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Relationship between Changes in Plasma Lipoprotein Concentrations and Fecal Steroid Excretion in Man during Consumption of Four Experimental Diets

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Summary

Limited information is available on the mechanism by which changes in nutrient intake influence plasma lipids. We compared the effects on plasma lipoprotein levels of 3 dietary modifications involving changes in total fat intake (27–40% of calories), cholesterol intake (100–250 mg/1000 kcal), the dietary polyunsaturated to saturated fatty acid ratio (0.3–1.0) and intake of vegetable-derived fiber and protein. On these 3 diets, plasma low density lipoprotein was reduced by 26–34%. Fecal bile acid excretion was similar on all diets (363–379 mg/day). There was no alteration in fecal bile acid output associated with an increase in polyunsaturated or total fat intake. Sterol balance became significantly more negative during consumption of only 1 of the 3 cholesterol-lowering diets. The observed reduction in plasma cholesterol levels was not associated with an increase in fecal bile acid output suggesting that diet-induced changes in circulating cholesterol are not maintained by

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an increase in sterol turnover but may reflect alterations in hepatic cholesterol and lipoprotein synthesis.

Key words: *Bile acids – Cholesterol – Dietary fat – Dietary fiber – Fecal steroids – Lipoproteins*

Introduction

Dietary modification of the lipoprotein-mediated risk factors for atherosclerotic heart disease (AHD) is widely advocated as a desirable public health goal and is extensively used in clinical practice [1]. Recommended diets have comprised, in varying proportion, reduction in fat intake, substitution of polyunsaturated for saturated fats and increased fiber content. The effect of such dietary changes on fecal bile acid output and concentration is of interest since it has been suggested that the hypocholesterolemic effect of polyunsaturated fatty acids is in part mediated by an increase in bile acid excretion. More recently, fecal bile acid concentration has been implicated as a risk factor for colonic neoplasms. In one carefully controlled study, fecal bile acid output was found to be less during consumption of a low fat diet than when fat intake provided 42% of energy [2]. When polyunsaturated fats were substituted for saturated fats, the reduction in plasma cholesterol level was accompanied in several short-term experiments [3–7] by an increase in fecal bile acid output; such an effect was not confirmed in other dietary studies [8–14].

With a view to identifying patterns of nutrient intake of high effectiveness in reducing plasma cholesterol, we have examined the individual and additive effects of alterations in dietary fatty acid, sterol and fiber intake on plasma lipoprotein levels and sterol balance in normal men. Three dietary modifications were studied; these included changes in total fat and cholesterol intake, dietary polyunsaturated to saturated (P : S) fatty acid ratio and intake of vegetable-derived fiber and protein. During consumption of one such diet, plasma low density lipoprotein (LDL) cholesterol was reduced by 34% [15]. In the present communication, we describe the effects of these dietary changes on fecal steroid excretion and composition and the relationship of such effects to changes in plasma lipoprotein levels in normolipidemic men.

Methods

The study population consisted of 12 monks aged 24–60 years (mean 45.1 years), residents of the Maria Toevlucht Abbey in The Netherlands. Their relative body weights ranged from 0.79–1.19 (mean 0.98). All were in good health as determined by baseline medical and biochemical examination. Habitual work and exercise patterns were maintained throughout the study and no serious or prolonged intercurrent illness occurred. The 12 participants were selected from a larger number of

volunteers on the basis of having the highest blood cholesterol levels (190–300 mg/dl), normal triglyceride levels and negligible alcohol intake.

Four diets were designed providing the nutrient intakes shown in Table 1. Normally available foods were purchased in case lots where practicable. Nutrients were calculated using a computer data bank and duplicate portions of the diets were analysed at the University of Wageningen to verify their conformity with calculated intakes. Diets were prepared and weighed by trained dietitians. All subjects maintained body weight within 1.5 kg except for the first 2 weeks of the initial dietary period when most subjects on all 4 diets lost 1–2 kg. Portion sizes were individually adjusted to conform with estimates of energy requirements and subjects were allowed ad libitum access to a gruel of appropriate composition to ensure that energy balance was maintained. Mean energy intake was 2 937 kcal/day. Diet A, the reference diet, approximated to a typical Western diet, providing 40% energy as fat, P : S ratio of 0.27 and 617 mg cholesterol/2 500 kcal. This diet contained white bread, potatoes, rice, sugar, legumes, eggs, cheese, butter, cream and whole milk with moderate amounts of vegetables, fruit and oil. Diet B represented a low-fat 'prudent diet' with 27% energy as fat, P : S ratio of 1.0 and 245 mg cholesterol/2 500 kcal. This was accomplished by replacing part of the fat in diet A with bread and potatoes and substituting low fat milk for whole milk and 60% linoleic acid margarine for butter. Egg consumption was also reduced. Diet C was similar in fatty acid and sterol composition to diet B but provided 2–3 times more dietary fiber; one-half instead of one-third of the protein was of vegetable origin. This diet contained whole wheat bread, rolled oats and increased amounts of raw and cooked vegetables, legumes and fruit. Brown beans (*Phaseolis vulgaris*) were a major source of vegetable protein in this diet. Diet D resembled diet C in terms of fiber and protein composition and P : S ratio (1.0), but total fat intake was not restricted (40% of energy intake). Like C, this diet contained large amounts of fruit and vegetables but less bread and potatoes and more margarine and oil. All diets contained identical amounts of mono- and disaccharides (Table 1).

Each diet was consumed for a 5-week period. Every participant consumed all 4 experimental diets; the subjects were divided into 4 groups of 3, each group receiving

TABLE 1

NUTRIENT COMPOSITION OF THE TEST DIETS

	Diets			
	A	B	C	D
Fat (% of energy)	40	27	27	40
Linoleic acid (% of energy)	4.6	8.1	8.4	12.4
Polyunsaturates (% of energy)	5.2	8.5	8.7	12.8
P : S ratio	0.27	1.01	1.00	1.01
Protein	14	14	14	14
Vegetable protein (% of protein)	34	34	52	49
Cholesterol (mg/2500 kcal)	617	245	252	245
Dietary fiber (g/2500 kcal)	19	20	55	53

1 of the 4 diets in turn in a Latin Square design in the sequence ABCD, BCDA, CDAB or DABC. The data of the Latin Square were analyzed by regression techniques to perform the analysis of variance with the computer package GLIM.

Blood samples were drawn weekly and lipoprotein analyses performed as described [16]. Since blood lipids reached a plateau by the end of week 3, values from weeks 3–5 were treated as within-subject replicates.

Feces were quantitatively collected for 5 days at the end of each 5-week study period. Fecal flow was adjusted by use of a marker. Radio-opaque polyethylene rings were ingested 3 times/day for 7 days prior to the fecal collection period and throughout the 5 days of fecal collection. Samples were pooled, homogenized, X-rayed to determine marker recovery and an aliquot freeze-dried and ground for steroid analyses.

Fecal bile acids were analysed by gas liquid chromatography (GLC) as their methyl-acetate derivative after alkaline extraction [17], enzymatic deconjugation and solvolysis [18] as described previously. Fecal neutral steroids were measured by GLC as their trimethylsilyl derivatives after thin-layer chromatographic separation of 3 major fractions as described by Miettinen et al. [19]. Recovery of cholesterol, coprostanol, lithocholate and deoxycholate was greater than 85%. The coefficient of variation for duplicate analyses was $\pm 5\%$. All samples were analyzed in duplicate.

Results

Fecal bile acid excretion

Fecal excretion of bile acids and neutral steroids is shown in Table 2. The major bile acids identified in the stool samples were lithocholic acid, 7-ketolithocholic acid, deoxycholic acid, 12-ketolithocholic acid, cholic acid, 3-ketocholic acid and chenodeoxycholic acid. Total fecal bile acid excretion was closely similar during the 5th week of ingestion of all 4 diets. The high polyunsaturated fat diet (D) resulted in a trend towards an increase in the relative proportion of chenodeoxycholate-derived bile acids excreted. There was no difference in the relative proportion of primary and secondary bile acids.

Fecal bile acid concentration expressed per gram of dry stool was similar during consumption of both low fiber diets ($A = 11.1 \pm 0.8$ mg/g, $B = 11.8 \pm 0.9$ mg/g) and was significantly lower during both high fiber diet periods ($C = 7.0 \pm 0.5$ mg/g and $D = 5.9 \pm 0.5$ mg/g) ($P < 0.01$ and $P < 0.01$, respectively, compared with A).

Fecal neutral steroid excretion

Total fecal output of cholesterol and its bacterially modified metabolites reflected the dietary intake of cholesterol and was significantly lower during consumption of diets B, C and D compared with the reference diet, A, which provided more than twice as great an intake of cholesterol. There was no difference in the proportions of cholesterol, coprostanol and coprostanone during any of the diet periods.

Total fecal steroid output and cholesterol balance

The output of cholesterol-derived neutral steroids plus acidic sterols was signifi-

cantly lower during consumption of diet B compared with the reference diet, A. Total steroid excretion during diets C and D was slightly and not significantly lower.

Cholesterol balance (defined as the difference between cholesterol intake [by dietary analysis] and total cholesterol-derived neutral and acidic sterol output) was negative during consumption of all 4 diets. Only during consumption of diet C did cholesterol balance become significantly more negative compared with the reference diet, A.

Relationship between plasma lipoprotein changes and fecal steroid excretion

Plasma lipoprotein concentrations after 5 weeks on each diet are shown in Table 2. Relative to diet A total cholesterol levels were 22%, 29% and 25% lower during consumption of diets B, C and D, respectively. Most of the decrease in plasma cholesterol ascribed to the test diets was accounted for by a decrease in LDL cholesterol. HDL cholesterol decreased slightly during diet periods B and C but was not altered by diet D [15].

There was no significant relationship between the observed changes in plasma total cholesterol concentrations and changes in fecal bile acid or neutral steroid output as observed during the 5th week of each dietary period. Similarly there was not a significant correlation between baseline plasma cholesterol levels (on diet A) and fecal bile acid output.

TABLE 2

FECAL STEROID EXCRETION AND PLASMA CHOLESTEROL LEVELS

n = 12, mean ± SE.

	Diets			
	A	B	C	D
Fecal bile acid output (mg/dl)				
Cholic acid and derivatives	197 ± 26	192 ±30	191 ± 29	163 ± 36
Cheno acid and derivatives	182 ± 25	182 ±19	176 ± 24	200 ± 27
Total	379 ± 45	374 ±45	366 ± 46	363 ± 49
Fecal neutral steroid output (mg/dl)				
Cholesterol	208 ± 90	130 ±46	124 ± 45	166 ± 64
Coprostanol and coprostanone	546 ±115	334 ±50 *	527 ± 76	464 ±107
Total	754 ±101	464 ±45 *	651 ± 81 *	630 ± 96 *
Total fecal steroid output (mg/dl)	1133 ±120	838 ±79 *	1017 ±105	993 ±134
Cholesterol intake (mg/dl)	676 ± 51	267 ±21	257 ± 18	315 ± 28
Cholesterol balance (mg/dl)	−457 ±100	−573 ±65	−776 ± 89 *	−678 ±123
Plasma cholesterol (mg/dl)	247 ± 10	195 ± 8 *	175 ± 7 *	186 ± 7 *
LDL cholesterol (mg/dl)	178 ± 11	131 ± 9	117 ± 7 *	122 ± 7 *
HDL cholesterol (mg/dl)	55.0± 3.1	48.4± 2.3 *	49.2± 2.3 *	52.2± 2.7
HDL_2 cholesterol (mg/dl)	10.1± 1.6	6.6± 0.7 *	8.9± 1.0	7.7± 1.1 *

* Significantly different from control diet A, $P < 0.05$.

Discussion

Since fecal steroid measurements were made during the 5th week of each dietary period and body weight and plasma lipid levels were stable from the 3rd to the 5th week of each experiment, it is likely that these observations represent steady-state conditions. The present study therefore indicates that the reduction in plasma cholesterol induced by diets B, C and D was not maintained by increased conversion of plasma cholesterol to bile acids.

Cummings et al. [2] reported that when dietary fat intake was increased from 21–42% of calories, fecal bile acid output rose from 140–320 mg/day. In the present study, a smaller change in fat intake was made and it was accompanied by altered fatty acid composition and altered cholesterol intake. Although on both high- and low-fat diets, our subjects demonstrated higher bile acid output than that reported in Cummings' study, we were unable to demonstrate any relationship between this dietary fat modification (i.e. diet A vs diet B) and bile acid excretion. Furthermore, diets C and D were similar in all respects except for the level of fat (27% and 40% of energy, respectively) and bile acid outputs were identical. Since the condition of our experiments differed, direct comparison with the study of Cummings et al. is not possible; our investigation was designed to identify combinations of changes in nutrient intake that would lead to maximum reduction in low density lipoprotein cholesterol levels by additive or synergistic effects, rather than to study effects of single dietary substitutions. However, the results of other studies in which individuals were fed solid food diets agree with our results. Thus, Whyte et al. [8] found no increase in acidic sterol output when sucrose was replaced by safflower oil. Anderson and Hellström [20] reported that bile acid synthesis was decreased rather than increased when dietary cabohydrate was replaced by fat. Lindstedt et al. [13] did not find a consistent increase in cholic acid turnover when dietary fat was increased from 35–60% of calories. More recently Brussard et al. [14] reported no difference in fecal bile acid excretion in subjects on diets containing 22% or 40% fat calories. Thus, in individuals consuming solid food diets, moderate changes in the intake of dietary fat do not appear consistently to alter the level of bile acid excretion.

In the present study the P : S ratio of diets fed varied from 0.4–1.0. Bile acid excretion was similar on diets A (high fat, saturated) and D (high fat, polyunsaturated). Diet D also differed from diet A being higher in fiber and lower in sterol. We have not therefore tested the effect of substitution of polyunsaturated fatty acids for saturated fatty acids in a single intervention on bile acid output.

The hypothesis that polyunsaturated dietary fat increases the conversion of cholesterol to bile acids has been tested in previous studies. Fecal bile acid excretion, biliary secretion of bile acid, and bile acid turnover have been studied by a variety of techniques, in man and in the rat, rabbit and monkey. The first reports indicated that isocaloric replacement of saturated fat by polyunsaturated fat led to increased bile acid output, sufficient in magnitude to explain the fall in serum cholesterol concentration [3–7]; simple titrimetric and colorimetric methods were employed, probably lacking adequate specificity. Experiments were often of short duration suggesting that steady-state conditions of bile acid turnover may not have been

achieved at the time of sterol measurements [8]. Subsequently, Grundy and Ahrens [11] and other investigators using more refined methodology (labelled sterol balance and gas-chromatographic quantitation of fecal sterols) failed to confirm these findings. Brussard et al. [14] also reported that fecal bile acid excretion was similar when the dietary P : S ratio was varied from 0.2–1.7. Several recent studies indicate an increase in acidic sterol output during initiation of a high P : S diet [21–24]. Our unpublished kinetic studies suggest that 24% of LDL is extravascular; hence the effective volume of distribution would be 0.056 of body weight. Assuming no net flux of cholesterol into tissue pools, the mean decrease in plasma LDL cholesterol noted on diet C represents for each of our subjects a loss of body cholesterol of 2 000–2 500 mg. This would support previous observations that steroid excretion may increase transiently during the period when plasma cholesterol levels are decreasing. We did not measure bile acid output during the phase when plasma cholesterol levels were actively falling. However, from the present data there is no evidence that such a change in steroid excretion is maintained once steady-state conditions exist.

Diet C differed from diet B only in the content of dietary fiber and vegetable derived protein. These changes also failed to alter bile acid excretion in spite of an additional 20 mg/dl decrease in plasma cholesterol. Although selected fiber sources such as pectin [25] were reported to increase acidic sterol output, bran [26] and other mixed sources of fiber fed at moderate levels of intake as in this experiment did not [27,28].

As expected, dietary fiber significantly reduced the concentration of bile acids in the stool; since it has been hypothesized that high fecal bile acid concentration is a promotor of colonic carcinoma [29] this effect of diets C and D may be potentially advantageous.

The fecal output of cholesterol and its bacterial degradation products reflected the dietary intake of cholesterol and was significantly reduced in all the test diets relative to diet A. We did not differentiate between the contribution of endogenous and exogenous cholesterol to fecal neutral steroid. The bacterial degradation of cholesterol was similar on all diets. It is well known that dietary cholesterol is the major factor affecting neutral steroid output. Nestel and Poyser [30] also demonstrated that neutral steroid excretion is reduced when dietary cholesterol is decreased.

In calculating cholesterol balance (input–output) steady-state conditions in terms of body weight, serum lipids and steroid excretion must be present. The first 2 conditions were demonstrably met. Lin and Connor [31] demonstrated that steroid excretion became constant after 4 weeks of dietary change. Since our measurements were made in the 5th week of each experiment, we assume that they too reflect the steady state. There was a trend for cholesterol balance to become more negative on all the test diets, particularly on diet C and the changes reached statistical significance only on diet C. Presumably this represents the interactive effects of an increase in dietary fiber and P : S ratio and a decrease in dietary SFA and cholesterol. However, there was a substantial reduction of plasma cholesterol during consumption of diets B and D without major or significant increases in negativity of steroid

balance, hence our data do not lend support to the concept that changes in plasma cholesterol are the result of altered external steroid balance. Lin and Connor [31] previously reported that cholesterol balance became more negative on low cholesterol diets. The total excretion of cholesterol-derived fecal steroids was significantly decreased relative to the control diet A only by diet B (low fat, increased P : S ratio, low fiber).

The present study has demonstrated that by making multiple changes in the intake and composition of dietary fat, cholesterol, protein and fiber, it is possible to achieve remarkable reductions in LDL cholesterol (27–35%). There is no evidence that the observed changes in circulating cholesterol concentrations are in any way mediated by an increase in bile acid turnover. However since we modified more than one variable at once (e.g. fatty acid and sterol intake) we cannot draw conclusions about the mechanism of action of individual dietary constituents on plasma lipoprotein levels. The effects of intake and composition of dietary fats on low density lipoprotein kinetics have been the subject of a recent study [32]. Changes in low density lipoprotein apo B synthesis largely determined the concentrations of the lipoprotein; altered fractional catabolism may have contributed to the effect of altering intake of fat. It is possible that these dietary-induced changes may primarily be mediated by altered hepatic synthesis and catabolism of lipoproteins and that changes in external steroid balance (which may be transient) are secondary to these effects.

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