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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1340 – 1344
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

The effect of an extract of green and black tea on glucose control in adults with type 2 diabetes mellitus: double-blind randomized study

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Received 12 December 2006; accepted 2 May 2007

Abstract

Recent evidence suggests that tea from *Camellia sinensis* (eg, green, oolong, and black tea) may have a hypoglycemic effect. We evaluated the ability of an extract of green and black tea to improve glucose control over a 3-month period. A double-blind, placebo-controlled, randomized multiple-dose (0, 375, or 750 mg per day for 3 months) study in adults with type 2 diabetes mellitus not taking insulin was performed. The primary end point was change in glycosylated hemoglobin at 3 months. The 49 subjects who completed this study were predominantly white with an average age of 65 years and a median duration of diabetes of 6 years, and 80% of them reported using hypoglycemic medication. After 3 months, the mean changes in glycosylated hemoglobin were +0.4 (95% confidence interval, 0.2-0.6), +0.3 (0.1-0.5), and +0.5 (0.1-0.9) in the placebo, 375-mg, and 750-mg arms, respectively. The changes were not significantly different between study arms. We did not find a hypoglycemic effect of extract of green and black tea in adults with type 2 diabetes mellitus.

1. Introduction

Besides water, tea is the most consumed beverage in the world. Tea is made from the leaves of the warm weather evergreen *Camellia sinensis*. *Green tea* refers to *Camellia sinensis* when it is cut and dried, *oolong tea* refers to the leaves after they have been left to partially oxidize before drying, and *black tea* refers to the leaves that have been completely oxidized before desiccation. Tea is a rich source of catechins, especially epigallocatechin gallate (EGCG), which are hypothesized to have multiple beneficial health effects [1,2].

There is some evidence that tea is a hypoglycemic agent. In vitro rat studies suggest that EGCC and other catechins and theaflavins help prevent hyperglycemia by enhancing insulin activity and possibly by preventing damage to β-cells [3]. Glucose levels in the blood of rats were reduced by black tea extract [4], by black tea [5] and green tea [5,6], and by EGCG [7-9]. A prospective epidemiological study done in Japan found that men and women who reported drinking 6 or more cups of green tea per day had one-third less the incidence of type 2 diabetes mellitus over 5 years [10]. In adults with type 2 diabetes mellitus, fasting blood glucose dropped considerably after 4 weeks of drinking 1.5 L of oolong tea per day from a mean of 223 to 160 mg/dL in a randomized crossover trial [11].

No studies in North America have evaluated the effect of tea on glucose control using a blinded design. We tested the hypothesis that extract of green and black tea improves glucose control in adults with type 2 diabetes mellitus using a double-blind, randomized, controlled trial.

2. Methods

2.1. Subjects

Criteria for inclusion into the study were patients with a diagnosis of type 2 diabetes mellitus of at least 6 months' duration who were not taking insulin and whose last known glycosylated hemoglobin (HbA_{1c}) fell between 6.5% and

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0026-0495/$ – see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.metabol.2007.05.018

9.5% and was done in the previous 6 months. Exclusions were pregnancy and treatment with warfarin therapy [12]. Subjects were recruited from the General Internal Medicine Clinic at Dartmouth-Hitchcock Medical Center and by a newspaper advertisement. Enrollment commenced in August 2005 and was completed in March 2006. The Committee for the Protection of Human Subjects at Dartmouth College approved this study (CPHS 17101).

2.2. Study agent

We used Teaflavin extract that is manufactured by Nashai Biotech (http://www.nashai.com; Nashville, TN). The extract is decaffeinated and is standardized to contain a minimum of 40% catechins from green tea and 20% theaflavins from black tea. Capsules contained 375 mg of tea. The placebo capsule was 375 mg of cellulose. Prior studies on tea extracts have shown them to be safe [13,14]. The extract used in this study was previously evaluated in a cholesterol-lowering study [15].

The 375-mg capsule used in this study contained 150 mg of green tea catechins (equivalent to the amount in 7 cups of green tea) and 75 mg of black tea theaflavins (equivalent to the amount in 35 cups of black tea). Other tea polyphenols comprise the remainder of the capsules (150 mg).

2.3. Randomization and blinding

Subjects were randomized using a list prepared with a random number generator. They were randomized in blocks of 12 in a 2:2:1:1 ratio to receive 2 capsules per day of extract, 1 capsule per day of extract, 2 capsules per day of placebo, or 1 capsule per day of placebo. This allocation gives an equal probability of randomization to the 3 dosage levels in this study: placebo (0 mg), single capsule (375 mg), and double capsule (750 mg). Study personnel, subject's clinicians, and subjects were blinded to subject's treatment arm.

2.4. Study visits and end points

The study consisted of one baseline visit and a visit at 3 months after randomization. At baseline, informed consent was obtained, demographic and treatment information were collected, and subjects underwent blood draw to measure HbA_{1c}. Subjects then received a bottle containing a 3-month supply of capsules. Subjects were asked to take the capsules at the same time every day, which was typically in the morning. Subjects were encouraged to avoid changes to their use of oral hypoglycemics (ie, increasing, reducing, or starting therapy) and to reduce or terminate consumption of tea (green, black, and oolong) during the 3 months of the study. Patients were contacted by phone at 2 and 8 weeks for completion of a study survey and for discussion of questions or concerns, including symptoms potentially related to the capsules. At 12 weeks, subjects returned for the final visit, at which time they were asked about treatment and lifestyle changes, compliance, and their belief about whether or not they were receiving tea or placebo using a Likert scale that ranged from 0 (absolutely believe they were receiving placebo) to 10 (absolutely believe they were receiving tea). At this time, subjects underwent a blood draw to measure HbA_{1c}. All visits and measurement of HbA_{1c} were conducted at the Dartmouth-Hitchcock Medical Center in Lebanon, NH.

2.5. Statistical analysis

Characteristics at baseline were compared between the 3 study arms to detect imbalance between study arms using analysis of variance for continuous variables (age, years with diabetes, body mass index, HbA_{1c}), Pearson χ^2 test for sex, and Fisher exact test for use of hypoglycemics. The Wilcoxon-Mann-Whitney test was used to compare the Likert belief scale between those receiving placebo and those receiving tea. In the text, means are presented with standard error of the mean in parentheses. Analysis of covariance was used to compare HbA_{1c} at 3 months between the 3 study arms (750 mg vs 375 mg vs placebo) while adjusting for HbA_{1c} at baseline. In addition, we tested for a dose-response association using linear regression of HbA_{1c} at 3 months on dosage and HbA_{1c} at baseline. Both of the latter 2 approaches are mathematically equivalent to the corresponding approaches in which the end point is replaced by change in HbA_{1c}. The analysis of variance, analysis of covariance, and linear regression were repeated using randomization tests to obtain robust P values (ie, P values not sensitive to departures from normality) because the sample sizes were small; but the P values were almost identical. All analyses were conducted using R 2.1.1 [16]. The planned sample size was a total of 48 subjects, with 16 randomized to each of the 3 arms based on a primary comparison of those receiving tea (combination of 375-mg and 750-mg arms) with the placebo arm, a minimal detectable effect of 0.5% in HbA_{1c}, a standard deviation of 0.5 in change in HbA_{1c} over 3 months, a type I error rate of 5%, and 80% power.

3. Results

A total of 54 subjects enrolled in the study and 49 completed follow-up. Three subjects dropped out in the first week of the study. One subject (receiving placebo) stated that the capsules were too large to swallow, one subject withdrew because of profuse sweating after ingestion of a single dose of tea extract (375 mg), and one subject (receiving 750 mg of tea) withdrew because of a systemic rash on day 2 of the study. These were the only reported adverse events. Two subjects (one each from the placebo and 750-mg arms) could not return for the scheduled second visit, leaving 49 subjects who completed the study.

Table 1 presents demographics and other characteristics at baseline according to study arm for the 49 subjects who completed the study. The mean age of enrollees was 65 years (range, 49-86 years). Fifty-seven percent were female, the

average duration since diagnosis of diabetes was 7 years (range, 1-26 years), and 80% reported prescriptions for oral hypoglycemics. All but 2 of the subjects were white. We also queried participants about intake of tea in the month before enrollment. Thirty-six percent of the subjects reported consuming at least one serving of green tea, 19% reported 4 or more servings, and 2 subjects reported daily intake. Fifty-one percent of the subjects reported consuming at least one black tea (hot or iced), 34% reported 4 in the past month, and 9% reported daily consumption. There were no significant differences between the 3 study arms with respect to any of these characteristics.

One subject in the 375-mg tea extract arm reported a doubling of his/her dose of metformin during the study, whereas another subject in the same arm reported stopping his oral hypoglycemic regimen (glyburide and metformin). There were no other reported changes in glucose-lowering medication.

There was no difference in the belief scale between those randomized to one of the 2 tea arms and those randomized to placebo (Wilcoxon-Mann-Whitney $P > .10$). Sixty-four percent expressed no belief one way or the other about whether or not they believed the study capsule they were receiving contained tea. Only 2 subjects reported missing more than 5 days of study pills. One of these was in the placebo arm and one was in the 750-mg arm.

The HbA_{1c} results at 3 months are displayed in Fig. 1 grouped by study arm. The mean increases in HbA_{1c} were 0.4 (95% confidence interval [CI], 0.2-0.6), 0.3 (0.1-0.5), and 0.5 (0.1-0.9) in the placebo, 375-mg, and 750-mg arms, respectively. There was no difference in the change in HbA_{1c} between the 3 groups (analysis of covariance, $P = .83$). The mean difference between those receiving tea (either 375 or 750 mg) and those receiving placebo was 0.0 (95% CI, −0.4 to 0.3). In addition, there was no significant linear dose-response association ($P = .70$). One of the subjects in the 750-mg tea extract arm had an increase of 3.1 in HbA_{1c} over the 3 months. We found that this subject had a history of elevated glucose (eg, HbA_{1c} over 9) and that the baseline value was less characteristic. When we repeated the analyses excluding this subject, there remained no significant difference between study arms. The mean increase in HbA_{1c} in the remaining subjects in the 750-mg arm was 0.3 (0.1). When we restricted analyses to subjects who reported little or no prior consumption of green or black tea, we found no difference between the placebo and tea extract arms.

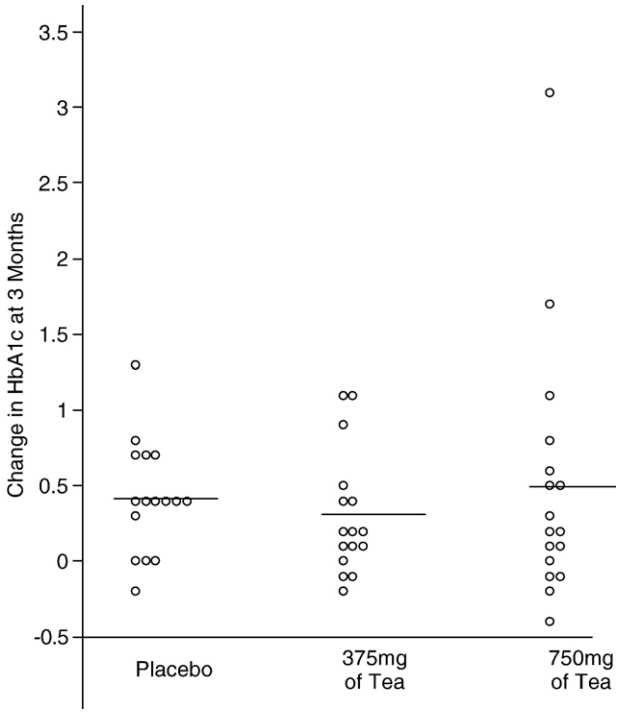

Fig. 1. Changes in HbA_{1c} at 3 months from baseline. The means in each study arm are indicated by the horizontal bars. There was no difference between the 3 arms ($P > .10$), between the placebo arm and the combination of the 2 tea extract arms ($P > .10$), or when the outlier in the 750-mg arm was excluded.

Table 1
Characteristics at baseline

	Placebo (n = 16)	Tea extract: 375 mg (n = 16)	Tea extract: 750 mg (n = 17)	P
Age (y)	68.5 (9.8)	60.6 (9.9)	67.1 (11.1)	.08
Sex	50% (8)	44% (7)	35% (6)	.69
Years with diabetes	8.7 (5.7)	7.5 (6.7)	4.9 (4.1)	.17
BMI (self reported)	30.7 (5.2)	34.3 (8.1)	34.8 (11.7)	.35
Use of prescribed oral hypoglycemics	81% (13)	88% (14)	71% (12)	.56
Servings of green tea in past month [a]	0 (0-1)	0 (0-3)	0 (0-5)	.34
Servings of black tea in past month a	0 (0-2)	1 (0-14)	4 (0-11)	.51
HbA_{1c} at baseline	7.1 (0.8)	7.2 (0.8)	7.1 (0.9)	.97

BMI indicates body mass index.
[a] Medians (interquartile range) with P value from Kruskal-Wallis test.

4. Discussion

This blinded, placebo-controlled, randomized trial of decaffeinated green tea extract in adults with type 2 diabetes mellitus did not demonstrate a beneficial effect on glucose control after 3 months. There were no effects of either a single capsule (375 mg) or 2 capsules (750 mg) a day in comparison with placebo. Those who received tea (either dose) had the same mean change in HbA_{1c} at 3 months, with a 95% CI of −0.4 to 0.3, which rules out the possibility that tea extract reduces HbA_{1c} by more than 0.4. The biggest reduction in anyone receiving tea (375 mg or 750 mg) was 0.4, and only 3 (8%) subjects had reduction of 0.2 or more. This suggests that if extract of green and black tea does have a beneficial effect, it is very small.

In the study by Hosoda et al [11], the effect of oolong tea was a 30% reduction in the fasting blood glucose of subjects

with type 2 diabetes mellitus after 1 month. However, in that study, which was not blinded, subjects drank approximately 1.5 L per day of oolong tea, which was not decaffeinated. A similar open-label randomized crossover trial was conducted in South Koreans with type 2 diabetes mellitus to evaluate the effect of 4 weeks of green tea dissolved in water on glucose, insulin, and inflammatory markers [17]. The South Korean study found a small nonsignificant lowering of fasting glucose after green tea and no differences in fasting insulin or inflammatory markers. Fukino et al [18] evaluated the effect of approximately 500 mg of green tea powder dissolved in hot water for 2 months in 66 adults with borderline diabetes or diabetes in Japan using an open-label randomized study and found a small but nonsignificant improvement in HbA_{1c}. Unlike these 3 open-label studies conducted in Asia, our study was conducted in predominantly white subjects and we used an extract that allowed blinding of subjects and study personnel. Furthermore, the extract was decaffeinated tea unlike the 3 studies above. However, it is unlikely that the absence of caffeine hampered any hypoglycemic effect of tea because caffeine has been shown to acutely impair glucose metabolism in persons with diabetes [19,20]. It is possible that tea is more effective when consumed continually over the day, as is typically the case with tea drinking, as opposed to receiving it in a single or double bolus, which was the case in our study. Our lack of a positive finding may also be due to the extract used in this study, which contained components from both green and black tea. Most of the subjects in our study had relatively good glucose control at baseline (mean HbA_{1c} of 7.1), whereas the subjects in the study by Hosoda et al [11] had poor glucose control on average (mean fasting blood glucose of $\geq$200 mg/dL at baseline). It may be that tea extract has a hypoglycemic effect in subjects with the worst glucose control. On the basis of the studies of Fukino et al [18], Hosoda et al [11], and Ryu et al [17], as well as ours, it cannot be ruled out that tea is effective at lowering fasting glucose levels; but it seems that it has at most a minor improvement on overall glucose control as measured by HbA_{1c}.

There was a significant loss of glucose control over 3 months in each of the 3 groups of this study, with the average rise in HbA_{1c} being 0.4. This might be due to the fact that clinicians of patients enrolled in our study tried to delay changes in hypoglycemic therapy until the end of the trial, or it could be due to seasonal variation in HbA_{1c}. A report has indicated that HbA_{1c} increases in the colder months [21]. In our study, the 22 subjects who enrolled before January had a mean increase of 0.6 in HbA_{1c}, whereas those 27 who enrolled in January or later had a mean increase of only 0.2.

Limitations of our study were as follows: (1) the use of an extract that contained components of both green and black tea that prevents us from making claims about all extracts of tea or tea as a beverage, (2) the reliance on subject reports of compliance, (3) the absence of fasting insulin or insulin sensitivity as an end point despite indications that tea's hyperglycemic effect is through enhancement of insulin activity, and (4) the insufficient power to detect effects of tea on HbA_{1c} of 0.5 or less. Strengths of our study were the successful blinding of subjects (only 3 subjects claimed to know whether they were on tea or not; and in those, one was wrong), the high rate of compliance (all subjects reported that they had taken capsules on all but a few days), the absence of cointerventions (only 2 subjects reported changing their hypoglycemic regimen), a previously unstudied population (American), and the evaluative period of 3 months that is long enough to evaluate an impact on HbA_{1c}.

5. Conclusion

We did not find a significant effect of extract of green and black tea on glucose control in adults with type 2 diabetes mellitus.

Acknowledgments

This study was supported by a grant from the Hitchcock Foundation (Lebanon, NH).

The authors would like to thank Nashai Biotech for supplying the Teaflavin capsules used in this study.

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