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Effects of High Polyunsaturated Fat Diet on Human Plasma Cholesterol Esterification and Transfer

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ABSTRACT

The reaction of lecithin cholesterol acyltransferase(LCAT) and cholesteryl ester transfer protein(CETP) are important in cholesterol esterification and transfer for the reverse cholesterol transport(RCT) system. The purpose of this study were to assess the effects of fatty acid unsaturation on RCT system. After 12 female human subjects consumed a prescribed high saturated fat diet prior to the period, two groups of six subjects were provided with a high PUFA(corn oil) or a high SFA(butter) as major fats in a 40 en % fat diet. Butter feeding increased plasma total-(34%), esterified-(96%), HDL_3-(23%), LDL-(20%), and VLDL plus LDL(35%) cholesterol while corn oil feeding decreased esterified-(25%), LDL(15%) cholesterol and TG(27%). There were significant differences of fats on total-($p=0.0001$), esterified-($p=0.0001$), total HDL-($p=0.005$), HDL_2-($p=0.01$) and LDL-($p=0.0001$) cholesterol. LCAT activity did not change during the period but highly correlated to apo A-I in HDL which was increased in the corn oil group. The 2.5 fold increased CETP activity in the butter group during the period might be related to changes in plasma VLDL plus LDL cholesterol levels which were increased in the butter group.

KEY WORDS : polyunsaturated fatty acids · reverse cholesterol transport mechanisms · LCAT · CETP.

Introduction

The net transfer of cholesteryl ester among lipoproteins during the reverse cholesterol trasnport(RCT) system is a vital step in normal cholesterol homeostasis[1)2)]. The three processes contribute to the RCT system : the LCAT reaction, lipid transfer between different lipoprotein by CETP or triglyceride transfer protein(TGTP), and lipoprotein lipase(LPL) hydrolysis of TG and phospholipid(PL) on peripheral tissues or hepatic lipase on the liver. The esterification of free cholesterol(FC) from peripheral cells by LCAT acting on high density lipoprotein(HDL_3 fraction) is 75 −80% of the total esterification of FC in body[1)2)3)]. LCAT is stimulated by HDL apolipoproteins, apo A-I and to a lesser extent by apo C-I, apo E and apo A-IV[4)]. Following esterification, the net transfer of HDL-derived CE delivered into TG-rich lipoproteins with CETP to the liver via apo E or LDL B/E receptors because liver is only organ of cholesterol elimination[5)]. Many researches have suggested that LCAT activity is increa-

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sed by longer chain unsaturated fatty acids, especially linoleic acid(C18 : 2), versus saturated fatty acids. Even though LCAT reaction is independent of the P/S ratio of the diets, LCAT activity is positively correlated with the relative mol % of linoleic acid versus oleic acid in plasma PL and CE[6)7)]. Since LCAT activity increases the ratio of CE to TG in HDL, the net transfer of CE from HDL to VLDL via CETP is also regulated by LCAT with a feedback mechanism. However, there is some evidence that RCT system depends on CETP rather than LCAT[8)9)]. First, the mass transfer of CE from HDL to VLDL has to continuosly occur because the fractional catabolism rate of VLDL is greater than that of HDL[8)9)]. Second, since LCAT activity results in alterations in the composition of lipoprotein, LCAT depends on CETP activity rate[8)9)]. Third, HDL can be directly catabolized by liver, but the rate of removal of HDL liprotein moiety from circulation is too low to explain this form of transport[8)]. Plasma CETP levels have two faces to induce the atherosclerosis. The higher rate of CETP activity induces by high cholesterol[10)] and high saturated fat diet might conversely produce abnormally CE-enriched β-VLDL or CE-enriched LDL(dysbetalipoproteinemia). Lower rate of CETP activity induced atheroma by limiting the flux of cholesterol 'out of HDL and accumulation of CE within tissues [11)].

Methods

Subjects and design

After approval from the Biomedical Human Subjects Review Committee of The Ohio State University, 12 subjects were selected from 30 volunteers by screening for the health questionnaire, a physical examination and blood chemistry analysis. Twelve healthy females aged 20 up to 55 years with ranging up to 5.17 mmol/l for the plasma total cholesterol and with fasting triglycerides levels no more than 1.33 mmol/l. Subjects had no known history of metabolic diseases and had not taken any medication that affects plasma lipid levels. Women were of interest because women are used less frequently than men as subjects in cholesterol metabolism studies. For the menstruating women, the menstrual stage was checked in order to keep the same stage for drawing blood. The 12 subjects were randomly assigned into two groups : 6 subjects were in a high polyunsaturated fatty acid(PUFA) group(corn oil) and 6 subjects were in a high saturated fatty acid(SFA) group (butter fat). Before starting the experimental diet, subjects were required to eat according to a self-selected high fat diet plan for one week to stabilize the dietary fat intake. During the standardizing periods, food records were analyzed using Nutritionist III software(Silverton, Oregon). Blood samples were drawn for plasma total-, free-, and esterified cholesterol, total HDL-, HDL_3- and HDL_2- cholesterol, LDL and VLDL+LDL cholesterol, and LCAT and CETP activity, at the baseline and after a 4 weeks experimental period to be compared. The individual apo E phenotypes distribution was used to explain the variation of the data for the plasma total-, HDL- and VLDL+LDL- cholesterol levels, LCAT and CETP activity to the two dietary fats.

Diets

The average Recommended Dietary Allowance (RDA) of energy for female adults aged 25 to 55 years old and weighing 55 kg was calculated to be about 1900 kcal/day. Total energy was adjusted to maintain a constant body weight whthin± 2 %. Seven day physical activity recalls were recorded prior to the experimental period to determine

variation in energy requirement. Food records or food questionnaires were completed for one week before the study in order to obtained baseline data from total food intake during the period of self-selected diet. All food was prepared and served in a metabolic kitchen during 4 weeks of experimental period and monitored and recorded : nutrient intake was analyzed using Food Processor II software(Esha Research, Salem, Oregon). For the 4 week experimental period, the proportions of carbohydrate, protein, and fat of the foods were 45, 15, 40% of total calories, respectively(Table 1). A high PUFA(corn oil) diet provided SFA, MUFA and PUFA, respectively, as 8, 12 and 20% of total calories(P : S ratio=2.5). A high SFA(butter) diet provided 21, 12 and 7 percent of total calories as SFA, MUFA, and PUFA(p : s ratio=0.3). PUFA or SFA was consumed at twice the amount recommended by national health organizations in order to maximize the effect of different dietary fats. Both experimental groups received similar menus except salad dressing and baked food products(cookies and cakes) which incorporated different test fats. Subjects solely consumed the diets provided by the investigators during the study period and were prohibited to consume any food other than that provided. The total alcohol intake was limited to 2 servings per week and restricted for 5 days before blood drawing. Smoking was prohibited. Also, subjects were asked to report any extra food or medicine taken during the study.

Analysis of plasma lipid

Blood was collected in 0.1% Na_2 EDTA after a 12 hour fast at the end of baseline and the experimental period. FC was analyzed by modified enzymatic method of the total cholesterol procedure[12]. Plasma CE levels were determined by the difference of total and FC. Plasma TG was analyzed by enzymatic procedures using TG-kits from Sigma Chemical Company, St. Louis, MO(#339)[13]. Plasma total HDL-, HDL_3-, and HDL_2 cholesterol were determined by precipitation methods[14] with dextran sulfate-Mg^{++} solution(dextran sulfate of 50,000 molecular : SOCHIBO, Boite Postale No. 18, 78142 Velizy-Villacoublay cedex, France). The cholesterol in the VLDL plus LDL was determined in the 1.063 kg/l infranate fractions by density gradient ultracentrifugation[15] with potassium bromide and the enzymatic method described above. To identify the fractions of VLDL+LDL and HDL after separation, aga-

Table 1. Composition of experimental diet

Variations	Corn oil	Butter
Energy(Kcal)	1900	1900
Carbohydrate(% of Kcal)	45	45
Protein(% of Kcal)	15	15
Fat(% of Kcal)	40	40
Saturated fatty acid	8	21[a)]
Monounsaturated fatty acid	12	12
Polyunsaturated fatty acid	21[b)]	7
P : S ratio	2.5	0.3
Cholesterol(mg)	240	240

a) Myristic acid content in butter diet was 9.2± 0.4% total methyl ester and much higher than in typical American diet.

b) The corn oil included much higher linoleic acid(48.1± 3.4% of total methyl ester) than in a typical American diet.

rose electrophoresis with a Ciba Corning system™(Palo Alto, CA) was used. LDL cholesterol was calculated by Friedewald's equation[16] : LDL cholesterol=total cholesterol−HDL cholesterol −0.2* triglycerides. Plasma total apo A-1 quantification in HDL was by radial immunodiffusion assay(RIA) methods(Tago, Inc. Burlingame, CA). The apo A-I data were adjusted to g in HDL/l plasma from standard unit of mg/dl.

LCAT and CETP activity(umol/l/hr)

[^{3}H] cholesterol esterification(LCAT activity) and transfer(CETP activity) was modified by the method of Stoke and Norum[17] and K.M. Channon[18]. [^{3}H] cholesterol-albumin emulsion solution was prepared before the enzymatic activity assay by mixing the dissolved 20 ul of stock [1a, 2a(n)-]-[^{3}H] Cholesterol(code TRK. 330, Amersham Co., Arlington Heights, IL) into 0.3 ml acetone(1 uCi=2.333×10^6 dpm) and 3 ml of albumin solution(50 mg bovine albumin in 1 ml of Tris buffer : pH 7.4). 500 ul of whole plasma and 50 ul of [^{3}H] cholesterol-albumin(0.3 uCi ; 6.7×10^5 dpm) were mixed with 1 ml Tris buffer(pH 7.4). This mixture was preincubated at ℃ for 1 hr with 200 ul of 10 mmol/l DTNB(5, 5'-dithiobio [2-nitrobenzoic acid]), LCAT inhibitor, to allow equilibrium of [^{3}H] cholesterol with endogenous FC. After preincubation, incubation was performed for 3 hrs with mercaptanol to inhibit DTNB. LCAT reaction can be stopped by putting into the ice. After lipid of plasma should be extracted by Folch method[19] and the radioactivity of FC and CE was fractionated by thin layer chromatography(TLC). Each band of FC and CE were scraped from the TLC plates into 5 ml LS cocktail (Scintiverse BOA, Fisher Co.) and were counted by LS counter. FC(Sigma) and CE(cholesterol oleate : Sigma) were used as standard of TLC. LCAT activity was calculated as a product of fractional esterification rate(FER : %/h) and unesterified cholesterol concentration(umol cholesterol esterified/ml plasma per hr) as follows :

$$LCAT = 1/t \times [FC] \times \frac{dpm\,[CE]}{dpm[FC] + dpm[CE]}$$

where, t=incubation time(3hrs)

[FC]=plasma content of FC at time 0 hr (umol/l)

dpm[FC]=radioactivity of FC in lipid extract

dpm[CE]=radioactivity of CE in lipid extract

CETP activity was determined by precipitation of VLDL and LDL from aliquots of incubated plasma by adding dextran sulfate-1.0 mol/l Mg^{++} solution. After the supernatant containing HDL was removed by centrifugation at 2700 rpm for 30 min at 4℃, 100 ul aliquots were taken for the radioactivity [dpm HDL] in the formula. Lipids were extracted from the precipitate(VLDL plus LDL) by the Folch method, and CE and FC were separated by TLC as describved above. CETP activity(umol CE transferred/l plasma per hr) was calculated by the formula shown below in which the 5.66 was the dilution factor for HDL. CETP activity was also adjusted to constant FC(100 mg/dl plasma) to correct for the fact that FC concentrations different among subjects. The total dpm was adjusted to correction of the 8.5% decomposition of radioactive FC.

$$CETP = 1/t \times [FC] \times \frac{dpm\,[_{pre}CE]}{\text{total dpm}} \times \frac{(\text{total dpm} - 5.66\text{dpm HDL})}{(dpm[_{pre}FC] + dpm[_{pre}CE])}$$

where, t=incubation time(3hrs)

[FC]=adjusted plasma contents of FC at time 0 hr

dpm[$_{pre}$FC]=radioactivity in FC of precipitate
dpm[CE]=radioactivity in CE of precipitate
total dpm=radioactivity in 50 ul aliquot of incubation
dpm HDL=radioactivity in 100 ul supernatant containing HDL(5.66 is a dilution factor)

Data analysis

Since the data from each variable were normally distributed, student's t-test, Pearson's correlation, and stepwise multiple regression, were used. The level of significant probability was set up(a=0.05) before analysis.

Results

Subject information and diet intake

There were no differences in mean age, weight, height and BMI between the two groups during the expermental period. Mean values for the energy expenditure are not different between two groups. The subjects consuming the butter diet showed higher energy intake than those of the corn oil even though the difference was not significant.

The plasma lipids

Major findings for the dietary fat effect on pla-

Table 2. Mean(±SD) values for the plasma lipid profiles in each dietary group

Variables	Corn oil		Butter		P-Value**
	Baseline	End	Baseline	End	(Corn vs butter)
Cholesterol(mmol/l)					
Total	5.3±0.5	4.8±0.5I	3.8±1.1	5.8±0.7*	p=0.0001
Free	2.2±0.3	2.6±0.3*	1.9±0.4	2.1±0.4	p=0.41
Esterified	3.1±0.4	2.3±0.4*	1.9±0.7	3.7±0.7*	p=0.0001
HDL cholesterol(mmol/l)					
Total	1.5±0.2	1.7±0.3	1.7±0.3	1.6±0.3	p=0.005
HDL_3	1.0±0.1	1.2±0.2	1.0±0.1	1.2±0.1*	p=0.89
HDL_2	0.5±0.3	0.5±0.2	0.7±0.4	0.4±0.1	p=0.01
TG & TG-rich lipoproteins cholesterol(mmol/l)					
TG	1.3±0.3	0.9±0.2	1.1±0.4	0.8±0.1	p=0.47
LDL[a)]	3.2±0.4	2.7±0.4	1.7±1.2	3.9±0.7*	p=0.0001
VLDL+LDL[b)]	3.7±0.7	3.7±0.6	3.1±0.6	4.1±1.1*	p=0.028
Apo A-I in HDL(g in HDL/l)					
Apo A-I[c)]	0.9±0.2	0.7±0.3*	0.8±0.1	0.7±0.1	p=0.41

* Student's t-test was used to test significance of changes in all lipid profiles between the beginning and the end of experimental period.

** Student's t-test was used to test significant difference in all lipid profiles between corn oil and butter groups.

a) Calculated by Friedwald's equation

b) Cholesterol was measured in the fraction of VLDL plus LDL obtained by the density gradient ultracentrifugation.

c) Apo A-I was measured in fraction of HDL obtained by density gradient ultracentrifugation.

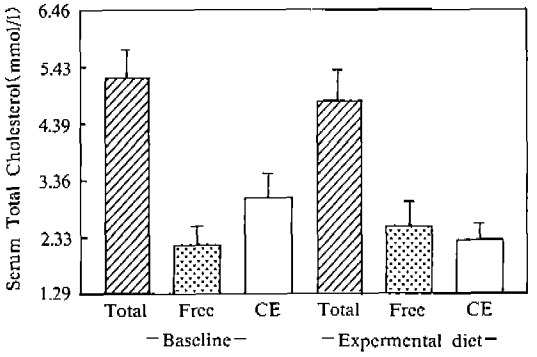

Fig. 1. The effect of corn oil on total-free-and esterified cholesterol during experimental period.

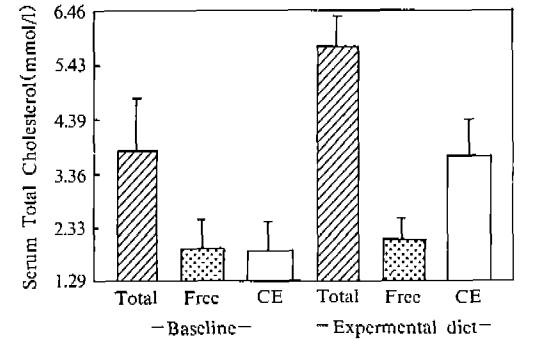

Fig. 2. The effect of the butter fat on total-, free-, and esterified cholesterol during the experimental period.

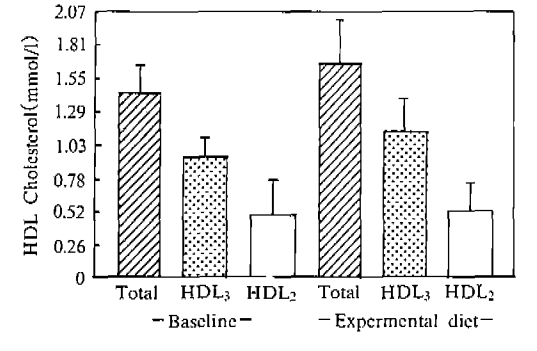

Fig. 3. The effect of corn oil on total HDL-, HDL_3- and HDL_2 cholesterol during experimental period.

sma lipids are shown in Table 2. A high corn oil diet significantly reduced plasma esterified-(25 %, p=0.006 : Fig. 1) and LDL(15.34%, p=0.05)

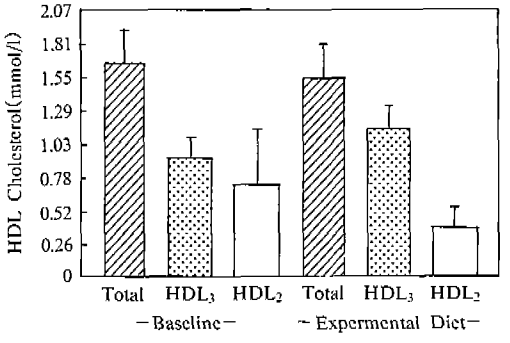

Fig. 4. The effect of butter fat on total HDL-, HDL_3-, HDL_2 cholesterol during experimental period.

cholesterol and TG(26.7%, p=0.05) compared to baseline. However, a high butter feeding significantly increased total-(33.94%, p=0.005) and esterified-(95.7%, p=0.001 : Fig. 2), LDL-(120%, p=0.004) and VLDL plus LDL-(35%, p=0.039) cholesterol during the experimental period. Even though there was no significant significant difference in period effect for two diets, there was a tendency to increase total HDL in corn group, to decrease HDL_2 and to increas HDL_3 in butter group(Fig. 3, 4). There were significant differences($p<0.01$) of dietary fats on total-($p=0.0001$), esterified-($p=0.0001$), total HDL-($p=0.005$), HDL_2-($p=0.01$) and LDL-($p=0.0001$) cholesterol. There were no difference of fats on triglyceride and apo A-I in HDL.

LCAT and CETP activity

LCAT activity did not change in both diets but CETP activity did increase in the butter group ($p=0.01$) during treatment period even though there was no dietary effect(Table 3). There was evidence that butter feeding tended to increase CETP activity more than corn oil feeding. The changes in CETP activity related to changes in plasma VLDL plus LDL cholesterol concentration, which increased in group fed butter. Table 4 showed the correlation(r) between changes in LCAT and CETP activity and changes in lipid

Table 3. Mean(± SD) values(umol/l/hr) for LCAT and CETP activity in each dietary group

Diet	LCAT activity	CETP activity
Beginning		
Corn oil	112.8± 21.0	13.7± 25.5
Butter	80.2± 17.6	41.7± 18.0
End		
Corn oil	135.7± 47.7	44.4± 34.8
Butter	105.2± 63.6	108.2± 41.7
P-value		
Dietary effect[a)]	0.88	0.21
Treatment effect[b)]		
for Corn oil	0.13	0.12
Butter	0.04	0.01*

a) Student t-test was used to test significant difference in LCAT and CETP activity between corn oil and butter groups.
b) Student t-test was used to test changes in LCAT and CETP activity between begining and the end of the period.
* Significant at $p<0.01$.

Table 4. Correlation(r) between changes in LCAT or CETP activity and changes in lipid profiles in plasma

Variables	LCAT activity	CETP activity
Cholesterol		
Total	+0.078	+0.525*
Free	+0.700*	+0.410
Esterified	−0.114	+0.384
HDL cholesterol		
Total	+0.161	−0.404
HDL_2	+0.128	+0.390
HDL_3	−0.053	−0.487*
TG & TG-rich lipoproteins		
TG	+0.435*	+0.102
LDL	−0.003	+0.533*
VLDL+LDL	−0.106	+0.539*

Significant at $p<0.01$.

profiles. LCAT activity was highly correlated with FC and TG($p<0.01$). However, CETP activity was highly and positively correlated with total-, LDL-and VLDL plus LDL cholesterol and negatively correlated with HDL_3 cholesterol($p<0.01$). In multivariate analysis after consideration of all the variables so far discussed the best model explaining variation in LCAT activity(Y) was $Y=0.38+2.61\times(FC)+29.4\times(Apo\ A\text{-}I)$($r=0.45$; $p<0.01$), and in CETP activity(Y) was $Y=11.86+0.94\times(VLDL+LDL)+1.86\times(FC)$($r=0.60$; $p<0.01$). The changes in LCAT activity was associated with higher levels of FC and apo A-I in HDL. Apo A-I was not affected by diet but plasma FC increased in the group fed corn oil. However, LCAT activity was not significantly influenced by corn oil feeding in this study.

Discussion

Recent reports for human studies[20)21)] suggested 37−43 en % fat affected plasma lipids. The effect of 45 en % dietary fat on plasma lipids was expected in this study strongly. A corn oil diet significantly reduced plasma esterified- and LDL cholesterol and TG compared to baseline, but high butter feeding significantly increased total-, esterified-, LDL- and VLDL plus LDL cholesterol during the experimental period. However, the effects of corn oil on the cholesterol of total HDL and HDL fraction are disputed and need reevaluation because many researchers have different results. Grundy et al., report that 10 en % from PUFA can either decrease[22)] or have or have no effect[23)] on plasma HDL cholesterol concentrations. But, in this study, corn oil increased total HDL 16% and HDL_2 7% similar to the finding of others[24)25)] while butter feeding decreased HDL_2 46% and increased HDL_3 23%. There was no significant differences between the effect of corn oil and butter fat on apo A-I similar to others. Therefore, lowering effects of PUFA on HDL should consider the cholesterol distribution between the HDL fractions.

There were no difference between subjects consuming corn oil and butter in LCAT activity al-

though the LCAT activity in both diets was increased above baseline. Changes in LCAT activity were positively correlated with changes in plasma FC($r=0.70$), and TG($r=0.44$) similar to the other [26]. LCAT activity was associated with concentrations of apo A-I in HDL and FC in multiple regression analysis as would be expected. Since Apo A-I was not affected by diet but plasma FC increased in the group fed corn oil, the effect of corn oil on LCAT activity will be expected in long term experiments. The correlation between CETP activity and plasma total cholesterol, TG or TG-rich lipoproteins tended to be positive in this study as similar as others. Changes in the CETP activity were related to changes in VLDL plus LDL cholesterol which increased in the group fed butter. This result was as similar as a preliminary study of 7 weeks of palm kernel/palm oil feeding on LCAT and CETP activities. Palm kernel/palm oil(C12 : 0, C14 : 0, and C16 : 0) feeding increased significantly total-, LDL cholesterol and CETP activity.

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Effects of PUFA on RCT system

= 국문초록 =

고 불포화 지방산 식이가 인체 혈청 Cholesterol의 Esterification과 Transfer에 미치는 영향

이 명 숙

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Lecithin Cholesterol Acyltransferase(LCAT)와 cholesteryl ester transfer protein(CETP)은 간과 간외조직간의 혈청 cholesterol 항상성을 유지하는데 중요한 기전인 reverse cholesterol transport system(RCT)에 매우 중요한 인자들이다. 본 연구의 목적은 RCT 기전의 식이 지질 효과를 추정하여 향 고지혈증 치료식이 연구의 중요한 자료를 제공하는데 있다.

4주의 인체대사 실험에서, 대상자 12명의 여성들은 실험 1주 전에 고 포화지질로써 적응시기를 거친 후, 각각 6명씩 high PUFA(corn oil)군과 high SFA(butter)군에 무작위로 배정되었다. Butter군은 total-(34%), esterified-(96%), HDL_3-(23%), LDL-(20%) 및 VLDL+LDL-(35%) cholesterol을 감소시켰다. Corn oil군은 esterified(25%) 및 LDL-(15%) cholesterol과 triglyceride(27%)를 감소시켰다. Corn oil과 butter fat군간의 식이 효과 차이는 total-($p=0.0001$), esterified-($p=0.0001$), total HDL-($p=0.005$), HDL_2-($p=0.01$) 및 LDL-($p=0.0001$) cholesterol에서 유의적이다. LCAT activity는 두 군에서 변화가 없으나, 4주 후 CETP activity는 butter군에서 2.5배 증가하였다. 이는 VLDL+LDL cholesterol 농도가 butter군에서 증가한 결과와 일치한다. LCAT activity는 corn oil 군에서 증가된 HDL의 apo A-I 농도와 free cholesterol과 정의 상관관계가 높은 반면, CETP activity는 total cholesterol과 LDL 및 VLDL+LDL cholesterol과 정의 상관관계가 높았다.