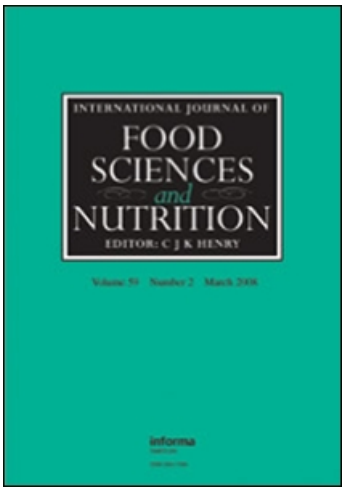

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Effects of kiwifruit consumption on serum lipid profiles and antioxidative status in hyperlipidemic subjects

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Abstract
Cardiovascular disease (CVD) is the most important adult health problem in the world. Epidemiological studies and laboratory experiments have shown that fruit and vegetable consumption has protective effects against CVD. The purpose of the study was to investigate the effects of consumption of two kiwifruit per day on the lipid profile, antioxidants and markers of lipid peroxidation in hyperlipidemic adult men and women in Taiwan. Forty-three subjects who had hyperlipidemia, including 13 males and 30 females, participated in this study. They were asked to consume two kiwifruit per day for 8 weeks. Anthropometric measurements were made. Before the intervention and at 4 and 8 weeks of the intervention, fasting blood samples were analyzed for total cholesterol, triacylglycerol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein cholesterol (HDL-C). Additionally vitamin E and vitamin C, the malondialdehyde + 4-hydroxy-2(E)-nonenal concentration, and the lag time of LDL oxidation were determined. No significant differences from baseline to 8 weeks of the intervention were detected for triacylglycerol, total cholesterol, or LDL cholesterol. However, after 8 weeks of consumption of kiwifruit, the HDL-C concentration was significantly increased and the LDL cholesterol/HDL-C ratio and total cholesterol/HDL-C ratio were significantly decreased. Vitamin C and vitamin E also increased significantly. In addition, the lag time of LDL oxidation and malondialdehyde +4-hydroxy-2(E)-nonenal had significantly changed at 4 and 8 weeks during the kiwifruit intervention. Regular consumption of kiwifruit might exert beneficial effects on the antioxidative status and the risk factors for CVD in hyperlipidemic subjects.

Keywords: *Kiwifruit intervention, blood lipid profiles, antioxidative status, risk factors, cardiovascular disease*

Introduction

Cardiovascular disease (CVD) is the most important adult health problem in wealthy countries and its related diseases have been among the top 10 causes of death by disease in Taiwan for many years. Diet, tobacco smoking, physical inactivity, family history, age (>45 years for men and >55 years for women), obesity, lipid profiles, hypertension and diabetes mellitus contribute to their wide diffusion (FAO/WHO Expert Consultation 1990; Department of Health 2005). Epidemiological, clinical, and biochemical studies have convincingly indicated that increased serum lipid concentrations, including triacylglycerol (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) concentrations, low-density and high-density

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lipoprotein cholesterol (LDL-C/HDL-C) and TC/HDL-C ratios, and low-density lipoprotein (LDL) oxidation are risk factors contributing to the development of CVD and atherosclerosis (Smith et al. 1992; Egger et al. 1999; Rywik et al. 1999). Oxidative damage and the production of free radicals in the endothelium are two of the factors involved in the pathogenesis of the atherosclerotic process that causes CVD (Schachinger and Zeiher 2000; Jarasuniene and Simaitis 2003).

Epidemiologic studies have shown an inverse association between fruit and vegetable intake and risks of CVD morbidity and mortality (Gaziano et al. 1995; Joshipura et al. 1999). Several individual nutrients, including potassium, antioxidative vitamins, and phytochemicals—which are abundant in fruits and vegetables—may contribute to the inverse association of the intake of these foods with the risks of stroke and mortality from CVD (Knekt et al. 1994; Tribble 1999; American Heart Association 2000). Kiwifruit contain very significant amounts of vitamin C, vitamin E, folic acid, and various phytochemicals, such as anthocyanidins and flavonols (Wills et al. 1986; Ferguson and Ferguson 2003). The present study was designed to evaluate the effect of consumption of two kiwifruit per day for 8 weeks on the lipid profile, antioxidant concentration, and the markers of lipid peroxidation in hyperlipidemic adult men and women in Taiwan.

Subjects and methods

Subjects

Forty-three subjects between the ages of 20 and 65 years were recruited for the study, including 13 males and 30 females. Subjects who had at least one of the following criteria were selected for the study: TG $\geq$160 mg/dl (1.8 mmol/l), TC $\geq$200 mg/dl (5.2 mmol/l), LDL-C $>$130 mg/dl (3.3 mmol/l), and HDL-C $<$40 mg/dl (1.0 mmol/l). All subjects acted as their own controls and were asked to maintain their usual dietary patterns and physical activity, and to refrain from taking any drugs that affect lipid metabolism, vitamin/mineral supplements, or commercial health foods during the study period. The study was approved by the Medical Ethical Committee of Taipei Medical University, and all participants gave informed written consent.

Experimental design

This study utilized a free-living, self-controlled diet design. Every subject participated in the complete 10-week study period, including a 2-week dietary stabilization period and an 8-week kiwifruit intervention period. During the kiwifruit intervention phase, each subject consumed two kiwifruit (100 g each) per day after lunch and/or dinner for 8 weeks. The kiwifruit (Chinese gooseberries) were of the green, 'Hayward' variety and were supplied at an optimum ripeness for consumption.

Anthropometric measurements

Body weight, height, and waist and hip circumferences were measured according to standard protocols before and after the kiwifruit intervention. Waist and hip circumferences were measured as the distance around the smallest area of your waist, usually just above the belly button, and the distance around the largest area of your hips, usually the widest part of the buttocks. Body fat was measured using a

Biodynamics Body Composition Analyzer (Biodynamics, Seattle, WA, USA) according to the principle of biochemical impedance analysis.

Blood collection

Overnight fasting blood samples were collected before breakfast at the start (as baseline values) and at weeks 4 and 8 of each 4-week intervention phase. Within 30 min of collection, the plasma was separated by centrifugation at 1,500 $\times g$ for 10 min at 4°C. Plasma was then aliquoted and stored immediately at −80°C and processed for serum lipid analyses (TC, TG, LDL-C, and HDL-C), plasma vitamin E and vitamin C, malondialdehyde+4-hydroxy-2(E)-nonenal (MDA+4-HNE) concentration, and LDL oxidation.

Biochemical measurements

Serum TC, TG, LDL-C, and HDL-C were measured using automated enzymatic methods (CHOD-PAP and GPO-PAP; RANDOX, Antrim, UK).

Both plasma vitamin C (Rose and Nahrwold 1981) and vitamin E (Hatam and Kayden 1979) were analyzed using reversed-phase high-performance liquid chromatography with an ultraviolet detector at 254 and 292 nm. A 4 × 250 mm and a 4 × 125 mm Lichrosphere 100RP-18 column (Merck, Darmstadt, Germany), containing 5 mm particles protected by a guard column, were respectively used for the vitamin C and vitamin E analyses. The mobile phase for vitamin C contained 0.5 mM PICB (1-pentane sulfuric acid sodium salt) adjusted to pH 3.1 with glacial acetic acid. Pure methanol was used as the mobile phase for the vitamin E analysis.

The lipid peroxides (MDA and 4-HNE) in plasma were determined using commercial kits (Merck; Calibiochem, San Diego, CA, USA) and measured by mixing 200 µl plasma with 650 µl *N*-methyl-2-phenylindole and 150 µl methansulfonic acid, incubating for 60 min at 45°C and reading the absorbance at 586 nm.

LDL was isolated using a rapid two-step density-gradient ultracentrifugation (Kleinveld et al. 1992). Plasma (0.4 ml) was adjusted to a density of 1.006 g/ml KBr solution in a polycarbonate centrifuge tube. The tubes were centrifuged in a Beckman Optima TLX ultracentrifuge (Beckman Instruments, Palo Alto, CA, USA) with a TLA-100.2 rotor at 80,000 rpm for 4 h at 4°C. After ultracentrifugation the LDL-containing fraction (0.4 ml) was collected into the orange-colored band of the tube. Further purification was added at a density of 1.1485 g/ml KBr solution on top of the LDL-containing fraction and was centrifuged at 80,000 rpm for 4 h at 4°C. The LDL-containing top layer was aspirated and dialyzed in the dark overnight at 4°C against 4 l phosphate-buffered saline. Protein content was measured by the method of Lowry et al (1951). It involves the addition of an acidic dye to protein solution, and subsequent measurement at 595 nm with a spectrophotometer. The bovine serum albumin was used as standard.

The oxidation of LDL was initiated by adding a freshly prepared $CuCl_2$ solution (*in vitro* Cu^{2+}-catalyzed oxidation) and kinetics of LDL oxidation were measured by monitoring the formation of conjugated dienes at 234 nm with a U 3000 spectrophotometer (Hitachi, Tokyo, Japan) at 2-min intervals at 37°C (Esterbauer et al. 1989). The time-course shows three consecutive phases: a lag-phase during which the

diene absorption increases only weakly, a propagation phase with a rapid increase of the diene absorption, and finally a decomposition phase. The lag time of lipid peroxidation is defined as the time interval between the initiation and the intercept of the two tangents drawn to the lag and propagation phase of the absorbance curve at 234 nm, and it was expressed in minutes.

Statistical analysis

All values are expressed as the mean ± standard deviation. Data were analyzed using SAS for WINDOWS software (version 8.2; SAS Institute Inc, Cary, NC, USA). The consumption effect was assessed by comparing the changes between groups using a paired *t*-test. $P < 0.05$ was considered statistically significant.

Results

Characteristics of subjects

All subjects tolerated the intervention well and completed the study. The demographic characteristics of 39 subjects (11 males and 28 females) who returned complete sets of data are presented in Table I. One-half of the subjects were overweight (body mass index > 24 kg/m^2). There was no significant change in body mass index or waist/hip ratio over the study period. After the intervention, however, there was a significant increase in body fat in men.

Effects of kiwifruit intervention on blood lipid profiles

More than three-quarters of subjects ($n = 43$) had hypercholesterolemia (total cholesterol > 5.2 mmol/l). None of the subjects who consumed kiwifruit for 8 weeks exhibited a significant change in the mean of the serum TG, TC, or LDL-C. However, the HDL-C concentration increased significantly and the LDL-C/HDL-C ratio and TC/HDL-C ratio decreased significantly after 8 weeks of consumption of kiwifruit (Table II).

Table I. Characteristics of all subjects.

Characteristic	Men ($n = 11$)		Women ($n = 28$)	
	Before intervention	After Intervention	Before intervention	After intervention
Age (years)	44.6 ± 13.3	44.6 ± 13.3	43.0 ± 11.2	43.0 ± 11.2
Height (cm)	172 ± 6.5	172 ± 6.5	159 ± 6.4	159 ± 6.4
Body weight (kg)	77.7 ± 14.8	78.4 ± 15.8	60.4 ± 9.5	60.1 ± 9.9
Body mass index (kg/m^2)	26.0 ± 3.8	26.2 ± 4.1	23.6 ± 3.1	23.5 ± 3.1
Body fat (kg)	25.8 ± 5.9	29.8 ± 6.4*	31.8 ± 7.3	32.5 ± 7
Waist (cm)	91.6 ± 7.2	90.3 ± 9.0	77.5 ± 9.3	78 ± 9.3
Hip (cm)	102 ± 5.8	101 ± 7.7	95.8 ± 6.3	95.2 ± 6.4
Waist/hip ratio	0.90 ± 0.04	0.89 ± 0.05	0.81 ± 0.06	0.82 ± 0.07

Data expressed as the mean ± standard deviation ($n = 39$). *Significantly differs from the value before the intervention by paired *t*-test ($P < 0.05$).

Table II. Concentrations of blood lipid profiles in subjects.

	Before intervention	At 4 weeks of intervention	At 8 weeks of intervention
TG (mmol/l)	1.26±0.82	1.17±0.82	1.15±0.83
TC (mmol/l)	5.64±0.63	5.58±0.84	5.61±0.80
LDL-C (mmol/l)	3.82±0.55	3.71±0.79	3.74±0.60
HDL-C (mmol/l)	1.40±0.39	1.39±0.41	1.54±0.44*
LDL-C/HDL-C ratio	2.87±0.78	2.80±0.76	2.56±0.72*
TC/HDL-C ratio	4.23±0.96	4.22±1.07	3.80±0.90*

Data expressed as the mean±standard deviation ($n=43$). *Significantly differs from the value before the intervention by paired t-test ($P<0.05$).

Effects of kiwifruit intervention on blood antioxidants and the markers of lipid peroxidation

Table III presents changes in the antioxidative status during the study. Antioxidants were determined by vitamin C and vitamin E, and lipid peroxidation was determined by the 'lag time' during LDL oxidation and the end products MDA+4-HNE. After 4 weeks of kiwifruit consumption, there was significantly higher plasma concentration of vitamin C (50.2 μmol/l versus 59.2 μmol/l). The plasma vitamin E concentration was significantly increased after 8 weeks of kiwifruit consumption (43.6 μmol/l versus 63.5 μmol/l). Similar to vitamin C, the LDL lag time (46 min versus 55 min) and MDA+4-HNE (12.4 μM versus 5.76 μM) concentrations also significantly increased and decreased, respectively, after 4 and 8 weeks of the intervention.

Discussion

Our data indicated that consumption of two kiwifruit per day for 8 weeks by hypercholesterolemic subjects appeared to reduce some indices of blood lipid profiles and was associated with diminished LDL-C/HDL-C and TC/HDL-C ratios. An increased antioxidative status was also associated with raised antioxidant plasma concentrations and reduction of lipid peroxidation. While measurement of serum lipid profiles is a recommended part of cardiovascular risk detection, the effects of kiwifruit on predictive value of specific lipid markers remains controversial. Duttaroy and Jorgensen (2004) showed that consuming two or three kiwifruit per day for 28 days in 30 healthy subjects only reduced the blood TG concentration by 15% ($P<0.05$). However, Rush et al. (2006) found that consuming a daily dose of kiwifruit for 3 weeks in 12 healthy subjects (one kiwifruit for every 30 kg body weight) showed no significant effects on plasma lipids. Kinosian et al. (1994, 1995) and Natarajan et al. (2003) reported that changes in ratios of LDL-C/HDL-C and TC/HDL-C ratios are better predictors of CVD risk reduction than changes in absolute concentrations.

Table III. Concentrations of antioxidative status in subjects.

	Before intervention	At 4 weeks of intervention	At 8 weeks of intervention
Vitamin C (μmol/l)	50.2±12.9	59.2±21.4*	55.3±17.2
Vitamin E (μmol/l)	43.6±19.3	46.8±23.7	63.5±43.7*
LDL lag time (min)	46.0±8.19	55.2±10.8*	51.5±7.77*
MDA+4-HNE (μM)	17.2±9.51	9.02±6.56*	5.67±4.00*

Data expressed as the mean±standard deviation ($n=43$). *Significantly differs from the value before the intervention by paired t-test ($P<0.05$).

According to our study, we suggest that the consumption of kiwifruit could have cardiovascular protective properties by increasing the HDL-C concentration and lowering the LDL-C/HDL-C and TC/HDL-C ratios in hypercholesterolemic subjects.

Kiwifruit provides 100 mg vitamin C, 2.2 mg vitamin E, 3.44 g dietary fiber and 4.56 mg polyphenols per 100 g (Royal Society of Chemistry, UK). The possible roles of kiwifruit on blood lipids and their ratios in the development of atherosclerosis and CVD risk: (a) the inhibitory activity of kiwifruit extracts on HMG-CoA reductase, which is the first enzyme of the metabolic pathway that produces cholesterol (Jung et al. 2005); (b) the mild laxative effects, possibly because of the high level of dietary fiber, which increased the total fecal cholesterol excretion (Rush et al. 2002); and (c) against oxidative damage by increasing the intake of antioxidant vitamins (β-carotene, vitamin C, and vitamin E) (Brown and Goodman 1998).

Epidemiological studies and laboratory experiments have shown that fruit and vegetable consumption has protective effects against CVD (Liu et al. 2000; Bazzano et al. 2002). This may in part be attributed to antioxidant vitamins and specific polyphenols that display powerful inhibition of oxidative stress. Wang et al. (1996) used the automated oxygen radical absorbance capacity assay and rated the antioxidant activities of commonly consumed fruits in the order plum > kiwifruit > apple > pear, and Collins et al. (2001) demonstrated significant antioxidant activity of kiwifruit *in vitro*. While the oxidation of LDL has been proposed as an important step in the formation of atherosclerotic lesions, many studies have reported that LDL oxidation was reduced in healthy volunteers after consuming polyphenol-rich fruits, foods, or beverages (Fuhrman et al. 1995; Day et al. 1997; Young et al. 1999; Hirano et al. 2000; Hodgson et al. 2000). Polyphenols, which are commonly found in fruits and vegetables, contain one or more aromatic hydroxyl groups that may act as antioxidants and reduce the exhaustion of vitamin C in plasma (Rice-Evans et al. 1996). However, the polyphenol compounds in kiwifruit require further identification. In our human intervention study, kiwifruit consumption provided a significant 'antioxidant capacity' as measured by the changes in the antioxidant status and lipid peroxidation.

In addition, vitamin C is suggested to play a part in reducing oxidative stress and protection of lipid membranes that might inhibit atherosclerotic lesions (Ness et al. 1996). Previous studies showed that vitamin C might improve the HDL-C concentration (Jacques 1992) and acted as a regulator for catabolism of cholesterol to bile acid (Simon 1992). A large prospective study in England indicated that a 20 μmol/l (equivalent to 3.5 mg/l) increase in plasma ascorbic acid could reduce the risk of cardiovascular death by 20%, with or without adjustment for other risk factors (Khaw et al. 2001). We therefore propose that the protective antioxidant effect of kiwifruit may be mediated by neutralizing certain free radicals or preventing LDL oxidation due to their high content of antioxidant vitamins and specific polyphenol compounds.

The main limitation of the present study is lack of placebo control, suggesting that it is probable that different results would have been obtained and we are unable to prove that the observed outcomes completely resulted from kiwifruit. However, epidemiological studies as well as laboratory experiments have provided very strong evidence that fruits and vegetables are beneficial for human health. Understanding that there is no easy manner to provide a placebo control (another fruit?), using the design of this study, how much does this lack of a placebo control influence the study results? Therefore, the consumption of kiwifruit could also be responsible for the protective effects on the risk factors of CVD in hypercholesterolemic subjects.

Conclusions

The present study demonstrated that consumption of two kiwifruit per day for 8 weeks can modulate the risk factors of CVD, antioxidants, and markers of lipid peroxidation by reducing the LDL-C/HDL-C and TC/HDL-C ratios, LDL oxidation, and MDA+4-HNE concentration and increasing the vitamin C and vitamin E concentrations. The results suggest that long-term consumption of kiwifruit might have some cardiovascular protective properties and beneficial effects on atherosclerosis, CVD risks and the antioxidative status in hypercholesterolemic subjects.

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