Original Article

Effect of High Fat Diet Without Cholesterol Supplementation on Oxidative Stress and Lipid Peroxidation in New Zealand White Rabbits

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Aim: Dietary fats may affect coronary artery disease risk by influencing factors other than serum cholesterol. The effect of diets containing coconut oil and sunflower oil without cholesterol supplementation on oxidative stress and lipid peroxidation was studied in male New Zealand White rabbits.
Methods: Animals assigned to four groups (control, cholesterol-fed, coconut oil-fed and sunflower oil-fed), given an isocaloric diet and studied for 6 months. The lipid profile, reduced glutathione, glutathione peroxidase, superoxide dismutase, vitamin C and lipid peroxidation were evaluated at the beginning of the study, at the third month and at the end of the study period.
Results: Serum lipid values did not show significant variation between animals fed coconut oil and sunflower oil, but total cholesterol, triglycerides and LDL-cholesterol were significantly higher and HDL-cholesterol was reduced in cholesterol-fed animals. Lipid peroxidation was higher in cholesterol-fed and sunflower oil-fed rabbits compared to controls and coconut oil-fed rabbits. Though other parameters such as reduced glutathione, glutathione peroxidase, superoxide dismutase and ascorbate did not vary between the two oil-fed rabbit groups, cholesterol-fed rabbits showed severe oxidative stress.
Conclusion: We conclude that in the absence of cholesterol supplementation, coconut oil intake up to 30% of daily energy supply did not cause hypercholesterolemia or oxidative stress in rabbits.

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Key words; Coronary artery disease, Reduced glutathione, Glutathione peroxidase, Superoxide dismutase, Ascorbate, New Zealand White rabbits

Introduction

Coconut oil is considered hypercholesterolemic and is believed to increase coronary artery disease (CAD) risk due to its high saturated fat content. A major proportion of the saturated fats of coconut oil are formed of medium chain fatty acids, which do not require a re-esterification process and are oxidized immediately for energy needs in the liver[1]. Due to this specific characteristic of medium chain fatty acids, it has also been reported that coconut oil cannot be considered hypercholesterolemic[2].

The incidence of CAD is high in Kerala (South West India), 7% among rural and 12% among urban populations[3]. A vast majority of the Kerala population uses coconut oil as the principal cooking medium. Though the conventional risk factors for CAD, such as diabetes, hypertension etc., are also high among this population, there has been a general belief among the population that the consumption of coconut oil, rich in saturated fat, is a major contributor to the rise in the incidence of CAD in this region. Based on dietary recommendations for the prevention of cardiovascular events, a considerable proportion of subjects in Kerala have replaced saturated fat in their diet with polyunsaturated fat. This has been achieved primarily by replacing coconut oil with sunflower oil as the cooking medium. We studied the effects of these two cook-

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ing oils on risk factors for coronary artery disease, such as oxidative stress and lipid peroxidation in rabbits.

Most previous experiments conducted in animals to study the effect of dietary fats on serum cholesterol and atheroma formation have supplemented the diet with cholesterol, and the results obtained are not uniform[4-7]. Various investigators have studied the effect of different dietary fats on lipid peroxidation in animals[8, 9], though their effect on antioxidant parameters has not been fully elucidated.

Aim: In this study, we compared the effect of two different dietary fats, coconut oil and sunflower oil, without cholesterol supplementation on antioxidant parameters and lipid peroxidation in rabbits.

Materials and Methods

Experimental Design

The Institutional Animal Ethics Committee approved the protocol for this study. Male New Zealand White rabbits, 3–4 months of age (procured from Lab Animal Breeding Station, Veterinary College, Mannuthy, Kerala), were divided into 4 groups and housed in individual cages. Animals in all groups were given isocaloric, standard rabbit feed (Gold Mohur rabbit feed), with fat content providing <5% of calories. Water was provided ad libitum. Group 1 with 6 animals was given standard rabbit diet and maintained as the control group. Group 2 had 5 rabbit, and was given standard diet and 0.5 g cholesterol/day to induce hypercholesterolemia. Groups 3 and 4 had 5 rabbits each and were given standard diet mixed with coconut oil and sunflower oil, respectively, to derive 30% of their total calories from the respective oil. The weight of the animals was recorded every month and the study was conducted for a period of 6 months.

Biochemical Analyses

Blood was drawn from the marginal ear vein after an overnight fast at the beginning of the study, after 3 months and at the end of the study period for various biochemical analyses. Total cholesterol, triglycerides and HDL-cholesterol were determined enzymatically in serum using kits from Accurex. LDL-cholesterol was calculated from Friedwald's equation[10]. Reduced glutathione (GSH) was estimated in erythrocytes by the method of Beutler *et al.*[11]. Glutathione peroxidase activity (GSH-Px) was estimated in erythrocytes, as described by Paglia and Valentine[12] and as modified by Lawrence and Burk[13]. Superoxide dismutase (SOD) was estimated in serum by the pyrogallol autooxidation assay, as described by Marklund and Marklund[14] and as modified by Nandi and Chatterjee[15]. Ascorbate was estimated in serum by the dinitrophenyl hydrazine assay[16]. Lipid peroxidation indicated by TBARS (thiobarbituric acid reactive substances) was determined in erythrocytes by the method of Jain *et al.*[17]. Hemoglobin was estimated by the cyanomethemoglobin method[18].

Results

Statistical Analysis

Statistical analysis was performed using SPSS software, version 11.0. The Kruskal-Wallis test was used to compare these parameters among the four groups at 0 months, 3 months and 6 months. The Mann-Whitney test was performed to establish groups that varied significantly and a p value of <0.05 was considered significant.

Lipid Profile

Baseline values of the lipid profile did not vary significantly among the four groups. The results of lipid profile analysis at 3 months indicated that group 2 animals had significantly elevated total cholesterol, triglycerides and LDL-cholesterol compared to other groups. The HDL-cholesterol concentration was found to be non-significantly reduced for this group at 3 months (**Table 1**). At 6 months, total cholesterol and LDL-cholesterol concentrations were further elevated among group 2 animals and HDL-cholesterol showed a significant decrease (**Table 1**). Triglyceride levels were significantly elevated for group 2 animals at 6 months compared to other groups, but had not increased considerably compared to 3 months (**Table 1**).

Antioxidant Parameters and Lipid Peroxidation

GSH was significantly reduced for group 2 animals at 3 months and 6 months compared to all groups (**Table 2**). Group 2 animals had reduced GSH-Px activity at 3 and 6 months, though the results did not attain statistical significance (**Table 2**). SOD activity of group 2 animals was significantly reduced at 3 months compared to controls and group 3 animals. At 6 months the SOD activity of these animals showed a significant reduction compared to all groups (**Table 2**). Ascorbate also showed significant reduction among group 2 animals at 3 and 6 months compared to other groups (**Table 2**). The rate of lipid peroxidation was found to be higher for group 2 animals compared to other groups at 3 and 6 months. Group 4 animals had significantly elevated lipid peroxidation at 3 months compared to group 3 animals, and at 6 months the

Table 1. Mean and standard deviation of serum lipid parameters at 0, 3 and 6 months

Parameters	Group 1 (Controls)	Group 2 (Cholesterol)	Group 3 (Coconut oil)	Group 4 (Sunflower oil)
Total cholesterol (mmol/L)				
0 months	1.89 ± 0.16	2.06 ± 0.20	1.92 ± 0.24	1.99 ± 0.35
3 months	1.83 ± 0.16	14.65 ± 0.73*	2.03 ± 0.16	1.92 ± 0.23
6 months	1.89 ± 0.09	17.56 ± 2.81*	1.97 ± 0.30	1.91 ± 0.12
Triglyceride (mmol/L)				
0 months	0.92 ± 0.09	0.80 ± 0.07	0.88 ± 0.06	0.79 ± 0.07
3 months	0.92 ± 0.17	1.28 ± 0.15*	0.93 ± 0.07	0.82 ± 0.07
6 months	0.85 ± 0.06	1.29 ± 0.11*	0.93 ± 0.13	0.79 ± 0.10
HDL-cholesterol (mmol/L)				
0 months	0.71 ± 0.13	0.81 ± 0.12	0.83 ± 0.09	0.78 ± 0.11
3 months	0.81 ± 0.12*	0.73 ± 0.06	0.76 ± 0.06	0.74 ± 0.12
6 months	0.75 ± 0.04	0.56 ± 0.08*	0.82 ± 0.11	0.72 ± 0.05
LDL-cholesterol (mmol/L)				
0 months	0.75 ± 0.32	0.89 ± 0.25	0.68 ± 0.33	0.84 ± 0.47
3 months	0.58 ± 0.22	13.33 ± 0.73*	0.83 ± 0.09	0.80 ± 0.27
6 months	0.74 ± 0.16	16.40 ± 2.76*	0.72 ± 0.26	0.82 ± 0.11

*p value < 0.05 compared to other groups.

Table 2. Mean and standard deviation of antioxidant parameters and lipid peroxidation at 0, 3 and 6 months

Parameters	Group 1 (Controls)	Group 2 (Cholesterol)	Group 3 (Coconut oil)	Group 4 (Sunflower oil)
Reduced glutathione (nmol/gHb)				
0 months	3.2 ± 0.4	3.3 ± 0.3	3.2 ± 0.3	3.3 ± 0.3
3 months	3.3 ± 0.1	2.8 ± 0.3*	3.3 ± 0.1	3.4 ± 0.4
6 months	3 ± 0.4	1.8 ± 0.3*	3.4 ± 0.2	3.2 ± 0.1
Glutathione peroxidase (IU/gHb)				
0 months	11.8 ± 1.9	11.7 ± 1.7	10.9 ± 1.2	11.6 ± 0.8
3 months	10.7 ± 0.7	9.5 ± 1.7	11.3 ± 0.9	11.5 ± 0.9
6 months	11.3 ± 0.9	8.8 ± 1.1	11.5 ± 1.2	10.9 ± 1.8
Superoxide dismutase (IU/mL)				
0 months	3.6 ± 0.4	3.6 ± 0.5	3.5 ± 0.4	3.6 ± 0.4
3 months	3.7 ± 0.4	3 ± 0.4$	3.8 ± 0.3	3.5 ± 0.36
6 months	3.5 ± 0.2	2.7 ± 0.4*	3.5 ± 0.3	3.4 ± 0.2
Vitamin C (μmol/L)				
0 months	15.89 ± 2.27	14.19 ± 1.70	14.76 ± 2.27	14.76 ± 2.27
3 months	15.33 ± 1.70	9.65 ± 2.27*	15.89 ± 1.13	15.33 ± 1.70
6 months	16.46 ± 0.56	8.51 ± 2.83*	16.46 ± 1.70	14.19 ± 1.70
TBARS (nmol/gHb)				
0 months	10.5 ± 1.5	10.8 ± 1.1	11.4 ± 1.5	11.1 ± 1.13
3 months	11.2 ± 1.4	16.4 ± 1.4*	10.2 ± 1.1	13.2 ± 2.4#
6 months	11.6 ± 0.5	18.1 ± 2.4*	11 ± 1.2	15.3 ± 1.2$

*p value < 0.05 compared to other groups, $$ p value < 0.05 compared to groups 1 and 3, # p value < 0.05 compared to group 3

result was significantly higher than in controls and group 3 animals (**Table 2**).

Discussion

Hypercholesterolemia is a major risk factor for CAD and numerous studies have investigated diet-induced hypercholesterolemia in animals. Most experiments in animals to elucidate the effect of dietary fat on serum lipids supplemented their diet with cholesterol, including studies showing that cholesterol supplemented coconut oil raises serum cholesterol compared to most other dietary fats, such as olive oil, rapeseed oil, sunflower oil or soybean oil[4, 19]. Another study has shown that coconut oil raises serum cholesterol and reduces HDL-cholesterol compared to olive oil, corn oil and avocado oil in rabbits[20]. Even though the animals in groups 3 and 4 in this study were consuming a diet high in oil content, they failed to develop dyslipidemia, which may be because their feed lacked cholesterol supplementation. It has been demonstrated in rabbits that replacement of coconut oil with olive oil did not reduce aortic cholesterol concentration and that olive oil did not impart further beneficial effects on atherogenesis although the plasma cholesterol level was reduced[21].

It has been reported that medium chain fatty acids of coconut oil raise triglyceride levels in humans, especially lauric acid, the principal fatty acid of coconut oil[22]. Studies conducted in chicks have shown that feeding coconut oil alone does not cause hypertriglyceridemia, but on supplementation with 1% cholesterol, severe hypertriglyceridemia resulted[23]. In rabbits, elevated triglyceride concentration on feeding coconut oil +0.5% cholesterol compared to olive oil +0.5% cholesterol was found to be due to increased hepatic secretion of VLDL and decreased hepatic clearance of VLDL triglyceride[24]. The results of this study show that diet containing coconut oil without cholesterol does not induce hypertriglyceridemia in rabbits. Previous reports stated that although polyunsaturated fats reduce CAD risk by bringing down total cholesterol levels, they also reduce HDL-cholesterol[25], but the rabbits given sunflower oil in our study did not show a significant reduction in the HDL-cholesterol concentration compared to controls or those provided saturated fat.

It is now well known that atherosclerosis is an inflammatory disease and oxidative stress may induce or aggravate the atherosclerotic process[26]. Antioxidant enzymes, such as SOD, catalase and GSH-Px, as well as vitamins C and E form the principal free radical quenching system in animals. Although studies have shown that dietary fat can cause changes in the antioxidant status, the exact mechanism by which dietary fats modulate the antioxidant status is not known. Oxidative stress is related to biological membrane composition and dietary fatty acids determine several biochemical parameters at the mitochondrial membrane level. A diet rich in polyunsaturated fat would render the membranes more prone to oxidation than saturated or monounsaturated fat[27]. The effect of various dietary fats on antioxidant parameters has not been well investigated in rabbits. Studies in rats have reported that those fed fish oil had elevated lipid peroxidation and reduced vitamin A and E concentrations compared to those fed coconut oil. Although a reduction was noticed in GSH-Px activity among fish oil-fed rats, no variations were observed in SOD activity between these two groups[28]. Similarly, another study in rats proved that a diet rich in polyunsaturated fat caused diminished SOD and catalase activity compared to saturated fat, despite its beneficial effects on serum lipids[29]. Although the parameters we considered to measure oxidative stress did not vary significantly between the two oil groups, a non-significant reduction in vitamin C and GSH-Px activity was observed among sunflower oil-fed rabbits compared to coconut oil-fed rabbits.

The cholesterol-fed animals in this study had significantly reduced SOD activity, vitamin C and GSH indicating that they had developed severe oxidative stress at 3 months in the study, which further aggravated at 6 months. It was shown previously in rabbits that cholesterol feeding reduced GSH-Px and catalase activity in the liver[30]. Investigators reported previously that increased oxidative stress observed after a high cholesterol diet may be the result of increased superoxide production. In addition to a direct toxic effect, superoxide anion can react with nitric oxide to give peroxynitrite radical or hydrogen peroxide[31].

It has been proved that cholesterol feeding would result in increased lipid peroxidation in rabbits[30], and a similar observation was made in this study also. Polyunsaturated fats have been shown to increase the rate of lipid peroxidation compared to saturated fats in Wistar rats[29]. In rabbits, corn oil although effective to lower lipid, was found to increase oxidative stress and induce endothelial damage compared to olive oil or butter[32]. The formation of promutagenic, exocyclic DNA adducts in the liver of rats, which are markers of DNA damage by lipid peroxidation, was found to be highest in sunflower oil-fed rats when compared to coconut oil, olive oil or rapeseed oil[9]. It was found that rats fed coconut oil have low susceptibility to lipid peroxidation compared to those on olive oil or sun-

flower oil diets[8]. Rats given fish oil had elevated lipid peroxidation rates compared to rats given coconut oil[28]. It was reported previously that polyunsaturated fatty acids, due to the presence of double bonds, are more prone to be attacked by free radicals and become oxidized readily. Monounsaturated and saturated fatty acids are more resistant to free-radical attack than polyunsaturated fats[33]. In our study, we found an increased rate of lipid peroxidation among sunflower oil-fed rabbits compared to coconut oil-fed rabbits and this lends support to earlier observations.

Thus, it may be observed from the present study that coconut oil, providing 30% of the total calories, does not induce hypercholesterolemia among New Zealand White rabbits, but offers better antioxidant capacity than sunflower oil as indicated by the lower lipid peroxidation rate among coconut oil-fed rabbits. The effect of dietary fats with cholesterol supplementation on serum cholesterol has been studied in animals, but their effect on antioxidant parameters, such as GSH, GSH-Px and SOD, remains to be investigated.

Conclusions

It may be concluded from this study that ingestion of coconut oil/sunflower oil, providing up to 30% of the total calories, did not cause significant variation in the serum lipids compared to controls. Although other markers of oxidative stress did not vary considerably, sunflower oil increased lipid peroxidation compared to coconut oil. Showing that, despite their lipid-lowering capability, polyunsaturated fats may exacerbate oxidative stress and increase susceptibility to atherosclerosis.

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