular Daily Intake of Black Tea Improves Oxidative Stress Biomarkers and Decreases Serum C-Reactive Protein Levels in Type 2 Diabetic Patients. Ann Nutr Metab 2010; 57: 40-9.

ABSTRACT

Background: *This study was undertaken to evaluate the possible effects of different daily doses of black tea intake on certain oxidative stress, inflammatory and metabolic biomarkers in patients with type 2 diabetes mellitus (T2DM).*

Method: *Forty-six patients with known T2DM were randomly assigned either to the test (n = 23, 57.0 ± 7.9 years) or the control (n = 23, 55.4 ± 8.3 years) group. Following a one week 'run-in' period, the test group received 150, 300, 450 and 600 ml of black tea (BT) during the weeks 1, 2, 3 and 4, respectively. The control group received 150 ml BT a day throughout the intervention period. Dietary, anthropometric and biochemical assessments were performed at the end of each week.*

Findings: *Serum total antioxidant capacity was enhanced similarly in both test and control groups. However, daily intake of 2 cups of BT by the test group showed a suppressing effect on serum malondialdehyde. Serum C-reactive protein significantly decreased and glutathione levels increased following the intake of 4 cups (600 ml) of BT a day.*

Conclusion: *Regular intake of BT had anti-oxidative and anti-inflammatory effects in patients with T2DM. These findings may, to some extent, explain the mechanisms underlying the protective effects of drinking tea against cardiovascular disease.*

SUMMARY

In this controlled trial subjects with known T2DM were randomised to an experimental group receiving increasing amounts of black tea over a 4 week period (150 ml/1 cup per day up to 600 ml/4 cups per day) or a control group that maintained consumption of 150 ml/1 cup BT per day throughout the intervention period.[22] To minimize variations in BT preparation, a package containing written instructions, a 150-ml drinking cup together with enough tea bags for the duration of the study were given to the subjects. Each tea bag contained 2.5 g dry Nooshineh Chaay brand tea (Lahijan, Iran) which was infused in 150 ml of hot water for 2 minutes. At the end of each week, a 24-hour dietary recall questionnaire was completed and a fasting blood sample was taken from each patient. All subjects were instructed to maintain their usual diet, glucose-lowering medication and physical activity habits throughout the study and to avoid consumption of listed, high polyphenol foods. Fasting blood glucose decreased significantly from run-in to week 1, but no significant difference between treatment and control groups was observed throughout the intervention period. In addition, no changes were observed in fasting insulin or insulin resistance (as measured by HOMA-IR) and the mean percent of HbA1c did not show any significant change by the end of the study between groups.

INTERPRETATION

This study by Neyestani *et al.* found no statistically significant effects of gradually increasing black tea consumption on glycaemic control during a 4 week intervention in diabetic subjects with hyperglycaemia. Black tea consumption is very popular in Iran where this study took place and the control group was maintained on 150 ml BT throughout the run-in and study periods. There is a possibility that even at these low levels of black tea consumption, the threshold of a potential black tea effect had already been reached as data from the EPIC-Interact study suggested that T2DM risk already tended to be lower with tea consumption between 1 - <4 cups per day.[10]

4.

CURRENT CONCLUSIONS ON BLACK TEA AND GLYCAEMIC CONTROL

Black tea represents over 90% of all tea sold in the Western world but most research effort has been focused on the health benefits of green tea. Causal relationships can only be established through controlled intervention trials and in reviewing data for this expert newsletter only seven intervention studies were identified that have investigated the effects of black tea on FBG or related parameters. Two of these studies had vascular function or other markers of cardiovascular health as primary outcome parameters and consequently study designs were not optimized or powered to identify changes in glucose metabolism.[23,24] Indeed both studies did not observe any effect of black tea on blood glucose levels. The intervention studies that were actually designed to test the effect of black tea on glycaemic markers used black tea in different formats and doses. In three studies, subjects consumed black tea infusions in volumes ranging from 150 - 600 ml as acute, single dose or chronically for up to 12 weeks.[21,22,25] Bryans *et al.* (2007) investigated effects of an instant black tea in an acute design[26] and MacKenzie *et al.* (2007) tested an intervention with capsules containing 150/300 mg catechins and 75/150 mg theaflavins for three months.[27] Of these five studies, four ended with a neutral outcome with only the study by Bahorun *et al.* suggesting a positive effect of black tea on FBG, but as discussed, the statistical approach used was not sufficiently robust.[21]

Recently a new approach was taken to identify possible benefit areas for black tea. Beresniak *et al.* performed an ecological study using a systematic data-mining approach on data from 50 countries participating in the World Health Survey to study six health variables, including diabetes.[28] Following principle component analysis, the "black tea" vector was found to be negatively correlated only with the "diabetes health" vector and a linear correlation analysis subsequently confirmed a significant statistical correlation between high tea consumption and low diabetes prevalence. While the strength of evidence from ecological studies is seen as weaker than prospective or even cross-sectional studies, the results of this "hypothesis-generating" study are in line with the findings of the EPIC-Interact prospective study, also reviewed in this newsletter, which indicates a positive association between black tea consumption and diabetes risk, but as yet, direct (cause-effect) evidence for a beneficial effect of black tea on glycaemic markers is limited.

5. Concluding Remarks

Key message: Observational and mechanistic studies provide support for hypotheses linking tea to glycaemic control, but the RCTs performed to date have been too small and weak to adequately test (i.e. confirm or reject) these hypotheses.

- Tea is a popular beverage throughout the world, and is particularly enjoyed in developing countries which are being most impacted by the diabetes "epidemic". Tea has the potential to make a positive contribution to a healthy diet and lifestyle through its low calorie content and hydrating properties which promote weight management and contribute to daily fluid balance. In addition, as reviewed in this newsletter, tea may also have other effects relevant to diabetes risk reduction.

- Epidemiological, *in vitro* and animal studies support the beneficial effects of dietary flavonoids on glucose homeostasis.[29] Tea is a major source of dietary flavan-3-ols, flavonols and polymeric flavan-3-ols (theaflavins and thearubigins). There is evidence to suggest that tea may play an active role in reducing glycaemia and maintaining insulin sensitivity, possibly through effects of flavonoids, present at high concentrations in the gut, on glucose absorption[30] or via direct effects on pancreatic beta-cells as suggested by animal data.[31] This is clearly still an emerging field of nutrition and health research with recent prospective epidemiological data (from the EPIC-Interact cohort) providing strong suggestive evidence for an association between tea consumption (likely to be mostly black in this European cohort) and reduced risk of T2DM. Three publications from this cohort provide indications that both tea and tea flavonoid (flavan-3-ols and flavonols) consumption is associated with lower T2DM risk,[6,10,11] but this association was not supported by results from a recent cross-sectional study which found anthocyanins and flavones, not flavan-3-ols, to be associated with improved insulin sensitivity.[12] There are feasible explanations for these different study outcomes but the body of epidemiological data is strong enough to warrant support for the randomised, controlled trials which are needed to provide the evidence for cause and effect.

- This newsletter has briefly reviewed the results of three meta-analyses of randomised controlled trials looking at the effects of green tea on glycaemic control.[14,15,18] Taken together these meta-analyses indicate a potential for green tea to exert at least a modest benefit in glycaemic control, as measured by FBG. The studies included in these meta-analyses were quite heterogeneous in relation to various aspects of their designs (e.g. subject characteristics, green tea dose, study duration, methods used to assess glycaemia and insulin sensitivity) and in most cases glycaemic parameters were not the primary outcomes of the study. In terms of black tea and glycaemic control, the available evidence is not strong. While a number of cohort studies have linked black tea consumption to reduced diabetes risk, the available evidence from randomised, controlled trials is weak, including that from the two recent studies reviewed here. [21,22]

- Many of the papers reviewed here concluded that larger (adequately powered), longer duration and high-quality RCTs are needed to conclusively establish the effect of tea on glucose homeostasis. In considering future study options, however, it has also been recommended to not only focus on chronic effects but to also look at acute, postprandial effects. In addition, it could also be considered to measure a range of peptides involved in glucose regulation beyond just insulin, for example interleukin-6, adipocytokines and incretins and to use the gold standard methods available.[32] Looking at frequent tea consumption throughout the day rather than one high daily dose could also be considered.

- As this newsletter was ready to go to press a new systematic review and dose-response meta-analysis of prospective cohort studies was published which had investigated the relationship between tea consumption and T2DM risk.[33] This review of data from 16 cohorts, found a significant, inverse association between tea consumption and T2DM risk with increased consumption of 2 cups of tea/d associated with a 4.6% reduced risk of T2DM. These results are in agreement with and strengthen the observations in the EPIC study (which was one of the 16 included in the meta-analysis) but the authors acknowledge that more well-designed observational studies that take account of the different characteristics of tea (e.g. type, strength and preparation method) are needed to fully understand the potential of the tea and T2DM association. It is important from a public health perspective that any benefits on glucose control, insulin sensitivity and T2DM which may come from a beverage such as tea, are fully and robustly explored.

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8. NOTES

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