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Acute effects of green tea (*Camellia sinensis*) intake instead of anti-diabetic drug on hepatic enzymes and atherogenic risk factors in type 2 diabetic patients

Mst. Afifa Khatun,[1] Utpal kumar Prodhan[2], and Nazibur Rahman[3,*]
[1]Food Technology Division, Institute of Food and Radiation Biology, Atomic Energy Research Establishment, GPO Box 3787, Savar, Dhaka-1000. Bangladesh
[2] Food Technology and Nutritional Science, Mawlana Bhashani Science and Technology University, Bangladesh
[3]Department of Biochemistry and Molecular Biology, Jahangirnagar University, Savar, Dhaka, Bangladesh
*Corresponding author: **Md. Nazibur Rahman** E-mail: *nazibanfs@yahoo.com*

Abstract

Green tea has been evidenced to have hypoglycemic effects. In this study, the effect of green tea intake instead of anti-diabetic agent has been examined on hepatic enzymes and lipid profiles in type 2 diabetic patients. 30 diabetic subjects from Kushtia district of Bangladesh were allowed to intake hot water extract of the Finlay green tea of Bangladesh (3 cups/day: 2gm tea/cup) for one month. Prospective analyses were performed with the baseline plasma measurements of liver enzymes (ALT, AST, GGT, ALP) and lipid profile (TG, Cholesterol, HDL, LDL). The authors observed that only ALT has been increased significantly in green tea consumed patients compared to control that could be explained as epigallocatechin-3-gallate, the active component of green tea, might not be a ligand for PPAR-gamma like the oral hypoglycemic drugs and thus inactivation of PPAR-gamma might induce accumulation of ALT in plasma. While other liver enzymes and the lipid factors did not show any significant alteration. This acute study presently cannot recommend Finlay green tea as a substitute of thiazolidinediones for the diabetic patients. Studies with various amount or type of green tea remain to be carried out to test their possibility as substitutes of hypoglycemic agents.

Keywords: green tea, liver enzymes, lipid profile, type 2 diabetes.

Introduction

Thiazolidinediones are a class of anti-diabetic drug. The medications in this class, which include troglitazone, pioglitazone, and rosiglitazone, act by enhancing insulin sensitivity at least in part via anti-steatotic effects in liver and muscle (Mayerson et al., 2002) and have been associated with decreased free fatty acids and serum triglycerides. But there are some data from animal studies suggesting that hepatic toxicity might be characteristic of the thiazolidinedione class (Boelsterli et al., 2002).

As a result of reports of severe idiosyncratic hepatotoxicity, troglitazone has been withdrawn from the US, European, and Japanese markets in 2000. In addition, neither pioglitazone nor rosiglitazone are approved in the US for use in combination with a sulfonylurea and metformin. Thus the impact of the drugs on hepatic inflammation and fibrosis is variable (Caldwell et al., 2001). Whilst there is, as yet, no direct evidence that the use of insulin or sulfonylureas has any adverse effect on the liver of diabetic patients, the putative role of insulin in the pathogenesis of

steatosis and fibrosis in Non-Alcoholic Fatty liver disease (NAFLD) suggests that these agents should be avoided if glycemic control can be achieved with other treatment modalities. In a study in rats treated with alloxan, green tea decreased serum glucose levels (Sabu et al., 2002), suggesting that catechins interact with glucose metabolism. Catechins also reduced plasma triglyceride levels in an oral glucose tolerance test in normal rats (Wu et al., 2004).

Green tea has antiproliferative activity in hepatoma cells and hypolipidemic activity in hepatoma-treated rats, and some studies report that it prevents hepatoxicity (Murase et al., 2002; Miura et al., 2001). Long-term feeding of tea catechins could be beneficial for the suppression of high-fat diet-induced obesity by modulating lipid metabolism, could have a beneficial effect against lipid and glucose metabolism disorders implicated in type 2 diabetes, and could also reduce the risk of coronary disease (Raederstorff et al., 2003; Loest et al., 2002; Murase et al., 2002; Tijburg et al., 1997; Miura et al., 2001). However, the acute effects of green tea extract on hepatic toxicity in Non-insulin-dependent diabetes mellitus (NIDDM) subjects remain unclear.

Considering above facts it can be hypothesized that green tea could be a suitable substitute for anti-diabetic drugs (thiazolidinedione derivatives) in type-2 diabetic patients. In support of the hypothesis there are few studies which demonstrated that long-term feeding of tea catechins could be beneficial for the suppression of high-fat diet-induced obesity by modulating lipid metabolism, could have a beneficial effect against lipid and glucose metabolism disorders implicated in type 2 diabetes, and could also reduce the risk of coronary disease[14-18]. Recently 'Finlays Daragaon Green Tea' has been manufactured and marketed by a company in Bangladesh. But it remains obscure whether that green tea prevents hepatotoxicity in type 2 diabetic patients. Therefore, the main objective of the present research was to investigate the level of liver enzymes and lipid profiles in diabetic patients after consumption of green tea extract instead of anti-diabetic drugs for 1 month.

Materials and Methods

Collection of Green tea

The experimental green tea named as Finlays Daragaon Green Tea has been collected from the supermarket at the production area: Srimangal, Moulovibazar district of Bangladesh. This tea was manufactured by the Consolidated Tea and Lands Co. (Bangladesh) Ltd.

Subjects and Physical measurements

Subjects (30 persons) in this study were type 2 diabetic patients of between 40 and 55 years of age and nonsmokers at the time of the study. None of the patients had known history of hepatitis and cardiovascular disease. No subject had clinical or laboratory signs of acute or chronic infection or took any medication at the time of the study. All subjects provided written informed consent before participation. The study was carried out in the diabetic patients of the Kushtia district, Bangladesh. Height, weight and BP were measured for each patient. BMI was calculated as weight/height^2 (kg/m^2) and was used as an estimate of overall adiposity. Duplicate measures of anthropometry were made following a standardized protocol, and averages were used in the analysis.

Study design and Biochemical measurements

The patients were allowed to intake hot water extract of green tea 3 cups/day (Approximately 3 gm tea in each cup) for 01 month. At the end of the study period, blood samples of those subjects were collected from the vein into a test tube and centrifuged for 10 minutes at 5000 rpm at 4ºC. The resultant plasma was stored at -80ºC for biochemical measurements. Prospective analyses were performed with the baseline plasma measurements of lipid profiles such as Triglycerides, Total cholesterol, HDL-cholesterol and LDL-cholesterol and liver enzymes like Alanine transaminase (ALT), Aspartate transaminase (AST), Gamma-Glutamyl Transferase (GGT) and Alkaline phosphatase (ALP). All the biochemical measurements were determined using standard clinical methods at the central BIHS (Bangladesh Institute of Health Science) laboratory of the Diabetic Association of Bangladesh with a biochemical analyzer using commercial kits [SERA-PAK®, Bayer corporation, Diagnostic division 511 Benedict Ave: Tarrytown, NY 10591, Local distributor-ACI diagnostics Bangladesh Ltd.].

Data analysis

Values represent the mean ± SE. The significance of differences between means was assessed by the student *t-test* after analysis of variance had been performed to establish that there were significant differences between the groups.

Results and Discussion

There are few hepatic enzymes such as ALT, AST, ALP, and GGT demonstrate altered physiologic condition. These enzymes showed altered characteristics when type 2 diabetic patients intake green tea extract for a short time as a substitute of oral hypoglycemic agents. It has been seen in figure 1 to 4 that all the liver enzymes tend to increase after acute consumption of green tea instead of the oral hypoglycemic agents. But only ALT increased significantly in green tea consumed diabetic patients. Here the baseline ALT level of the diabetic patients using anti-diabetic drug has been treated as control.

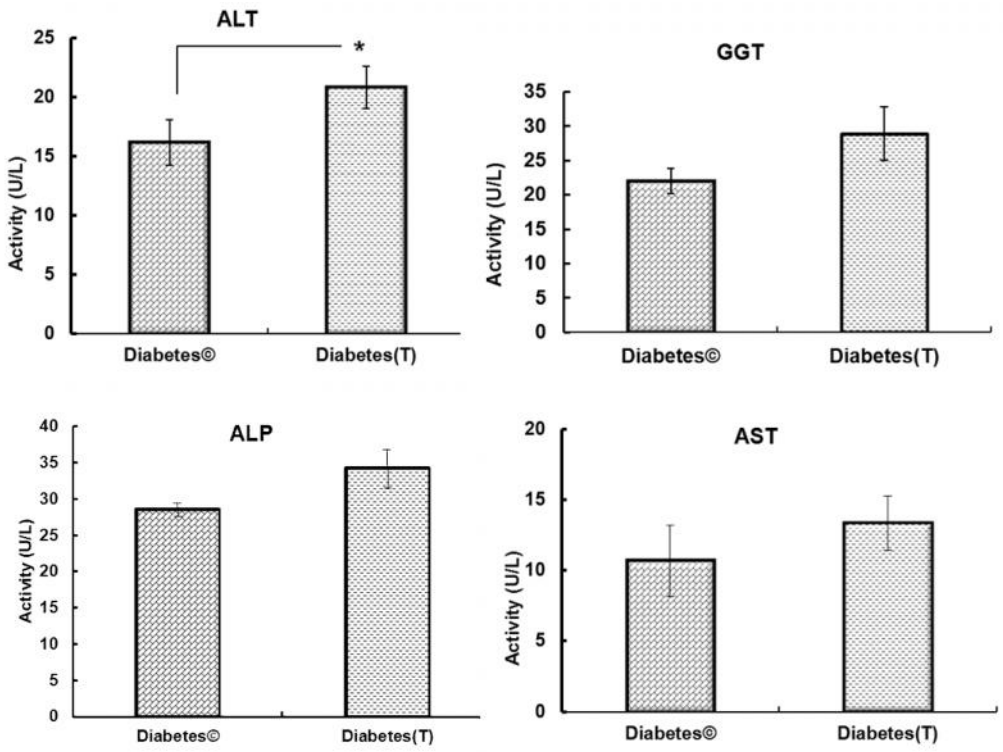

*Figure 1: Effects of green tea extract on the liver enzymes level in plasma from Diabetes (control) and Diabetes (green tea). Data are expressed as mean±SEM. *P<0.05 or less vs. Diabetes (control).*

Plasma lipid profiles like total cholesterol, triglycerides, HDL, and LDL did not increased significantly while remain similar in diabetic patients one month after consumption of green tea instead of any anti-diabetic drug (Figure 2).

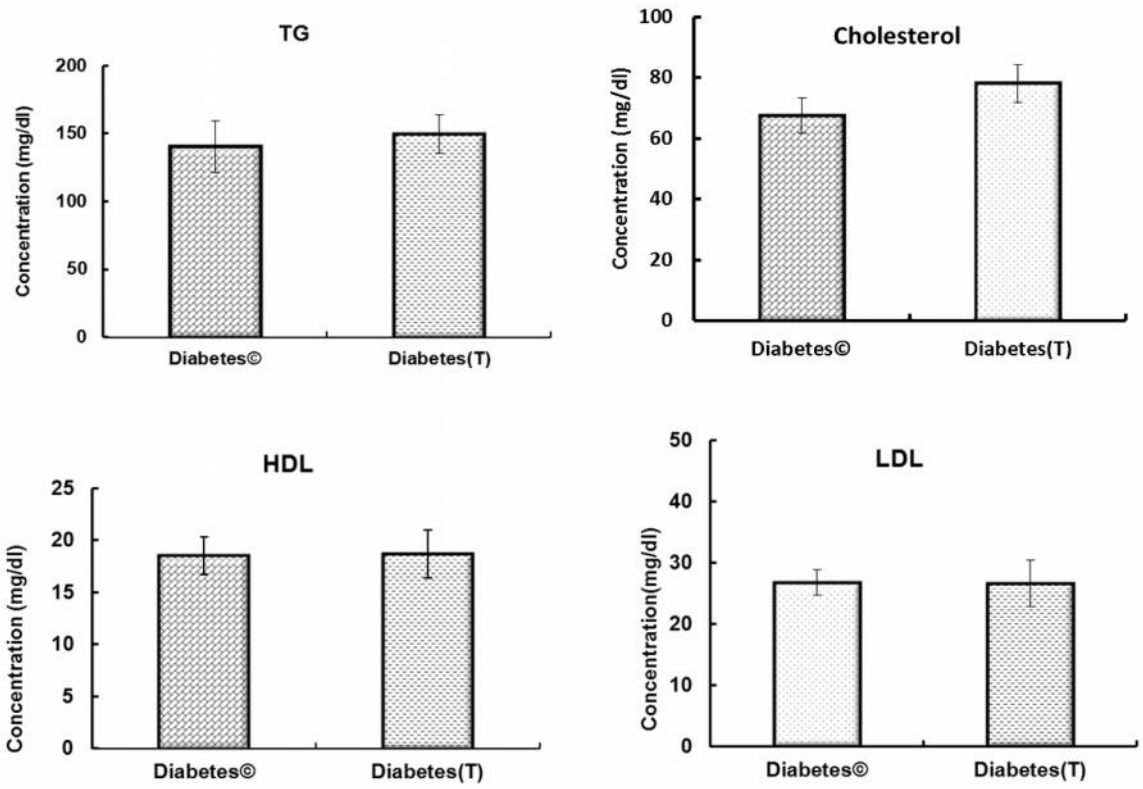

*Figure2. Effects of green tea on the concentration of Triglycerides (TG), LDL- cholesterol, HDL- cholesterol, and total cholesterol in plasma from Diabetes (control) and Diabetes (green tea) were analyzed enzymatically. Data are expressed as mean ± SEM.*P<0.05 or less vs. Diabetes (control).*

In this study diabetic patients are allowed to intake green tea extract instead of oral hypoglycemic drugs for one month. Thiazolidinediones or 'glitazones' are a new class of anti-diabetic drug and are often referred to as 'insulin sensitisers'. These ligand-activated transcription factors belonging to the peroxisome proliferators-activated receptor (PPAR) family share a common mode of action that involves heterodimerization with the nuclear receptor RXR and subsequent binding to specific DNA-response elements in the promoter of target genes. Binding of ligands to PPARs leads to recruitment of coactivators and chromatin remodeling, resulting in initiation of DNA transcription (Bocher et al., 2002; Smith et al., 1997). Therefore, synthetic PPAR agonists (e.g., Thiazolidines) are widely used for the treatment of insulin resistance and dyslipidemia. O,kBut, as a result of reports of severe idiosyncratic hepatotoxicity, thiazolidinediones have been withdrawn from the US, European, and Japanese markets in 2000.

The effect of green tea extract on hepatic enzymes has been studied in this case because both alanine amino transferase (ALT) and gamma glutamyl transferase (GGT) have been shown to be associated with hepatic pathology and the development of diabetes independent of direct measures of insulin sensitivity and secretion (Vozarova et al., 2002; Hanley et al., 2004). Several possible mechanisms have been proposed to explain how hepatic enzymes increase the risk of the metabolic syndrome and diabetes.

One possible explanation is that GGT and ALT levels even within the normal range correlates with increasing hepatic fat (Tiikkainen et al., 2003). It has been suggested that the elevation of hepatic enzymes could be an expression of excess deposition of fat in the liver as exemplified by nonalcoholic fatty liver, which is closely related to obesity and visceral fat deposition and now regarded as a feature of the insulin resistance syndrome (Marchesini et al., 2001).

The increased expression of ALT in the green tea consumed diabetic patients could be explained in the following way. Epigallocatechin-3-Gallate, the active component of green tea, could not be ligand for PPAR-gamma like the oral hypoglycemic drugs. So inactivation of PPAR-gamma might induce accumulation of TG in hepatocytes and thereby increase ALT in plasma.

It has been observed in this study that plasma cholesterol slightly increased in subjects consumed green tea extract rather than hypoglycemic drugs. This phenomenon has been supported by (Mochizuki et al., 2004) who demonstrated that if the positive isomer of eppigallocathechin-3-gallate predominantly presents in the green tea it might increase serum cholesterol slightly. But there is a scientific evidence regarding the green tea intake levels that, plasma cholesterol apparently decreases only when green tea intake is >0.5% of the diet (Yokozawa et.al., 1999). It's true that the level of consumption of tea could not be optimized to that desired quantity in this study. However chronic dose response study remains to be carried out in future.

Conclusion

In conclusion, in this study the author could not verify the method of processing and also the chemical constituents of green tea produced by Finlay Tea Company in Bangladesh. With the observed result the author at present can not recommend Finlay green tea of Bangladesh for the diabetic people as a substitute of oral hypoglycemic agents. But studies with other green teas or chronic dose response studies remain to be carried out to test their possibility as substitutes of oral hypoglycemic agents.

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