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8-2012

Hypercholesterolemia and dietary stanols and/or sterols: Summary

Children's Mercy Kansas City

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Office of Evidence Based Practice – Dietary Stanols and Sterols Specific Care Question

Specific Care Question:

What is the efficacy of treating a child with hypercholesterolemia with dietary stanols and/ or dietary sterols?

Team Members:

Team Leaders: Tracy Kelly, MS, RD; Stephanie Jones, MS, RD; Karen Stephens MS, RD

Evidence Based Scholars: Carlson, E.; Gutierrez, C. L.; & Pirvu, D. S.

Office of EBP: Allen, N. H.

Significance and importance of the question:

Plant sterols and stanols have been shown to reduce serum cholesterol and LDL cholesterol in adults. Theoretically they are an attractive option for either primary or complementary therapy for children with familial hypercholesterolemia, but research in children has not shown the effect as clearly. There are many over the counter supplements that contain sterols and stanols. As a food supplement the amount of sterol available from the supplements is variable and is not regulated. The cost of the products and the caloric burden of the products to obtain the treatment effect are important factors when considering this therapy. Most food products that contain plant sterols/stanols state “at least 0.4 grams per serving of plant sterols, consumed twice a day with meals for a daily total intake of at least 0.8 grams as part of a fat controlled diet may reduce the risk of heart disease.”

Phytosterols are plant-derived compounds that are similar to cholesterol in both structure and function. Phytosterols compete with dietary cholesterol for intestinal absorption. Food sources of phytosterols are whole grains, unrefined plant oils, nuts, seeds and legumes. Phytosterols is the “collective” name for plant sterols and plant stanols. (Linus Pauling Institute at Oregon State University, 2012)

Search Strategy and Results:

((“Sterols”[Mesh] OR “Phytosterols”[Mesh]) OR “plant stanol ester”[Supplementary Concept]) AND “Pediatrics”[Mesh]

“plant stanol ester”[Supplementary Concept] AND “Phytosterols/therapeutic use”[Mesh]

- 63 articles were identified, and three were chosen.
- Subsequent articles were identified by combing reference lists for applicable studies.
- The Evidence Based Guideline of the Academy of Nutrition and Dietetics (AND, formerly the American Dietetic Association), two systematic reviews/ meta-analyses were selected and synthesized. Two cohort studies are included in the synthesis, as well.

Method Used for Appraisal and Synthesis:

AND’s Evidence Based Guideline was analyzed using the AGREE Instrument.

Systematic reviews and meta-analysis were appraised using Grade Profiler (GradePro).

Critically Appraised Topic (CAT) format was used for cohort studies.

Summary: Based on:

- AND Evidence Based Guideline- The guideline scored an 85% on the AGREE Instrument. The AGREE Trust does not set minimum scores to evaluate guidelines. However this is a strong score. The guideline did not meet the following items:
 - outcome criteria for monitoring the guideline were not defined
 - The procedure for updating the guideline was not transparent
 - The guideline was reviewed by dietitian experts. Review by experts from other fields is not apparent
 - Steps to pilot the guideline were not described
 - Patients’ views and preferences were not openly sought

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- Shafiq (2010), a Cochrane Review, states conclusions cannot be drawn regarding the utility of cholesterol lowering diet, or any other dietary manipulation to decrease serum cholesterols of persons with familial hypercholesterolemia. Although treatment favors cholesterol lowering diets, and the inclusion of plant sterols and stanols, the research conducted to date employ the cross-over design and are underpowered. They are not parallel RCTs. The amount of sterol/stanols given to study subjects is not noted. Since effect of dietary manipulation cannot be shown, the appropriate amount of substances to consume for a desired effect is not known.
- Talati (2009) includes 14 studies and reaches the same conclusion as Shafiq (2010). Studies included in this analysis are also underpowered and have wide variation in the amount of sterols and stanols given to study subjects.
- Becker (1992) reported on the safety of various doses of sitosterol and bezafibrate pastils in children. The only significant potential adverse effect in children was a decrease in serum hemoglobin; it was described as a slight decrease. Although the therapy appears safe, it is not known if it is effective. Although decreases in serum lipids were seen in this study they were not significant. There was no wash-out period between various treatments and cumulative effect of treatments is not known. No control group was used therefore the estimate of the effect is uncertain.
- Matsuyama (2007) did not report significant changes on cholesterol. This study is problematic in that only 7 subjects from 4 families are included in the report. The genetic disposition of the subjects may play a role in the results. Again, a control group was not used in the study, so estimate of the effect is uncertain.

Recommendation:

- **From the included documents, the dietitian should consider incorporation plant sterols and stanols ester enriched foods into a cardio-protective diet (AND, 2009). The recommended dose for adults is two to three grams per day. Doses exceeding 3 grams per day do not appear to provide additional benefit. Research done in children has not been useful to clarify a dose for children.**
- **There is no evidence to date that absorption of carotenoids, retinol, and tocopherols is decreased when phytosterols are added to the diet.**
- **Caloric burden of the phytosterols should be considered when adding the supplements.**
- **Cost burden of the phytosterols should be considered when adding the supplements.**

Reviewers: Geetha Raghuvver, MD, Karen Stephens, MS,RD, LD

Updated December 2011, January 2012, March 2012, August 2012

Office of Evidence Based Practice – Dietary Stanols and Sterols Specific Care Question

Author(s): Allen, N

Date: 2012-03-21

Question: Should cholesterol lowering diet vs. no dietary intervention or nutritional advice be used in subjects with hyperlipidemia?

Bibliography: Academy of Nutrition and Dietetics. (2011, March). Nutrition Guideline: Disorders of Lipid Metabolism (DLM).

[Web page]. Retrieved from <http://www.adaevidencelibrary.com/topic.cfm?cat=4528>

As a major recommendation the AND guideline makes the following recommendations regarding sterols and stanols:

The AGREE Score for the Guideline is 85%. It is a strong score. The AGREE Trust does not set minimum scores to ascertain viability of guidelines; rather scores are used to inform potential guideline users of the strength of the guideline.			
Recommendation	Amount	Strength of evidence (AND rating system)	Other
The dietitian should consider incorporating plant sterols and stanols ester enriched foods into a cardio protective diet.	Consume two to three times per day for a total consumption of two to three grams per day.	Rating : Strong (AND believes the benefits of the approach clearly exceed the harms) Conditional- a conditional recommendation can be stated in IF/THEN terminology.	Amounts above three grams do not provide additional benefit Can be taken with statin drugs
No evidence to date that absorption of carotenoids, retinol and tocopherols is decreased when there are increases in dietary phytosterols	NA	Rating: Fair (AND believes the benefits outweigh the harms, but the quality of the evidence is not as strong) Imperative- an imperative recommendation can be stated using “REQUIRE or MUST”.	Should not be used in individuals with the rare genetic disorder of sitosterolemia Consider caloric burden of spreads and other food sources that contain sterols and stanols. Consider cost of sterol and stanols supplements/foods

Office of Evidence Based Practice – Dietary Stanols and Sterols Specific Care Question

Author(s): Allen, N

Date: 2012-03-16

Question: Should cholesterol lowering diet vs. no dietary intervention or nutritional advice be used in subjects with hyperlipidemia?

Bibliography: Shafiq, N., Singh, M., Kaur, S., Khosla, P., & Malhotra, S. (2010). Dietary treatment for familial hypercholesterolemia. Cochrane Database of Systematic Reviews, doi: 10.1002/14651858.CD001918.pub2

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cholesterol lowering diet	No dietary intervention or nutritional advice	Relative (95% CI)	Absolute		
Fasting total cholesterol (follow-up 1-2 months; measured with: serum (mmol/l); Better indicated by lower values)												
1	randomized trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	19	-	MD 0.40 lower (0.95 lower to 0.15 higher)	LOW	CRITICAL
Fasting serum LDL cholesterol (follow-up 1-2 months; measured with: serum concentration; Better indicated by lower values)												
1	randomized trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	19	-	MD 0.27 lower (0.79 lower to 0.25 higher)	LOW	CRITICAL
Fasting HDL cholesterol (follow-up 1-2 months; measured with: serum concentration; Better indicated by lower values)												
1	randomized trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	19	-	MD 0.11 lower (0.34 lower to	LOW	CRITICAL

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										0.12 higher)		
Fasting triglyceride (follow-up 1-2 months; measured with: serum concentration; Better indicated by lower values)												
1	randomized trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	19	-	MD 0.06 higher (0.43 lower to 0.55 higher)	LOW	CRITICAL

¹ Cross over design

² Randomization not described

³ Unclear how drop outs were treated

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Author(s):

Date: 2012-03-16

Question: Should plant stanols be added to cholesterol lowering diet vs. cholesterol lowering diet alone be used for subjects with hyperlipidemia?

Bibliography: Shafiq, N., Singh, M., Kaur, S., Khosla, P., & Malhotra, S. (2010). Dietary treatment for familial hypercholesterolemia. Cochrane Database of Systematic Reviews, doi: 10.1002/14651858.CD001918.pub2

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plant stanols added to a cholesterol lowering diet	Cholesterol lowering diet alone	Relative (95% CI)	Absolute		
Fasting total cholesterol (follow-up 6 weeks; measured with: serum cholesterol; Better indicated by lower values)												
1	randomized trials	serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	14	-	MD 0.81 higher (0.11 lower to 1.73 higher)	MODERATE	CRITICAL
Fasting LDL cholesterol (follow-up 6 weeks; measured with: serum concentration; Better indicated by lower values)												
1	randomized trials	serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	14	-	MD 0.82 higher (0.04 lower to 1.68 higher)	MODERATE	CRITICAL
Fasting HDL cholesterol (follow-up 6 weeks; measured with: serum concentration; Better indicated by lower values)												
1	randomized trials	serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	14	-	MD 0.05 higher (0.26 to 0.16 higher)	MODERATE	CRITICAL
Fasting triglycerides (follow-up 6 weeks; measured with: serum concentration; Better indicated by lower values)												
1	randomized	serious ^{1,2,3}	no serious	no serious	no serious	none	14	14	-	MD 0.11	MODERATE	CRITICAL

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	trials		inconsistency	indirectness	imprecision						higher (0.24 lower to 0.46 higher)		
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¹ Cross over design

² Blinding not described

³ Randomization not described

Office of Evidence Based Practice – Dietary Stanols and Sterols Specific Care Question

Author(s): Allen, N

Date: 2012-03-16

Question: Should plant sterols be added to cholesterol lowering diet vs. cholesterol lowering diet alone be used for subjects with hyperlipidemia?

Bibliography: Shafiq, N., Singh, M., Kaur, S., Khosla, P., & Malhotra, S. (2010). Dietary treatment for familial hypercholesterolemia. Cochrane Database of Systematic Reviews, doi: 10.1002/14651858.CD001918.pub2

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plant sterols added to a cholesterol lowering diet	Cholesterol lowering diet alone	Relative (95% CI)	Absolute		
Fasting total cholesterol (follow-up mean 8 weeks; measured with: serum concentration; Better indicated by lower values)												
1	randomized trials	serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	38	-	MD 0.61 higher (1.10 lower to 1.32 higher)	MODERATE	CRITICAL
Fasting LDL cholesterol (follow-up 8 weeks; measured with: serum concentration; Better indicated by lower values)												
1	randomized trials	serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	38	-	MD 0.63 higher (0.12 lower to 1.38 higher)	MODERATE	CRITICAL

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Fasting HDL cholesterol (follow-up 8 weeks; measured with: serum concentration; Better indicated by lower values)												
1	randomized trials	serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	38	-	MD 0.01 lower (0.16 lower to 0.14 higher)	MODERATE	CRITICAL
Fasting triglycerides (follow-up 8 weeks; measured with: serum concentration; Better indicated by lower values)												
1	randomized trials	serious ^{1,2,3}	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	38	-	MD 0.02 lower (0.18 lower to 0.14 higher)	MODERATE	CRITICAL

¹ Cross over design

² Randomization not described

³ Blinding not described

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Results Author(s): Carlson, E., Gutierrez, C., Pirvu, D., & Allen, N.

Date: 2011-12-09

Question: Should sterols and stanols vs. be used for hypercholesterolemia?

Bibliography: Talati, R., Sobiera, J., Makanji, S. S., Phung, O. J., & Coleman, C. (2010). The comparative efficacy of plant sterols and stanols on serum lipids: a systematic review and meta-analysis. *Journal of the American Dietetic Association*, 110, 719-726.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sterols and stanols		Relative (95% CI)	Absolute		
Total cholesterol (follow-up 3-16 weeks; measured with: serum cholesterol; Better indicated by lower values)												
14	randomized trials	serious ^{1,2}	no serious inconsistency ^{3,4,5}	no serious indirectness	serious ⁶	none	227	227	-	MD 1.106 lower (4.12 lower to 1.9 higher)	□□□□ LOW	CRITICAL
LDL cholesterol (follow-up 3-16 weeks; measured with: serum level; Better indicated by lower values)												
13	randomized trials	serious ^{2,3,4,5}	no serious inconsistency	no serious indirectness	serious ^{6,7}	none	219	219	-	MD 0.35 lower (2.98 lower to 2.28 higher)	□□□□ LOW	CRITICAL
HDL cholesterol (follow-up 3-16 weeks; Better indicated by higher values)												
13	randomized trials	serious ^{1,2,3,4,5}	no serious inconsistency	no serious indirectness	serious ^{6,7}	none	219	219	-	MD 0.28 lower (1.18 lower to 0.62 higher)	□□□□ LOW	CRITICAL
Triglyceride level (follow-up 3-16 weeks; Better indicated by lower values)												
13	randomized trials	serious ^{1,2,3,4,5}	no serious inconsistency	no serious indirectness	serious ^{6,7}	none	219	219	-	MD 1.80 lower (6.8 lower to 3.21 higher)	□□□□ LOW	CRITICAL

¹ 8 of the studies were funded by industry

² 10 of the studies were cross over design; washout periods between treatment are not described

³ Sterol dose varied between 1.6 gram/day to 3.25 gram/day.

⁴ Stanol dose varied between 0.6 gram/day to 2.75 gram/day

⁵ Follow up time varied between 3-16 weeks.

⁶ Low numbers of subjects were included in each study

⁷ Confidence intervals are very wide

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Critically Appraised Topic (CAT):

Author, date, country, and industry of funding	Patient Group	Level of Evidence (Oxford)	Research design	Significant results	Limitations
<p>Becker, M. 1992 (Germany)</p>	<p>Seven children (5.3-10.8 y with severe familial hypercholesterolemia) Total s. cholesterol > 300 mg/dayL and LDL cholesterol > 250 mg/dL Children came from 4 families— that is 3 subjects were siblings and two other subjects were siblings as well.</p>	<p>Oxford Level 4 Case series</p> <p><u>Outcomes:</u> <u>Laboratory</u></p> <ul style="list-style-type: none"> • Total cholesterol • LDL cholesterol • HDL cholesterol • Triglycerides • Apolipoprotein A-I • Apolipoprotein B • C/Apolipoprotein B 	<p>After a 3 month diet control period, the following treatments were used sequentially:</p> <ol style="list-style-type: none"> 1. sitosterol pastils (3 X 2 grams/day for 3 months) 2. bezafibrate (2 X 200 mg/day, 11-22 mg/kg/day for three months) 3. sitosterol (3 X 1 gram/day combined with bezafibrate (200 mg/day) for 24 months) 	<p>All seven children completed the study Significant reduction in total and LDL cholesterol (17%) during administration for sitosterol compared to diet alone.</p> <p>Total cholesterol, LDL cholesterol and triglyceride were decreased by 32 %, 41% and 36% respectively when bezafibrate was added</p> <p>Total and LDL cholesterol were reduced by 38% and 48% respectively on half the dose of each sitosterol and bezafibrate</p> <p>HDL cholesterol increased 17% during bezafibrate therapy</p> <p>Apolipoprotein AI did not change during therapy.</p> <p>Apolipoprotein B concentration decreased during all therapies.</p> <p><u>Safety parameters:</u> Sitosterol: slight but significant decrease in serum hemoglobin and a decrease in alkaline phosphatase activity. Bezafibrate: alkaline phosphatase activity decreased and iron concentration increased by 26%. Combined therapy, serum ferritin level increased by 20% in two subjects. Acceptability of supplements and compliance to the treatments was good.</p>	<p>There was no control group. The estimate of the effect is uncertain.</p> <p>No washout periods between treatments, effect of previous treatment on outcome values unknown.</p>

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				Gall bladder ultrasounds normal after treatment	
Matsuyama, T. 2007	22 children aged 6-17 years with hyperlipidemia	Oxford Level 4- Case series	Children with hyperlipidemia were treated with bread made with a 4% phytosterol containing diacylglycerol (PS/DAG) Intake was 10 g per day. Children were followed for 6 months of active treatment, and 4 months thereafter for follow up.	There was no significant change in total cholesterol levels for all subjects. For the subjects (n=7) with familial hypercholesterolemia, the total cholesterol levels were significantly lower after 4 months of treatment. LDL-C was significantly lower in all subjects after 4 months of treatment. There was not significant change in HDL-C for all subjects at 4 months. Lipoprotein (a) was significantly lower at 2 and 4 months, the change was greater in subjects with familial hypercholesterolemia. Sitosterol and campesterol were elevated when subjects were consuming the supplement, but were within normal range. The sterol levels returned to baseline when subjects were no longer supplementing.	There was no control group. The estimate of the effect is uncertain.

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Supplementary Information (March 2012)

Study	Product	Price	Dose	Number to meet dose	Daily cost	Daily calories
Becker 1992 Also dosed bezafibrate, a cholesterol lowering drug in with the 3 g phytosterol dose. None of the food products contain bezafibrate.	Benecol Smart Chews- 0.8 g of plant stanols per 2 chews, 20 calories per chew	19.99 112 Chews	Sitosterol 6gram/day	15 chews	\$2.68	300
			Sitosterol 3gram/day	8 chews	\$1.34	150
	Oatmeal Square 0.8 g sterol per square 180 kcal per square	\$12.00 12 squares	Sitosterol 6gram/day	8 squares/day	\$8.00	1440
			Sitosterol 3gram/day	4 squares/day	\$4.00	720
	Centrum Cardio 0.4 g phytosterol /tablet	\$9.99 60 Tablets	Sitosterol 6gram/day	15 tablets/day	\$2.50	NA
			Sitosterol 3gram/day	8 tablets/day	\$1.33	NA
	Cholest-Off- 900 gram/sterol/stanols per 2 caplet serving	\$14.35 240 Caplets	Sitosterol 6gram/day	7 caplets/day	\$0.41	NA
			Sitosterol 3gram/day	4 caplets/day	\$0.24	NA
	Cardio Chews - 0.4 g phytosterol per chew, 30 calories per chew	\$11.79 28 Chews	Sitosterol 6gram/day	15 chews/day	\$6.30	450
			Sitosterol 3gram/day	8 chews/day	\$3.37	240
	Smart Balance® HeartRight® Fat Free Milk- 1 cup 0.4 g plant sterols, 110 calories/cup	\$3.49 ½ gallon	Sitosterol 6gram/day	15 cups/day	\$6.54	1650
			Sitosterol 3gram/day	7.5 cups/day	\$3.27	825
	Minute Maid® HeartWise® Orange Juice 1cup, 1 gram plant sterol, 110 calories/cup	\$2.78 8 Cups	Sitosterol 6gram/day	6 cups	\$2.08	660
			Sitosterol 3gram/day	3 cups	\$1.04	330

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Study	Product	Price	Dose from Study	Number of product to meet study dose	Cost / study dose / day	Calories to get dose
Matsuyama 2007	Benecol Smart Chews- 0.8 g of plant stanols per 2 chews	\$19.99 112 Chews	10 g Phytosterol/day	Product does not contain phytosterol		
	Oatmeal Square 0.8 g sterol per square 180 kcal per square	\$12.00 12 squares		12.5 squares	\$12.50/day	2160 calories/day
	Centrum Cardio 0.4 g phytosterol /tablet	\$9.99 60 Tablets		25 tablets	\$4.10/day	NA
	Cholest-Off- 900 mg/sterol/stanols per 2 caplet serving	\$14.35 240 Caplets		12 caplets	\$0.71/day	NA
	Cardio Chews - 0.4 g phytosterol per chew.	\$11.79 28 Chews		25 chews	\$10.70	750 calories/day
	Smart Balance® Heartright® Fat Free Milk- 1 cup 0.4 g plant sterols	\$3.49 for ½ gallon		25 cups/day	\$5.45/day	2750 calories/day
	Minute Maid® Heartwise® Orange Juice 1cup, 1 gram plant sterol	\$2.78 8 Cups		10 cups	\$3.48/day	1100 calories/day

Benecol Smart Chews- http://benecolusa.com/products/index.jhtml?id=benecol/products/pr_smartchews.inc

CardioChews- <http://www.directionsforme.org/index.php/directions/product/VITAMINS/00850877000807>

Centrum- http://www.centrum.com/?s_kwcid=TC|17281|centrum%20multivitamin||S|b|11848485795

CholestOff Complete- <http://www.naturemade.com/Products/Health-Solutions/Cholestoff-Complete>

Corazonas Oatmeal Squares- <http://www.corazonas.com/snacks>

Minute Maid® Heartwise® Orange Juice - <http://productnutrition.thecoca-colacompany.com/products/minute-maid-heart-wise-orange-juice>

Smart Balance® Heartright® Fat Free Milk- <http://www.smartbalance.com/products/heartright/heartright-fat-free-milk>

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