Vervet monkeys and whole-food diets for studying the effects of dietary lipids on plasma lipoprotein metabolism and atherosclerosis

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It is well established that some species of nonhuman primates are models of choice for polygenic hyperlipoproteinaemia and atherosclerosis induced and promoted by diets as occur in man. The Vervet monkey (*Cercopithecus aethiops*) has proved to be one such model. Our group has used this model extensively to determine the effects of a variety of dietary lipid components on plasma lipoprotein metabolism and atherosclerosis against a background of a Western atherogenic or prudent diet. The diets fed in all these studies were formulated entirely from cooked foods that are normal components of Westernised diet with no extra synthetic cholesterol added.

This model has been used successfully to evaluate the effect of fish oil, amount and degree of dietary fat unsaturation and w-6/w-3 fatty acid ratio and lipid-lowering agents on plasma lipoprotein metabolism and atherosclerosis. Dietary manipulation in this model is simple, relatively inexpensive and offers almost unlimited options for future dietary intervention studies.

Key words: African Green monkey, dietary lipids, plasma lipoprotein metabolism, atherosclerosis

Introduction

It is well established that some species of non-human primates are models of choice for polygenic hyperlipoproteinaemia and atherosclerosis induced and promoted by diets as occur in man[1-9]. The Vervet or African Green monkey (*Cercopithecus aethiops*) has proved to be an excellent model for studying the effects of a variety of dietary lipid components on plasma lipoprotein metabolism[3,4,9-12] and atherosclerosis[13-16]. The potential for using this primate to study the effect of lipid-lowering agents on plasma lipoprotein metabolism and atherosclerosis was recently demonstrated[17].

Direct comparison of results from the various studies is difficult because of differences between species and diets administered to experimental animals of the same species. The purpose of this communication is therefore to review results of our own studies which used the African Green monkey, and diets that are realistic for man[1,11-13,15-17].

Materials and methods

Vervet monkeys were all healthy and conditioned to the laboratory environment for six months or more[18,19]. Diets fed were either an average Western diet (WD), a prudent diet (PD) or a high carbohydrate diet (HCD), which have been described in detail elsewhere[1,20]. The period of time diets were fed ranged from four to 47 months. Diets were composed entirely of normal food items for humans without any added cholesterol and spanned a realistic nutritional range.

Comparison of the effect of the amount and degree of unsaturation of dietary fat on plasma low density lipoproteins

Kruger et al[12] studied the effects of the degree of unsaturation and of the amount of dietary fat on low density lipoprotein (LDL) concentration and composition in the African Green (Vervet) monkeys (12 females; age 1.5-4.5 years). Animals received diets with fat contents of 41, 31 and 18% energy each with a low and high polyunsaturated to saturated fatty acid ratio (P/S; 0.27-0.38 and 1.13-1.47; major fatty acids were palmitic and linoleic acids) for a period of two months. Cholesterol content of the diet was low (6.0-9.3mg/100Kcal). LDL cholesterol concentrations showed significant decreases when the dietary fat content decreased from 31 to 18% of energy. Dietary P/S ratio only affected LDL cholesterol concentrations during moderate (31% of energy) fat intake. Low density lipoprotein cholesterol increased with a decrease in dietary P/S. The changes in LDL cholesterol concentrations were the result of changes in the number of circulating LDL particles as the molecular composition was not significantly affected between dietary periods. Dietary fat changes had no influence on the high density lipoprotein cholesterol and plasma triacylglycerol concentrations. During the high P/S diets, the percentage of linoleic acid (18:2 w6) in LDL esterified cholesterol (CE) and adipose tissue triacylglycerol (TAG) increased as compared to the low P/S diets.

Results of this study provides evidence that the amount of dietary fat had a greater influence on plasma cholesterol concentration than a moderate change in dietary P/S in Vervets. The effects of dietary fat on plasma cholesterol were mainly through changes in LDL cholesterol concentrations. The animals showed marked individual differences in LDL cholesterol concentration response to both the amount and the degree of unsaturation of fat in the diet.

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The finding that LDL particle mass was also not influenced significantly by dietary fat changes supports findings in both Vervets[13] and humans[21]. The loading of LDL with esterified and unesterified cholesterol and increased LDL particle mass reported in some studies in non-human primates fed an atherogenic diet probably resulted from excessive cholesterol intake[22-24,28].

The influence of fish oil supplementation on plasma lipoproteins and arterial lipids in Vervets[16]

Details of the study were described previously[16]. Briefly, the experimental design was as follows: Vervets (20 males, 17 females; all adults) were divided into four comparable groups, two groups were retained on the Western atherogenic diet (WAD), based on milk, eggs, meat, legumes, cereals, sugar, fruit, vegetables, butter and sunflower oil (35% E fat, 31.0 mg chol/100Kcal), one of which was supplemented with fish oil (WAD/FO; n = 9), while the other received a sunflower oil (WAD/SO; n = 9) supplement. The remaining two groups were changed from the WAD to a high carbohydrate diet (HCD). One group was supplemented with the same FO supplement (HCD/FO; n = 9) and the other group received the sunflower oil (HCD/SO; n = 10) supplement. Nine female Vervets that were never exposed to the WAD served as a reference group and received a high carbohydrate diet. Vervets were terminated after 20 months.

Fish oil supplementation did not change the cholesterol concentrations of plasma cholesterol or LDL significantly (Table 1). Vervets of the WAD/FO group had an increased (2.7 times; p≤0.001) content of total cholesterol in their aortic intima compared to the WAD/SO group. The same trend was also evident after FO was supplemented to the HCD.

Table 1. The effect of fish oil on lipoprotein and arterial total cholesterol levels[16]

	WAD/SO n=9	WAD/FO n=9	HCD/SO n=10	HCD/FO n=9	HCD n=9
Plasma (mg/dL)	333 (125.2)	345 (121.0)	146 (23.1)	144 (20.6)	181 (24.2)
LDL (mg/dL)	300.9 (158.9)	265.9 (134.2)	49.5 (21.2)	49.7 (13.6)	86.9 (26.6)
Intima (mg/mg protein)	32.5 (26.6)	89.2† (78.3)	44.2 (70.9)	83.7* (125.2)	10.5 (4.9)

WAD: Western atherogenic diet; SO: Sunflower oil; FO: Fish oil; HCD: High carbohydrate diet; (values in parenthesis are ± SD)
Significant difference between WAD/FO and WAD/SO or HCD/FO and HCD/SO: *p<0.01; †p<0.001

EPA was increased 7.5 and 6.5-fold respectively (both p≤0.001) in plasma and aortic intima PC (Table 2). Dihomogamma-linolenic acid (C20:3 w6; DGLA p≤0.01) and arachidonic acid (C20:4 w6; AA p£0.001) levels were reduced in the plasma PC after FO supplementation of the WAD, and similar effects were seen after supplementing the HCD with FO. In the aorta intima the AA was also reduced (P≤0.001) on the WAD/FO. Docosahexaenoic acid (C22:6 w3; DHA) was also increased after FO supplementation. In the plasma and aorta intima PC, EPA and AA respectively demonstrated the strongest negative and positive correlations with the intimal CE and FC contents (Table 3).

Table 2. The effect of fish oil on the fatty acid composition of plasma and intima phosphatidylcholine fatty acids[16]

	WAD/SO n=9	WAD/FO n=9	HCD/SO n=10	HCD/FO n=9	HCD n=9
Plasma					
C18:2w6	25.6 (2.2)	18.1† (2.1)	33.3 (2.9)	23.6a* (1.6)	31.5 (1.5)
C20:3w6	1.5 (0.1)	1.2* (0.1)	2.6 (1.4)	1.1a* (0.3)	3.9 (1.2)
C20:4w6	12.1 (1.0)	9.4† (0.5)	8.0 (1.0)	5.9† (0.7)	8.8 (0.8)
C20:5w3	0.8 (0.1)	6.0† (0.7)	0.4 (0.1)	5.3a* (1.1)	0.3 (0.1)
C22:6w3	5.5 (1.0)	8.2† (1.5)	3.0 (0.4)	7.6† (0.8)	3.0 (0.5)
Intima					
C18:2w6	5.7 (0.8)	7.4* (1.3)	6.3 (1.0)	7.0 (1.7)	5.1 (0.8)
C20:3w6	1.0 (0.3)	1.3 (0.2)	1.1 (0.4)	1.1 (0.3)	1.0 (0.2)
C20:4w6	19.6 (1.9)	15.0† (1.8)	18.0 (2.8)	15.5 (2.5)	20.4 (1.9)
C20:5w3	0.2 (0.1)	1.3† (0.4)	0.1 (0.1)	0.6a* (0.1)	ND
C22:6w3	3.1 (0.7)	3.7 (0.9)	2.1 (0.5)	3.0* (0.7)	2.3 (0.5)

WAD Western atherogenic diet; HCD High carbohydrate diet
SO Sunflower oil; FO Fish oil; [a]Males; ND Not detected
Significant difference between WAD/FO and WAD/SO or HCD/FO and HCD/SO. *p<0.01; †p<0.001

Table 3. Correlation coefficients (r) and p-values between the esterified cholesterol (CE) and free cholesterol (FC) content of the aorta intima and plasma and intimal phosphatidylcholine (PC) fatty acids[16].

	Intima-FC		Intima-CE	
PC Fatty acid	*r*	*p*	*R*	*p*
Plasma				
C20:4w6	-0.66	0.0029	-0.53	0.0245
C20:5w3	0.75	0.0004	0.57	0.0126
Intima				
C20:4w6	-0.73	0.0007	-0.72	0.0005
C20:5w3	0.78	0.0001	0.59	0.0095

The effect of diet on the metabolism of EPA[27]

Controversy surrounds the beneficial effects of EPA on lipo-protein metabolism because researchers showed that EPA does lower plasma cholesterol concentrations in primates[25] while others suggested a cholesterol elevating effect[15]. Although many factors could possibly explain these divergent results obtained with EPA, difference in the diets which were supplemented could be important[26].

In a study reported by van Rooyen[27], Vervet monkeys (20 adult females) receiving either a WAD or HCD were supplemented with (2400 mg/day) EPA concentrate (Callandish Pharmaceuticals, 50% free acid) for 24 weeks after which time EPA supplementation was withdrawn. Animals then continued on their respective diets for a further 12 weeks during which time the EPA contents of the erythrocyte membrane phosphatidylcholine (EMB-PC), phosphatidylethanolamine (EMB-PE), plasma CE and TAG were carefully monitored. This information was then used to

calculate the relative rates of disappearance from the various tissues.

Although the rates of disappearance differed significantly between the various tissue compartments, rates of disappearance of EPA in the WAD animals were invariably statistically significantly slower than in the HCD animals (Table 4). These results are in agreement with the results from LDL turnover studies by Weight *et al*[11] who reported a slower rate of clearance of ^{125}iodine labelled LDL in monkeys fed a WAD compared to animals fed a prudent HCD diet, suggesting a slower rate of metabolism of plasma lipoprotein in animals fed a WAD. In the EPA treated groups, plasma total cholesterol levels increased by 17% in association with the WAD and decreased by 20.8% in association with the HCD. High density lipoprotein cholesterol levels were reduced in both diets by EPA supplementation.

Table 4. Summary of the comparison of the estimated half-life (t½) (median of the individual median measurement in days) of eicosapentaenoic acid (EPA)[27].

Compartment	WAD	HCD
EMB-PE	43.5	31.3
EMB-PC	34.3	22.6
Plasma CE	23.5	14.1
Plasma TAG	17.4	9.4

EMB: Erythrocyte membrane; PC: Phosphatidylcholine; PE: Phosphatidylethanolamine; CE: Esterified cholesterol; TAG: Triacylglycerol; WAD: Western atherogenic diet; HCD: High carbohydrate diet

***The effect of cholesterol and type of fat in the diet on the LDL composition of the African Green monkey*[28]**

Malan[28] studied the effect of cholesterol and type of fat in the diet on the LDL composition of African Green monkeys (15 adult males) receiving diets containing a constant amount of fat (40% of energy) and which varied only in the amount of cholesterol (16.4 or4.0 mg/100kcal) and in the type of fat (P/S; 0.3 or 1.2) present in the diet. Cholesterol was found to exert a significant and independent effect on the LDL total cholesterol, LDL-CE, LDL free cholesterol (LDL-FC), LDL apolipoprotein B (LDL-apoB) and LDL total phospholipid (LDL-TPL) concentrations.

There was significant interaction between cholesterol and P/S in their effect on the LDL composition. The effect of the cholesterol was significant only at low P/S ratio. The high cholesterol, low P/S diet was characterised by an enrichment of the LDL particles with CE at the expense of TAG as well as by a significant increase in the LDL molecular weight (MW).

Although the P/S also exerted significant effects on the LDL composition, it was less marked than that of cholesterol. At low cholesterol diets, the P/S significantly affected the CE and FC content of the LDL and the LDL-MW which were all relatively increased during the high P/S diets compared to the low P/S diets. At a high cholesterol content in the diet, the increase in the P/S caused significant decreases in the TPL content of the LDL and in LDL-MW.

Results of this study concerning the LDL compositional changes in response to increased intake of dietary cholesterol are consistent with those from previous studies using nonhuman primates.

***Atherogenic and prudent diet experiments*[1,13,15,20,29]**

Five papers were published based on results of an experiment which incorporated major improvements in methodology in relation to atherosclerosis, diets and clinical control. One hundred adult female, non-pregnant, premenopausal Vervets were used. Environment in terms of photoperiod, temperature, air circulation and access by potential disease vectors was controlled.

Fixation of arteries for microscopy is the most critical part of the methodology to optimise visualisation of atherosclerosis[1,17,30]. An improved procedure commenced under surgical anaesthesia by flushing of the heart and arterial system with isotonic saline at physiological pressure (100 mm Hg) and flow, which prevented agonal clotting[1]. Perfusion of the arteries with fixative via the left ventricle, with lung function supported by a ventilator, followed immediately after the flushing, with the heart still beating. This method enhanced qualitative results and enabled definition of atherosclerosis by precise cellular, extracellular and morphometric criteria for the first time, including peripheral and coronary atherosclerosis. As a result, a strong positive relationship between atherosclerosis, hypercholesterolaemia and known dietary risks, was confirmed in adult female Vervets. The prudent diet was not associated with definitive atherogenesis, but failed to regress components of advanced atherosclerotic plaque, such as cholesterol crystals, calcification and fibrosis, within 20 months. This implied that for Vervets the prudent diet would be more effective for preventing atherosclerosis than treating advanced lesions, and this may well apply to people. Significant coronary atherosclerosis and myocardial sequelae, such as infarction and fibrosis, did not develop in adult females at dietary risk for 47 months.

In addition to measurement of true atherosclerosis, 50 variables were monitored at regular intervals, and included plasma lipograms, 23 chemical pathology variables, haematology and body weights[20]. Treatment durations of 15, 20, 27 and 47 months defined a time scale of atherosclerosis in response to well controlled dietary challenge in adult females. Atherogenic and prudent diets were realistic for Westernised people, and no extra pure cholesterol was added because this is not relevant to the human experience. Dietary compliance was proven by measuring food intake. The other treatments were constant exposure to either atherogenic, prudent or reference (= negative control high carbohydrate) diets. The reference diet was realistic for Third World people. Mean plasma total cholesterols (mg/dL) in Vervets fed the respective diets stabilised at 147 (reference diet), 174 (prudent diet) and 376 (atherogenic diet). Dietary change from atherogenic for 20 months, back to prudent for 27 months was tested, and the result confirmed that the prudent diet completely reversed hyperlipidaemia. The phenomenon of hyper- and hypocholesterolaemic responders was confirmed and this models a similar situation with polygenic atherosclerosis in people. Hypercholesterolaemic response ranged between individuals from 81 to 505 mg/dL, or 623%. Red blood cells, platelets and associated parameters increased in association with the atherogenic diet compared to the prudent diet, haemoglobin was the same and haemoglobin per red cell decreased. Activities of rate limiting enzymes for cholesterol synthesis in liver were not conclusively

related to diet. Dietary ascorbic acid requirements under the conditions of the experiment were defined. Statistically significant increases in calcium, zinc, vitamin E, and decreased vitamin B_6 were associated with the atherogenic compared to the prudent diet (in plasma or serum)[20]. A contribution to definition of folic acid and vitamin B_{12} requirements resulted from a separate study which detected very low folate status after chronic intakes of the atherogenic diet[31].

Atlantic pilchard fish oil[15,16]

Supplementation of atherogenic and therapeutic diets with fish oil was for 20 months, and commenced after long-term (average of 24.5 months) exposures to the atherogenic diet to accelerate progression of atherosclerosis. Processing of peripheral, coronary and cerebral arteries, and aortas, for detection of atherosclerosis was again improved in that saline and fixative used to perfuse the circulation during anaesthesia were continuously oxygenated. This is reported to prevent terminal sloughing of endothelium due to hypoxia, which creates false lesions[30]. Cerebral arteries were perfused by canulation of a common carotid artery, with the opposite carotid tied-off to prevent short circuiting of perfusate by shunting through vertebral arteries. Jugular veins were severed to prevent pressure build-up in the cerebral circulation.

Atlantic pilchard (*Sardinops oscellata*) fish oil is relatively rich in eicosapentaenoic and docosahexaenoic w3 polyunsaturated fatty acids. In control groups, sunflower (*Helianthus annuus*) replaced the fish oil to supply the same quantity of polyunsaturate (m/m) in the form of 18:2 w6 linoleic acid. Twenty adult male and 17 adult female Vervets were used in this study, which enabled confirmation that atherogenesis is more pronounced in males. Compliance was proven by physical records of food consumption and by measured changes in w3 fatty acid content of tissues. Results did not provide any evidence that the fish oil was anti-atherogenic. The therapeutic diet effectively reversed lipid infiltration into arteries, as indicated previously by the prudent diet, but again components of advanced atherosclerosis such as cholesterol crystals, calcification and fibrosis did not regress in 20 months. There was minimal cerebral atherosclerosis, possibly because the walls of cerebral arteries are thin, almost like veins, which minimises tissue available for lipid accumulation. This suggests that the main pathogenesis of infarctive stroke may be by occlusive embolisation from carotid thrombi.

Summary and conclusions

The African Green monkey (*Cercopithecus aethiops*) has proven to be a suitable model for studying the effects of a variety of dietary components on plasma lipoprotein metabolism and atherosclerosis against a background of a Western atherogenic or prudent diet. The diets used in our studies were realistic, formulated entirely from cooked foods that are normal components of the diet of Westernised people with no extra synthetic cholesterol added. Very often diets are loaded with synthetic cholesterol and saturated fat, on the pretext of speeding up results. Our own results confirmed that this practice will almost invariably result in packing of cholesteryl esters into cores of enlarged LDL particles. This method is fundamentally flawed and is not a valid model for human atherosclerosis. It has been strongly criticised by pathologists[32,33]. In contrast, experience with realistic diets showed LDL particles of relatively normal composition to also be atherogenic[13]. Models of human atherosclerosis Types I-VII[32,33], as defined by anatomical, cellular and extracellular criteria, have been achieved by our methods[1,15,17]. Duration of exposure to a natural ingredient atherogenic diet should, however, be at least three years in adult males and four years in adult females. Individuals allocated to treatments should further be matched for sex, age, and plasma lipids[1,15,17,20]. Experience also showed that it is important to use untreated reference controls to check for effects not due to treatments or sampling error such as stress and subclinical disease[1,12,17,20].

Dietary manipulation in the African Green monkey is simple, relatively inexpensive and offers almost unlimited options for dietary intervention studies.

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Asia Pacific Journal of Clinical Nutrition (1997) Volume 6, Number 1: 17-21

以非人類的靈長動物模型研究膳食脂類對血漿脂蛋白代謝和動脈粥樣硬化的影響

摘要

由膳食誘導和助長高脂蛋白血症和動脈粥樣硬化的非人類的某些靈長動物模型已很好地建立. 作者以Vervet 猴子爲對象, 建立這種模型. 測定不同脂類組成的膳食對血漿脂蛋白代謝和動脈粥樣硬化的影響, 并與西方致動脈粥樣硬化膳食相比較. 這些研究的所有膳食均按配方制成, 是正常西方人群的膳食組份, 没有額外加入膽固醇. 用這一模型成功地評估了魚油, 膳食中的不飽和脂肪的量和濃度, ω6/ω3 脂肪酸比值和降血脂制劑對血漿脂蛋白代謝和動脈粥樣硬化的影響. 該模型的膳食制作簡單, 相對便宜, 并對未來膳食干預研究提供極大的選擇.