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Full Length Research Paper

Chronic administration of psidium guajava tea lowers free fatty acid levels in the metabolic syndrome

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Abstract

According to WHO statistics, the epidemic of type 2 diabetes mellitus is unrelenting, especially in the developing economies and the worldwide prevalence of diabetes is projected to increase dramatically by 2025. The objective of the study was to compare the effect of guava leaf tea and *ad libitum* fat intake on non-esterified fatty acid, triglyceride and glucose levels in volunteers with the metabolic syndrome. 3 groups of patients were on high-fat diet, low- fat diet and guava leaf tea and 3 parameters of the metabolic syndrome determined for nine months. While high-fat diet increased non-esterified fatty acid and triglyceride levels after nine months, guava leaf tea and low fat-diet decreased non-esterified fatty acid and triglyceride levels significantly (P < 0.05) with the Duncan Multiple Range showing the guava leaf tea effect as more significant. In conclusion, guava leaf tea offers significant benefits in attenuating some risk factors associated with the metabolic syndrome in humans.

Keywords: Guava leaf tea, Low-fat diet, High-fat diet, Free fatty acids, Glucose homeostasis.

INTRODUCTION

Glucose homeostasis is the process of maintaining blood glucose at a steady state within narrow limits (DeFronzo, 1988; Szablewski, 2011) and impaired fasting plasma glucose is associated with increased incidence of type 2 diabetes mellitus and cardiovascular events (Yeboah et al, 2011).

Chronically elevated non-esterified fatty acid or free fatty acid levels has several detrimental effects on glucose homeostasis (Ruderman et al, 1969; Hsu et al, 2010).

Free fatty acids have emerged as a major link between obesity and insulin resistance (Boden, 2002). Free fatty acids interfere with insulin signaling via protein kinase C-induced serine phosphorylation of insulin receptor substrate-I in the liver and also interfere with insulin suppression of glycogenolysis. Moreover, free fatty acids, at elevated glucose concentration, are now known to be associated with increased production of the more toxic isoforms of ceramide (Galadari et al, 2013), a cause of pancreatic beta-cell toxicity and insulin resistance. Aging per se increases the susceptibility to free fatty acid-induced insulin resistance (Einstein et al, 2010) and older men recruit fatty acids from adipose tissue in excess of the energy needs of respiring tissue (Toth et al, 1996). This may explain the increased susceptibility to obesity-related insulin resistance with age (Catalano et al, 2010).

Free fatty acids from stored triglycerides (Jensen, 2006; Triplitt, 2011) and diet-derived chylomicrons (ClinicalTrials.gov identifier NCT00911482) raise cardiometabolic risk. They may increase vascular tone and blood pressure by increasing sympathetic drive and vascular α1-adrenergic receptor reactivity while impairing endothelium-dependent vasodilation (Egan et al, 1996).

Non-fasting triglyceride is also noted to be strongly correlated with atherogenic cholesterol-rich remnant lipoprotein particles and a predictor of incident cardiovascular disease (Miller et al, 2011). Subjects who start with a normal glucose tolerance and later develop type 2 diabetes have increased triglyceride levels before the onset of type 2 diabetes (Haffner, 2003).

Consistent with the above, decrease in body fat mass and calorie restriction attenuate free fatty acid levels and that may provide anti-ageing effects (Bergamini et al, 2003; 2004) for a decrease in free fatty acids decreases insulin signaling leading to an increase in autophagy and lysosomal proteolysis, the anti-ageing cell repair mechanisms.

Also, lowering free fatty acid levels reduces insulin resistance in obese non-diabetic individuals (Boden, 2008). Therapeutic applications of this knowledge is hampered by the lack of cheap readily accessible methods to measure free fatty acid levels and by the present lack of safe medications to lower plasma free fatty acid levels (Boden, 2011).

Dietary patterns (Maghsoudi and Azadbakht, 2012) that may induce weight loss (Salas-Salvado et al, 2011) have a role in prevention, progression or management of diabetes mellitus. Epidemiologic and interventional studies suggest that weight loss is the main driving force to reduce diabetes risk (Salas-Salvado et al, 2011; Hanxman et al, 2006). Lower percent of calories from fat and increased physical activity predict weight loss.

The guava tree (Psidium guajava linn.) is a member of the myrtaceae family which may be found in tropical and subtropical countries (Uboh et al, 2013; Belemtougri et al, 2006). Leaves of the guava tree have been used as food and as folk medicine with anti-inflammatory, anti-hypertensive and anti-diabetic properties. It has been reported that oral administration of guava leaf extract had anti-obesity effects, reducing body weight gain, adipogenesis and improving insulin resistance (Yoshitomi et al, 2012) with no exhibition of acute or chronic toxicity (Deguchi and Miyazaki, 2010). The main constituents of guava leaves are phenolic compounds, isoflavonoids, gallic acid, catechin, epicathechin, rutin, naringenin and kaemferol. The pulp is rich in ascorbic acid and carotenoids (Barbalho et al, 2012). Rutin may decrease triglyceride accumulation in adipocytes while catechin and the terpenoids, betulinic acid and lupeol may aid in prevention of type 2 diabetes mellitus. Pentacyclic triterpenoids that may be found in guava leaf tea possess insulin-mimetic and insulin sensitizing activities (Jung et al, 2007).

The aim of the study was to examine the differential effect of *ad libitum* low- and high- fat diets (Astrup et al, 2000) versus guava leaf tea intake on glucose, triglyceride and non-esterified fatty acid (free fatty acid) levels in patients with the metabolic syndrome. Various diets, such as the Dietary Approaches to Stop Hypertension (DASH) and Prudent diets, are advanced for the prevention of diabetes mellitus and hypertension (Hinderliter et al, 2011; Mozaffarian et al, 2011; Stephen, 2009; Villegas et al, 2004). Their evolution is rational due to the lack of suppression of circulating free fatty acids and hypercholesterolaemia during weight loss on a high-fat, low carbohydrate diet (Hernandez et al, 2010).

MATERIALS AND METHODS

3 groups of adult patients, aged between 55-65 years, of either sex voluntarily participated in the study after approval by the ethical committees of the Faculty of Clinical Science, AAU and of Oseghale Memorial Medical Centre, Ekpoma. The Psidium guajava was confirmed by the department of botany, Ambrose Alli University, Ekpoma.

Patients with severe hypertension, stroke, severe liver or kidney disease, smokers and drug addicts were excluded from the study.

They had impaired fasting glucose initially with fasting blood glucose above 100 mg/dl (American Diabetic Association, 2003)

Estimations of fasting glucose (Automatic kit), triglycerides (Automatic kit) and non-esterified fatty acids (Wako NEFA diagnostic kit) were done at 1, 4 and 9 months by GSP Laboratories, Ekpoma. Specimens for fatty acid determinations were taken to the Laboratory frozen to minimise effect of plasma lipase.

Patients on guava leaf tea took the tea twice a day boiling about 40 grams of guava leaves in 100ml of water for 10 minutes till tea is brown. Patients had demonstrations on method of preparation before they were followed-up with oral interviews two-weekly. Effect of the diets on appetite was also noted.

Ad libitum low-fat diet is the modified DASH dietary pattern which eliminates poultry and fried foods restricting fat intake to about 40-60 grams/day (Stephen, 2009; Personal Communication, 2008)

Statistical analysis was by Matt-Whitney non-parametric test and ANOVA and differences between means were considered significant at $P < 0.05$. Duncan Multiple Range was used as *post-hoc* test.

RESULTS

Table 1 show that guava leaf tea decreases glucose, triglyceride and free fatty acid level in blood significantly at 9 months ($P < 0.05$); more significantly than *ad libitum* low-fat diet using Duncan Multiple Range as *post-hoc* test (Table 2). While Table 3 show that high-fat diet increases glucose, triglyceride and free fatty acid levels in blood significantly at 9 months ($P < 0.05$). Patients on guava leaf tea also reported appetite decrease more than those on low-fat diet.

Table 1. Effect of chronic administration of guava leaf tea on glucose, triglycerides and non-esterified fatty acid levels in blood

Month	0	1	4	9	% decrease
Glucose	101.00**±2.70**	90.40**±3.00**	86.00**±2.90**	84.00**±4.00**	16.80
Triglycerides	121.00**±5.00**	98.00**±4.00**	96.90**±6.00**	95.70**±2.07**	13.00
Free fatty acid	14.70**±3.29**	14.00**±2.50**	13.50**±5.60**	12.10**±2.91**	8.16

Guava leaf tea decreased glucose, triglyceride and free fatty acid level in blood significantly at 9 months (P<0.05) compared to levels at presentation.

Table 2. Effect of low-fat diet on blood glucose, triglycerides and non-esterified fatty acid levels in blood

Month	0	1	4	9	% decrease
Glucose	100.40±3.10	90.60±3.22	90.00±2.64	89.00±3.11	11.00
Triglycerides	120.00±2.50	115.10±6.40	114.50±2.80	114.00±2.44	5.00
Free fatty acid	14.60±4.05	14.50±2.23	14.50±5.00	13.50±2.00	7.50

Low-fat diet decreased glucose, triglyceride and free fatty acid levels in blood significantly at 9 months (P<0.05) compared to levels at presentation.

Table 3. Effect of high-fat diet on glucose, triglycerides and non-esterified fatty acid levels in blood at 9 months.

Month	0	1	4	9	%increase
Glucose	103.00±2.00	104.60±1.90	110.50±6.02	115.00±2.54	11.50
Triglycerides	120.50±2.70	121.00±2.00	134.00±2.32	135.30±4.50	12.70
Free fatty acid	24.10±5.06	30.70±3.19	45.30±4.45	45.10±3.10	89.50

High-fat diet increased glucose, triglyceride and free fatty acid levels in blood significantly at 9 months (P<0.05) compared to levels at presentation.

DISCUSSION

Previous workers (Sanda et al, 2011; Chen et al, 2010; Mukhtar et al, 2004) have noted the beneficial effect of guava leaf extract on parameters of the insulin resistance syndrome due to its phytochemicals such as polyphenols, meroterpenoids and pentacyclic triterpenoids. Beta-sitosterol glycosides and brahmic acid from guava leaves decrease blood glucose (Peng et al, 2008), total cholesterol and triglycerides (Uboh et al, 2013).

Guava leaf extract may activate AMP-activated protein kinase (AMPK) to increase fat oxidation (Yoshitomi et al, 2012), decrease hepatic gluconeogenesis and increase transport of glucose into muscle. And because of the folkloric use of guava leaf, it may also activate beta-endorphins and inhibit histone deacetylase IIa for its hypoglycaemic effects. Deguchi and Miyazaki (2010) reported also that guava leaf extract is capable of inhibiting alpha-glucosidase enzymes such as alpha-amylase, maltase and sucrase and this may contribute to the results observed.

Present study is in agreement with the previous reports on the hypoglycaemic and hypolipidaemic effects of guava leaf and is the first to compare guava leaf use to dietary measures on some parameters of the metabolic or insulin resistance syndrome.

Present study adds that guava leaf tea is more significant in reversing impaired glucose homeostasis and progression of impaired fasting glucose than *ad-libitum* low-fat diet. The greater effect of guava leaf tea in decreasing free fatty acid levels may mean that it may increase insulin sensitivity more than *ad libitum* low-fat diet (Salgin et al, 2012). Ursolic acid found in guava leaf decreases free fatty acids, tumor necrosis factor-α and increases expression of peroxisome proliferator-activated receptor α (Wang et al, 2012(B).

Study also supports previous reports (Lichtenstein et al, 2000; Winzell and Ahren, 2004; van den Brom et al, 2012) that high-fat is detrimental to glucose homeostasis and it also caused relative increase in free fatty acid levels in this study. Diets higher in saturated fat have been noted to be associated with poor glycaemic control (Delahanty et al, 2009). High-fat diet may be associated with insulin resistance by up-regulating the synthesis of ceramides (Shah et al, 2008), inflammatory cytokines and transcription factors such as nuclear factor-κB (Wang, 2012; Yerneni et al, 1999) and protein kinase C (Gutterman, 2002) which can be suppressed by the pentacyclic triterpenoids, ursolic acid and oleanolic acid found in guava leaf and other medicinal plants (Wang et al, 2012(B); Takada et al, 2010; www.pharmatutor.org).

In conclusion, guava leaf tea lowers glucose, triglyceride and free fatty acid levels in the metabolic or insulin resistance syndrome comparable to low-fat diet and deserves further exploration.

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