Published in final edited form as:

J Pediatr. 2009 April ; 154(4): 557–561.e1. doi:10.1016/j.jpeds.2008.10.045.

Plasma Plant Sterols Do Not Reflect Cholesterol Absorption in Smith-Lemli-Opitz Syndrome Children

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Abstract

Objective—In adults, the ratio of plant sterols to cholesterol in plasma correlates with dietary cholesterol absorption. We hypothesized that this correlation could be validated in children with Smith Lemli-Opitz syndrome (SLOS), a cholesterol synthesis disorder.

Study design—We obtained measurements of cholesterol absorption by a direct radioisotope cholesterol absorption method during 9 SLOS subject visits. We measured plasma sterols in 22 SLOS subjects and 16 controls, as well as dietary intake of cholesterol and sitosterol (n=11 SLOS).

Results—The correlations of 2 plasma plant sterol ratios (sitosterol/cholesterol and campesterol/cholesterol) with direct cholesterol absorption measurement were poor ($R = -0.33$ and $R = -0.25$, respectively), significantly lower than the published correlation in adults ($R = +0.73$) ($P < 0.02$).

Conclusions—Although the ratios of plant sterols to cholesterol in plasma has been used as a surrogate for cholesterol absorption in adults and children, these ratios may not accurately reflect cholesterol absorption in children with SLOS. These ratios should not be used as a surrogate for cholesterol absorption in children without further validation.

Keywords

sitosterol; phytosterols; gas chromatography; dietary cholesterol; dietary phytosterols; plant sterols; clinical study; children

INTRODUCTION

The Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive condition with multiple malformations and mental retardation (OMIM# 270400) caused by mutations in the gene (*DHCR7*) encoding the final enzyme in the cholesterol biosynthetic pathway, 7-dehydrocholesterol Δ^7 -reductase (*DHCR7*; E.C. 1.3.1.21)(1). This enzyme defect results in low concentrations of cholesterol in plasma and tissues and high concentrations of the

precursors: 7-dehydrocholesterol and its derivative 8-dehydrocholesterol. These abnormal concentrations likely contribute to the clinical features. Even though hypercholesterolemia is a well-known risk factor for cardiovascular disease, it is important to remember that cholesterol is essential for normal development and function. For example, cholesterol is a necessary component of cell membranes, a substrate for bile acids and steroid hormones, a signal for synaptogenesis (2), a major component of myelin, and a necessary component for the activation of sonic hedgehog proteins (3).

Monitoring the absorption of dietary cholesterol is important in SLOS, because dietary cholesterol is widely used as a potential treatment. The absorption of dietary cholesterol in children with SLOS has been demonstrated indirectly by the increase in plasma cholesterol after cholesterol consumption (4–8). In addition, we recently directly measured cholesterol absorption in children with SLOS (9). Due to the risk of radiation exposure, this method is used only twice in the SLOS children and not at all in controls in our studies, limiting the utility of this method in testing potential treatments. A stable isotope method using ^{13}C -cholesterol administered orally and D_7 -cholesterol administered intravenously has been reported in children to measure cholesterol absorption (10). The stable isotopes, however, are expensive and the instrumentation needed for isotope ratio mass spectrometric analysis is not widely available. Furthermore, because the measurements can only be done invasively with an intravenous catheter and multiple blood samples, this technique is limited to older, larger children. A simpler and lower risk method available to children of all ages is needed in the study of SLOS as well as other conditions affecting cholesterol metabolism.

A correlation between the ratios of plant sterols to cholesterol in plasma (μmol plant sterols/ mmol cholesterol) and direct measure of cholesterol absorption has been described for adults (11–13). There are no published data showing a similar correlation in children. If the correlation between the ratios of plant sterols to cholesterol in plasma and cholesterol absorption were validated in SLOS children, then this method could allow for simple, relatively non-invasive monitoring of dietary cholesterol absorption. We obtained measurements of cholesterol absorption by a direct radioisotope cholesterol absorption method during 9 SLOS subject visits. We also measured the ratios of plant sterols to cholesterol in plasma (μg sitosterol/ mg cholesterol and μg campesterol/ mg cholesterol) to determine if these ratios correlated with the direct cholesterol absorption measurement.

METHODS

Subjects

Twenty-two subjects with SLOS were enrolled in this study, 2 of whom were siblings. Nineteen were admitted to the Oregon Health & Science University (OHSU) General Clinical Research Center (GCRC) for 1-wk visits as part of our ongoing research. In 3 of the 22 subjects, we measured the plasma sterols in blood samples that had been shipped to us between visits. Prior to visits of 5 of the children the parents were instructed to feed their child an essentially cholesterol-free diet at home for 2–3 weeks before the admission; the dietary cholesterol intake ranged from 1.9 to 4.3 mg/kg/d. Thirteen children received a high cholesterol diet usually with added egg yolk; the cholesterol content ranged from 14.2 to 50.0 mg/kg/d. Four children received a high cholesterol diet with simvastatin. Due to the common finding of feeding difficulties in SLOS, 8 of the children were fed via gastrostomy-tube. Sixteen control children were enrolled for blood samples; 4 were siblings of the SLOS children and 12 were patients who required a blood draw for other reasons. The OHSU Institutional Review Board approved these studies and written informed consent was obtained.

Plasma Sterol Analysis

Plasma samples were saponified and extracted into hexane by the same procedures described previously (7, 14). Concentrations of the trimethylsilyl ether derivatives of individual plasma sterols were measured by capillary-column gas chromatography (GC) with a CP-Wax 57 column (25M, 0.32mmID; Chrompack-Varian, Walnut Creek CA). Internal standard (5 α -cholestane) and authentic standard of cholesterol were used for calibration. The most abundant plant sterols in plasma are campesterol and sitosterol. Because 7-dehydrocholesterol and campesterol co-elute on GC, campesterol was measured by gas chromatography-mass spectrometry (GCMS) as described earlier (15). Because plasma sitosterol and campesterol are transported with cholesterol in lipoproteins, the absolute concentrations of sitosterol and campesterol ($\mu\text{g/dL}$) were adjusted for concentration of cholesterol (mg/dL) (analyzed simultaneously from the same sample) and are expressed as a ratio: plasma plant sterol/cholesterol ($\mu\text{g plant sterol /mg of cholesterol}$).

Food Analysis

During each 1-week visit, all food given to subjects was weighed before and after consumption, and exact amounts of food consumed were calculated by GCRC bionutrition staff. The study dietitian calculated the cholesterol content of the food consumed during each visit using the program Food Processor (ESHA Research, Salem, OR). Additionally, a composite, made up of 10% of the total gram weight of food consumed, was blended and an aliquot was analyzed for cholesterol content by GC. Cholesterol measured in food aliquots was highly correlated with the cholesterol calculated from weighed samples ($\text{mg cholesterol/g food}$) ($R=0.989$). Because the database of plant sterol composition of foods is less comprehensive than that of cholesterol, the 3 predominant dietary plant sterols (sitosterol, campesterol and stigmasterol) were not calculated by the study dietitian and were only measured in the food aliquot by GC. Sitosterol represented $70 \pm 5\%$ of the total plant sterols, and there was a close correlation of sitosterol with total plant sterols ($R=0.99$) indicating that sitosterol, the most abundant plant sterol in the diet, is proportional to the total plant sterols consumed.

Cholesterol absorption

Direct measurement of dietary cholesterol absorption was obtained by fecal dual isotope ratio method during 9 SLOS subject visits (one child was evaluated twice during separate admissions). The concentrations of plasma plant sterols and cholesterol were available for each visit. This method was described previously (9). The dosing plan was reviewed and approved by the OHSU Radiation Safety Committee. In brief, a radioactive test meal was provided with an age based dose of the radioisotopes 4- ^{14}C cholesterol and 5,6- ^3H sitostanol, and carrier cholesterol (0.4mg) in canola oil mixed with cholesterol from egg yolk ($14.5 \pm 1.0\text{mg/kg}$). This cholesterol mix was added to appropriate food or formula and administered to the child. The same dietary protocols were used for children who were gastrostomy-tube fed or orally fed. Radioactivity of blood samples obtained at 24 and 48 h after the meal verified the absorption of the ^{14}C -cholesterol. Stools collected over the 4 to 6 days following the meal were pooled, homogenized with equal amounts of water, and frozen until analyzed. The radioactivity of an aliquot of the stool (0.5 to 1.0g) was determined according to the method described previously (9, 14). Although 13 cholesterol absorption tests were initially completed, 4 were excluded due to low recovery in the stools of the radioactive sitostanol which is unabsorbed by the digestive tract. This suggests incomplete collection of the stools during the visit.

Statistical analysis

Data are expressed as mean $\pm$ SD. Correlations of the ratios of plant sterols to cholesterol with directly measured cholesterol absorption in children were determined by linear mixed modeling that accounted for the correlation within sibling groups and were compared to published correlations in adults with normal cholesterol. A T-test was used to compare concentrations of sitosterol in plasma.

RESULTS

Cholesterol absorption

Nine cholesterol absorption test results are reported in Figure 1. None of these were reported in our previous study (9). The mean plasma cholesterol specific activity (dpm/mg cholesterol) for 24 and 48 h after the test meal was similar to values reported earlier (Table 1)(9). ^3H -sitostanol was not detected in any of the plasma samples. In subject 1, ^{14}C -cholesterol was not detected in the usual plasma sample volume of 0.2ml probably due to the very low concentration of cholesterol and an inadequate blood sample from the infant. There was a negative correlation between the ratio of sitosterol to cholesterol in plasma and direct measure of cholesterol absorption ($R = -0.33$) (Figure 1)(Table 3; online). Although the number of test results is small, this correlation was significantly lower ($p < 0.02$) than the correlation of 0.73 that has been published for adults (11). The correlation of the ratio of campesterol to cholesterol in plasma with cholesterol absorption ($R = -0.25$) was also significantly lower ($p < 0.01$) than 0.73.

Plasma sitosterol concentrations in SLOS and controls

To determine if the lack of correlation was due to differences in the ratios of plant sterols to cholesterol in plasma in children with SLOS compared to controls, plasma sitosterol and cholesterol concentrations were measured in 22 SLOS children and 16 controls having a similar age range. (Table 2). The mean plasma sitosterol concentration of the SLOS children was significantly lower than controls ($P < 0.001$). Values in the literature of sitosterol concentrations for children are similar to ours, ranging from 187 to 289 $\mu\text{g/dL}$ (16–19). The ratios of sitosterol to cholesterol in the children with SLOS were higher (but not significantly higher) than the ratios in control children. These ratios are similar to those in the literature ranging from 1.23 to 2.17 for children (19–22) and 1.04 to 1.70 for adults (23–26).

Dietary cholesterol, sitosterol or fat intake and plasma sitosterol

During 11 of the 1-week visits we measured dietary consumption of cholesterol, sitosterol, campesterol, stigmasterol, and fat. Due to study protocol, dietary cholesterol had a wide range: some children were fed an essentially cholesterol free diet and others were fed a high cholesterol diet. There was also a wide range of the consumption of dietary sitosterol (0.1 to 6.3 mg/kg/d). All children had an adequate consumption of dietary fat: the percent of total kilocalories from fat ranged from 24 to 48. There were no strong correlations among any of these dietary components with ratios of sitosterol to cholesterol in plasma (Figure 2). Due to the small sample size, however, we are unable to rule out possible weak correlations between diet and plant sterol concentrations.

DISCUSSION

Determination of cholesterol absorption in relation to whole body cholesterol metabolism is of interest in both clinical and fundamental respects, especially in children with SLOS. Methods developed to directly measure cholesterol absorption use radioisotopes (27) or stable isotopes (28). Due to the limitations and risks of these methods, we evaluated the

correlation between the ratios of plant sterols to cholesterol in plasma (used as a surrogate for cholesterol absorption in adults) and directly measured cholesterol absorption to determine whether if this ratio would be a reliable surrogate for cholesterol absorption in children with SLOS. We did not find a strong correlation between the ratios of plant sterols to cholesterol in plasma and directly measured cholesterol absorption in children with SLOS.

Four of the 22 children in our study were administered statins with a high cholesterol diet as a potential treatment. There are conflicting data in the literature regarding the effect of statins on the absorption of dietary cholesterol (29, 30). There were no significant differences of concentration or ratio of sitosterol to cholesterol in this small subgroup. It may be prudent, however, to monitor dietary cholesterol absorption in the children with SLOS provided with high cholesterol diets and statins in research trials.

Dietary plant sterols have been shown to affect the absorption of cholesterol (31–33) and the plasma concentration of plant sterols(19). In addition, low amount of dietary fat could potentially limit fat and sterol absorption by limiting bile acid secretion. Despite the wide range of dietary cholesterol and of dietary plant sterol intake there appears to be no strong effect of these dietary components on the ratios of plasma sitosterol to cholesterol in plasma. We also considered the possibility that a low rate of bile acid synthesis in SLOS might account for the lack of correlation. In an earlier report, we quantified bile acid synthesis by the sterol balance method in SLOS and control children on a very low cholesterol diet (14) and found no significant difference in total bile acid synthesis. Another possible reason for lack of a correlation could be inaccurate cholesterol absorption determination. This seems highly unlikely since the mean fractional cholesterol absorption of the 9 test meals ($36 \pm 10\%$) was similar to our previously reported values ($27 \pm 7\%$). These percents are lower than those reported for adults, $43.7 \pm 8.4\%$ (34), there are no data, however, of direct measure of cholesterol absorption in healthy children that could be used for comparison. Furthermore, our approach to ensuring adequate collections and our internal controls (see methods) makes it highly likely that the direct cholesterol absorption measures were accurate. Perhaps the lack of correlation is specific to SLOS. The depressed cholesterol synthesis in SLOS may have a unique effect on the intestinal mucosa cells that alters the absorption and processing of sterols.

Several authors have reported ratios of plant sterol to cholesterol in children as a surrogate for cholesterol absorption based on studies in adults (20–22, 35, 36). Our results call into question this assumption. This surrogate may be found to be valid in normal control children, but not in SLOS; we cannot determine the validity in normal healthy children in the present study, as we could not measure cholesterol absorption directly in that group. Unless a correlation of the ratio of plant sterols to cholesterol in plasma with cholesterol absorption is demonstrated in children, reports using the plant sterol ratios as a surrogate for cholesterol absorption in children should be interpreted with caution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the OHSU General Clinical Research Center staff: particularly Martha McMurry and Dr. Dawn Peters (statistician) and Jean O'Malley (statistician). We thank all health care providers who assisted in the care of these patients and for subject referrals to us. Dr. Melanie Gillingham provided control samples, and Dr. Jean-Baptiste Roulet provided guidance and useful discussion. We especially appreciate the willingness of the children and families to participate in the study.

Source of funding: National Heart, Lung, and Blood Institute (RO1 HL-073980), the General Clinical Research Center Grant (MO1 RR-000334), and the Oregon Clinical and Translational Research Institute, Grant (UL1 RR024140) from the National Center for Research Resources, a component of the National Institutes of Health (NIH,) and NIH Roadmap for Medical Research.

ABBREVIATIONS

SLOS	Smith Lemli-Opitz syndrome
GC	gas chromatography
GCMS	gas chromatography mass spectrometry
OHSU	Oregon Health & Science University

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Figure 1.

The correlation coefficients of ratios of sitosterol to cholesterol in plasma (filled diamonds) ($R = -0.33$) and the ratios of campesterol to cholesterol in plasma (open circles) ($R = -0.25$) (μg plant sterol/mg cholesterol) with the fractional cholesterol absorption (percentage of the amount given) were poor. These were significantly lower than similar correlations in adults $R = +0.73$, (11).

Figure 2.

Correlations between each dietary component and the ratio of sitosterol to cholesterol were low:cholesterol intake (Panel A, mg/kg/d, filled diamonds) $R=0.10$; dietary sitosterol intake (Panel B, mg/kg/d, open circles) $R=0.19$; and dietary fat intake (Panel C, % of total calories, filled squares) $R=0.40$.

Table 1
Radioactive test meal and specific activity of plasma cholesterol in the direct measure of cholesterol absorption.

subject	age yr	wt kg	Cholesterol in test meal mg	μCi	Plasma cholesterol*	
					24 hr dpm/mg	48 hr dpm/mg
1	0.4	4.3	60	1.11	ND [†]	ND [†]
2	0.5	5.5	81	1.21	421	389
3	1	6.4	83	1.16	167	193
5a	1.9	9.7	135	1.22	300	379
5b	2.4	10.3	142	1.22	332	288
6	2.9	13.7	212	2.27	281	290
7	3.1	10.9	154	3.6	446	450
16	9.3	20	312	3.66	301	459
17	10.2	20.5	324	3.7	256	361
mean					313	351
SD					89.1	89.7

* specific activity as dpm of ^{14}C cholesterol/mg cholesterol

[†] ND not detected