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Evidence for an inverse relation between plasma triglyceride and aortic cholesterol in the coconut oil/cholesterol-fed rabbit

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Summary

Rabbits fed a commercial chow diet containing 0.5% cholesterol and 14% coconut oil developed more severe hyperlipidemia and atherosclerosis than rabbits fed the same diet containing olive oil in place of coconut oil. Average plasma cholesterol was twice as high in the coconut oil/cholesterol-fed rabbits than in olive oil/cholesterol-fed rabbits. Final plasma triglycerides, although highly variable, were approx. 20-fold higher than basal plasma triglyceride in coconut oil/cholesterol-fed rabbits; plasma triglyceride in olive oil/cholesterol-fed rabbits remained unchanged throughout the study period. In coconut oil/cholesterol-fed rabbits, a direct relationship between plasma triglyceride and aortic cholesterol was not found. Plasma cholesterol and aortic cholesterol were also not correlated at a statistically significant level ($r = 0.26$, $P > 0.25$). However, when both plasma cholesterol and triglyceride were simultaneously introduced as predictors of aortic cholesterol, the correlation between these plasma lipids and aortic cholesterol became highly significant ($r = 0.64$, $P < 0.02$). Aortic cholesterol increased in proportion to plasma cholesterol concentrations but appeared to be inversely related to plasma triglyceride levels.

Key words: Atherosclerosis; Hypertriglyceridemia; Hypercholesterolemia; Coconut oil; Olive oil; Lipoproteins

Introduction

It is well established that, in the rabbit, addition of cholesterol to the diet, regardless of the type or amount of fat added, produces a marked hypercholesterolemia that subsequently leads to atherosclerosis. It is also known that addition of saturated fat to the diet of a number of species leads to an increase in plasma cholesterol; the mechanism by which this occurs still remains unclear. Less well known is the influence that dietary triglyceride has on plasma triglyceride levels in rabbits, as well as in other species, and how plasma triglyceride may influence the development of atherosclerosis.

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The present study was undertaken to investigate whether plasma triglyceride plays an important role in the atherosclerotic process. Coconut oil in conjunction with cholesterol feeding was used as a model to induce hypertriglyceridemia in rabbits. Previous studies have shown that coconut oil feeding causes moderate hypertriglyceridemia as well as hypercholesterolemia in rabbits and other species fed cholesterol-free, semisynthetic diets [1–4]. A few coconut oil studies that include cholesterol feeding have been conducted in rabbits. Kritchevsky et al. [5] demonstrated in various studies that rabbits fed 2% cholesterol and 6% coconut oil had more lesions, as determined by visual evaluation, than rabbits fed 2% cholesterol and 6% unsaturated oils. In other studies, the level of dietary coconut oil or cholesterol was too low to cause substantial increases in either plasma triglyceride or cholesterol [6,7].

In the present experiments, we investigated whether rabbits fed a commercial chow diet containing 0.5% cholesterol and 14% coconut oil develop more severe hyperlipidemia and subsequently more severe atherosclerosis than rabbits fed the same diet containing 14% olive oil in place of coconut oil. Furthermore, we asked whether the development of atherosclerosis can be attributed directly to the level of hypercholesterolemia induced by coconut oil plus cholesterol feeding, or whether the hypertriglyceridemia accompanying coconut oil feeding is a significant factor in this process.

The first study was designed to ascertain that commercial chow containing coconut oil plus cholesterol does, in fact, produce a marked hypertriglyceridemia in rabbits. From our findings in the first study, a second, larger experiment was designed to investigate the role of coconut oil-induced hypercholesterolemia and hypertriglyceridemia in atherogenesis.

Materials and methods

Animals and diets

In study 1, 12 female New Zealand White (NZW) rabbits (Becken Research Animal Farm; Sanborn, NY), weighing between 1.7 and 2.4 kg, were separated into 2 groups of 6 (olive oil, n = 6; coconut oil, n = 6). In study 2, 20 female NZW rabbits, weighing between 1.7 and 2.8 kg, were separated into groups of 5 (olive oil) and 15 (coconut oil). Rabbits were housed individually and allowed free access to water. Rabbits were fed daily 100 g of a commercial chow diet (Purina Lab Rabbit Chow 5321; St. Louis, MO) containing 0.5% (by weight) cholesterol, USP (ICN Biochemicals Inc., Cleveland, OH) and 14% (by weight) of either olive oil (Fellipo Berio and Co., Lucca, Italy) or hydrogenated coconut oil (ICN Biochemicals Inc., Cleveland, OH). Cholesterol was dissolved in oil at 120 °C and then added to the chow while agitating for 3 min in a mixer. The duration of study 1 was 87 days and of study 2 was 95 days. Body weights were recorded weekly, and daily food consumption records were kept. All protocols were in accordance with Cornell University Guidelines.

Analyses

Fasting blood samples were collected from the marginal ear vein (4% NaN_3, 0.4 M EDTA, pH 7.4, 0.01 ml/ml blood) approx. every 10 days. Plasma cholesterol was analyzed by the ferric chloride method of Zak et al. [8] after saponification [9] or by an enzymatic method (Autoflow Cholesterol High Performance Kit (236691); Boehringer Mannheim Biochemicals, Indianapolis, IN). Plasma triglyceride was analyzed by either the method of Sardesai and Manning [10] or by an enzymatic method (Reagent Set Triglycerides GPO (701912); Boehringer Mannheim Biochemicals, Indianapolis, IN). Plasma lipoproteins were separated (Beckman 50.3 rotor, 10 °C, 1.62×10^8 $g \times$ min) into 2 density classes, $d <$ and > 1.019, as described by Havel et al. [11]. Following saponification [9], the cholesterol concentrations of the 2 fractions were determined by the method of Zak et al. [8].

At the end of each study, the rabbits were killed by an overdose of sodium pentobarbital (Premo Pharmaceuticals Laboratories, Inc., Hackensack, NJ). The aortas were removed and rinsed in a 0.9% NaCl solution. Excess fat was carefully removed from the adventitial side of the aorta. Aortas were then opened longitudinally, divided into thoracic and abdominal sections, weighed and stored at −20 °C for later analysis. Livers were also excised and weighed. Abdominal

and thoracic aortas were extracted overnight in 20 vols. of a 2:1 (v/v) chloroform/methanol solution. Aliquots were dried, saponified [9] and analyzed for total cholesterol content by the method of Zak et al. [8].

Average plasma lipids

Average plasma cholesterol values for each group over each time period were determined as follows: the area under the plasma cholesterol-time curve for each rabbit was determined and divided by the time period. These individual average plasma cholesterol values were then averaged for each group. Average plasma triglyceride values for each group were determined by the same calculation.

Data were analyzed for statistical significance by Student's *t*-test. Linear regression and multiple linear regression were determined by the least-squares method (SAS; Statistics Version, 5th edition).

TABLE 1

PLASMA CHOLESTEROL AND TRIGLYCERIDE AND AORTIC CHOLESTEROL IN RABBITS FED CHOLESTEROL AND FAT

Rabbits were fed for 87 days 100 g daily of chow containing 0.5% cholesterol and 14% (by weight) of either olive oil or coconut oil. For determination of average values, refer to Methods: Average plasma lipids. Values are means ± SE.

	Olive/chol (n = 5)		Coconut/chol (n = 6)	
	Average	Final	Average	Final
Plasma cholesterol (mg/dl)	772 (±91)	1226 (±231)	1086 (±209)	1924 (±322)
Plasma triglyceride (mg/dl)	100 (±11)	132 * (±45)	380 (±155)	963 (±325)
Aortic cholesterol (mg/g tissue)	10.4 (±4.0)		13.2 (±2.8)	

* Significantly different between olive/chol and coconut/chol groups, $P < 0.05$.

Results

In study 1, 11 rabbits appeared healthy and no significant differences in food consumption, weight gain or liver weight were found between the two groups; one rabbit from the olive oil group died due to respiratory complications. Although no statistically significant differences in average plasma triglyceride, average plasma cholesterol and aortic cholesterol content were found due to a small sample size (Table 1), the plasma triglycerides of most coconut oil/cholesterol-fed (CNO/chol) rabbits were substantially higher than the triglycerides of olive oil/cholesterol-fed (OO/chol) rabbits which remained essentially at basal levels. However, at all time points the variability among the CNO/chol rabbits was so large that a particular plasma triglyceride pattern was not evident. The same observation was made about plasma cholesterol; in general, plasma cholesterol was higher in CNO/chol animals, but the variability was too great for the difference to be statistically significant. Although the mean aortic cholesterol in CNO/chol rabbits was higher than the OO/chol group, the difference was not statistically significant.

The final plasma triglyceride values for CNO/chol rabbits ranged from approx. 150 mg/dl to 2400 mg/dl. It appeared, therefore, that in some rabbits only a mild hypertriglyceridemia whereas in others a more marked to severe hypertriglyceridemia was induced with coconut oil plus cholesterol feeding. With this information, the second study was designed.

By increasing the number of CNO/chol rabbits, we took advantage of their inherent variability to produce a large range of hypertriglyceridemia. We were then able to compare the aortic cholesterol content with the level of hypertriglyceridemia and discover whether a relationship between the two exists. Five OO/chol rabbits were also included in this experiment as 'controls'. Olive oil feeding did not produce hypertriglyceridemia in the first study; therefore, OO/chol rabbits would ensure a hypercholesterolemic but normotriglyceridemic group for comparison.

In study 2, the data for one rabbit from the CNO/chol group has not been included in the analyses; this animal ate sparingly for the last 20 days of the experiment. Rabbits in both groups gained weight equally (OO/chol, mean ± S.D. = 13.0 ± 2.5 g/day; CNO/chol, 11.4 ± 2.9 g/day), and no significant differences in daily food con-

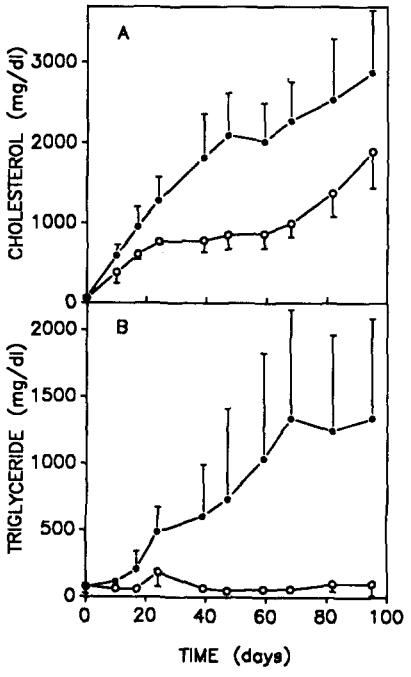

Fig. 1. Plasma cholesterol (A) and plasma triglyceride (B) concentrations in rabbits fed coconut oil/chol (●) or olive oil/chol (○) over a 95 day period. At all time points, n = 14 for coconut oil/chol rabbits and n = 5 for olive oil/chol rabbits. Error bars represent standard deviations.

sumption were observed. Liver weights also did not differ.

Starting plasma cholesterol and triglyceride levels did not differ significantly between OO/chol and CNO/chol rabbits. After 17 days of feeding, differences in plasma cholesterol and triglyceride levels between the 2 groups were significant ($P < 0.01$) and continued to be so for the duration of the study. Fig. 1A shows the plasma cholesterol profiles for both groups over the 95-day period; at every time point, the mean cholesterol concentration for the CNO/chol group was approximately twice that of the OO/chol group. The final plasma triglyceride concentrations in the CNO/chol rabbits were on average 20-fold higher than basal levels for that group, as well as 20-fold higher than the OO/chol group (Fig. 1B, Table 2). As expected, the range of plasma triglycerides of CNO/chol rabbits was very large. Final plasma triglyceride concentrations ranged from approx. 200 mg/dl to 3000 mg/dl. In OO/chol rabbits, there was essentially no change in plasma triglyceride throughout the 95-day period (Fig. 1B)

TABLE 2

PLASMA CHOLESTEROL AND TRIGLYCERIDE AND AORTIC CHOLESTEROL IN RABBITS FED CHOLESTEROL AND FAT

Rabbits were fed for 87 days 100 g daily of chow containing 0.5% cholesterol and 14% (by weight) of either olive oil or coconut oil. For determination of average values, refer to Methods: Average plasma lipids. Values are means ± SE. Differences between groups for all variables are statistically significant at at least $P < 0.01$.

	Olive/chol (n = 5)		Coconut/chol (n = 14)	
	Average	Final	Average	Final
Plasma cholesterol (mg/dl)	895 (±43)	1892 (±205)	1770 (±91)	2870 (±210)
Plasma triglyceride (mg/dl)	83 (±17)	102 (±39)	781 (±102)	1339 (±199)
Aortic cholesterol (mg/g tissue)	12.1 (±1.7)		25.7 (±2.7)	

Fig. 2 illustrates the distribution of cholesterol between $d <$ and > 1.019 lipoproteins as a fraction of total plasma cholesterol at three time points. Data from both studies have been included in this figure. Absolute $d > 1.019$ (HDL and LDL) cholesterol concentrations were 2–2.5 times higher in the CNO/chol group than in the OO/chol group at each time point. It is interesting that even though the mean plasma total cholesterol of the OO/chol group increased substantially between time points, the cholesterol concentration in the $d > 1.019$ fraction remained approx. 160 mg/dl. In contrast, the cholesterol concentration of the $d > 1.019$ fraction of the CNO/chol group increased between the first and second time point; from the second to the third time point the cholesterol of this fraction reached approx. 400 mg/dl. Preliminary determinations in this laboratory (Quig and Zilversmit, unpublished data) indicate that in CNO/chol rabbits, cholesterol in the HDL fraction is very low; hence, most of the cholesterol in the $d > 1.019$ fraction is in LDL.

Average plasma cholesterol and triglyceride values over the 95-day period and the average aortic cholesterol content for the 2 groups are

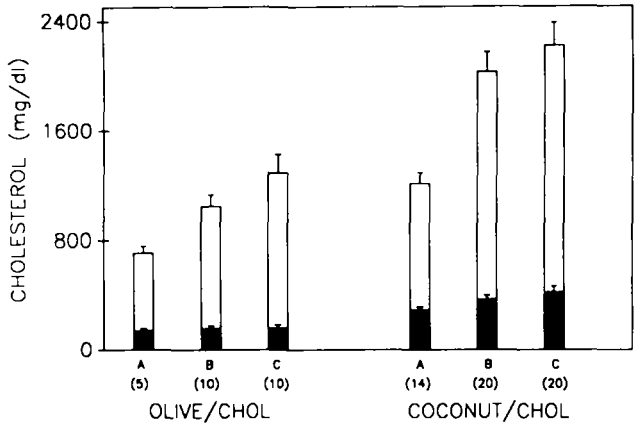

Fig. 2. Plasma cholesterol in $d < 1.019$ (□) and $d > 1.019$ (■) in olive oil/chol and coconut oil/chol rabbits: (A) 23 days; (B) 63–68 days; (C) 87–95 days. Data from study 2 only are included in (A) since no data from study 1 were available. Data from study 1 and 2 are included in (B) and (C). Numbers in parentheses represent number of rabbits. Error bars represent standard error of the mean.

given in Table 2. Mean aortic cholesterol content in CNO/chol rabbits was 25.7 ± 2.7 mg/g and 12.1 ± 1.7 mg/g in OO/chol rabbits; the difference between the 2 groups was found to be significant ($P < 0.001$).

In the CNO/chol group, a correlation between plasma cholesterol and triglyceride was found ($r = 0.60$; $P < 0.05$). Average plasma triglyceride and aortic cholesterol were not correlated; average plasma cholesterol and aortic cholesterol content were also not significantly correlated in this group ($r = 0.26$). However, a multiple linear regression with plasma cholesterol and triglyceride as predictors of aortic cholesterol content determined the following equation:

$$\text{Aortic cholesterol} = 0.43 + 0.020(\text{cholesterol}) - 0.014(\text{triglyceride})$$

in which aortic cholesterol is expressed as mg/g and plasma lipids as mg/dl. The standard errors of the estimated partial regression coefficients of plasma cholesterol and triglyceride are 0.006 and 0.007, respectively. Plasma cholesterol contributed significantly ($P < 0.004$) to aortic cholesterol; plasma triglyceride appeared to be inversely related to aortic cholesterol ($P < 0.08$).

Discussion

The foregoing experiments show that a more severe hyperlipidemia and atherosclerosis can be induced in rabbits fed an atherogenic diet containing coconut oil and cholesterol when compared to rabbits fed an atherogenic diet containing olive oil and cholesterol. Previous studies have demonstrated that rabbits fed coconut oil at varying levels without cholesterol have moderately elevated plasma triglyceride and cholesterol levels. Rabbits fed a semisynthetic diet containing 15% coconut oil without cholesterol for 5 months showed an 8-fold higher serum cholesterol and a 3-fold higher serum triglyceride than rabbits fed chow [1]. In a similar study [2], rabbits were fed a casein–sucrose cholesterol-free diet containing 14% coconut oil for 10 months; both serum cholesterol and triglyceride were approx. 6 times higher than control levels. A short term study (22 days) showed that rabbits fed a semipurified diet containing 10% coconut oil showed serum cholesterol levels 2.5 times greater than rabbits fed a commercial diet or a semipurified diet containing 10% corn oil. Serum triglyceride levels were not reported [3]. It is worth noting that feeding semipurified diets containing casein or a casein-sucrose mixture without cholesterol or coconut oil can also cause hypercholesterolemia, although not as marked as the level achieved with the addition of coconut oil [12].

Final plasma triglycerides of coconut oil/cholesterol rabbits were approx. 20-fold higher than plasma triglycerides in rabbits fed olive oil/cholesterol. The 20-fold increase is much greater than those reported in previous studies [1,2]. This finding suggests that either dietary cholesterol, which was not a component of the diets in previous studies, or the resulting hypercholesterolemia may play an interactive role with coconut oil in causing the large elevation in plasma triglyceride.

Plasma cholesterol was also significantly more elevated in the coconut oil group than in the olive oil group, even though both groups consumed the same amounts of cholesterol. Studies have indicated that rabbits fed cholesterol-free, semisynthetic diets containing saturated fats other than coconut oil exhibit higher plasma cholesterol levels than rabbits fed unsaturated oils [1,2,12]. It is well known that saturated fats increase plasma cholesterol in humans. Thus, the observed increase in plasma cholesterol in coconut oil rabbits above the cholesterol levels of olive oil rabbits may be directly attributed to the coconut oil which is highly saturated.

Plasma cholesterol, plasma triglyceride, and aortic cholesterol in coconut oil/cholesterol rabbits were lower in study 1 than study 2. Three out of 6 coconut oil/cholesterol rabbits in study 1 had very low plasma cholesterol compared to all other coconut oil/cholesterol rabbits. These rabbits also had relatively low aortic cholesterol which contributes to a lower mean. There were no differences between studies in the olive oil/cholesterol groups.

Two 14% coconut oil studies (22 days and 16 months) determined that most of the plasma cholesterol was located in the VLDL fraction [3,7]. We separated plasma cholesterol into two density classes ($d <$ and > 1.019) at several time points. Most of the plasma cholesterol was found in the $d < 1.019$ which comprises VLDL and IDL. The distribution of plasma cholesterol between VLDL and IDL is not known at this time, however.

Brattsand [1] found that, with 15% coconut oil feeding, most cholesterol was located in the LDL fraction until total serum cholesterol exceeded 600 mg/dl. At total serum cholesterol levels between 600 mg/dl and 1400 mg/dl, average LDL cholesterol did not exceed 400 mg/dl and most of the remaining cholesterol was found in the VLDL fraction [1]. Our results in CNO/chol rabbits extend Brattsand's findings, i.e., $d > 1.019$ cholesterol (LDL and HDL) in CNO/chol rabbits did not exceed approx. 400 mg/dl even at total plasma cholesterol concentrations greater than 2500 mg/dl.

Although we expected to find a significant correlation between plasma and aortic cholesterol [13,14], these experiments demonstrate that, in the coconut oil/cholesterol-fed rabbit, plasma cholesterol and aortic cholesterol are not correlated. However, when the combined effect of plasma cholesterol and triglyceride are considered, plasma cholesterol becomes a very significant predictor of aortic cholesterol ($P < 0.004$) while plasma triglyceride appears to have a negative effect. Therefore, although the partial regression coefficient for plasma triglyceride is of borderline significance ($P < 0.08$), its presence in the multiple linear regression equation greatly enhances the precision whereby plasma cholesterol predicts the quantity of aortic cholesterol. These results suggest, therefore, that very high levels of plasma triglyceride may have a protective effect against the development of atherosclerosis. Other models of hypertriglyceridemia have shown similar findings: for example, cholesterol-fed rabbits given cortisone or hydrocortisone developed more severe hypercholesterolemia and hypertriglyceridemia than just cholesterol-fed rabbits; yet, significantly less lipid was found in the arteries of the cortisone group [15–19]. Since the effect of cortisone administration on the arterial wall is largely unknown, however, the hypertriglyceridemia may not be responsible for the lower lipid levels found in the arteries of such rabbits [20]. A number of studies have shown that alloxan-diabetic, cholesterol-fed rabbits that exhibit very marked levels of hypertriglyceridemia are protected against atherosclerosis even in the presence of very high levels of plasma cholesterol [21–26]. The injection of various detergents in rabbits has also been shown to produce hypercholesterolemia and marked hypertriglyceridemia accompanied by a reduced arterial cholesterol accumulation [27,28].

Although the underlying mechanisms in these models have not been clarified, it may be possible to explain their antiatherogenic effect on the basis

of lipoprotein particle size. Stender and Zilversmit [29] compared the simultaneous influx of HDL, LDL and VLDL into the artery and found that arterial influx was inversely related to the molecular size of these lipoproteins. In a later report, Nordestgaard et al. [30] proposed that the lipoproteins of markedly hypertriglyceridemic, diabetic, cholesterol-fed rabbits might be too large to penetrate the endothelial layer of the arteries. In these rabbits, a substantial fraction of plasma cholesterol was found in large, triglyceride-rich VLDL particles; the authors suggest that this "sequestered" cholesterol is less atherogenic than cholesterol found in smaller lipoproteins [30].

The data in the present paper show that CNO/chol rabbits exhibiting a mild to moderate level of hypertriglyceridemia (200–800 mg/dl) have greater aortic cholesterol than coconut oil/cholesterol-fed rabbits with much higher plasma triglycerides (> 800 mg/dl) even at similar levels of plasma cholesterol. These studies do not indicate whether the lower range of plasma triglyceride is atherogenic, neutral or protective.

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