

## Original Investigation

# Flaxseed in Pediatric Hyperlipidemia

## A Placebo-Controlled, Blinded, Randomized Clinical Trial of Dietary Flaxseed Supplementation for Children and Adolescents With Hypercholesterolemia

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**IMPORTANCE** Nonpharmacological management of hypercholesterolemia in children is challenging with few available options.

**OBJECTIVES** To determine the safety and efficacy of dietary flaxseed supplementation in the management of hypercholesterolemia in children.

**DESIGN** Four-week placebo-controlled, blinded, randomized clinical trial.

**SETTING** Specialized dyslipidemia clinic at a tertiary pediatric care center.

**PARTICIPANTS** Thirty-two participants aged 8 to 18 years with low-density lipoprotein cholesterol from 135 mg/dL (3.5 mmol/L) to less than 193 mg/dL (5.0 mmol/L).

**INTERVENTION** The intervention group ate 2 muffins and 1 slice of bread daily containing ground flaxseed (30 g flaxseed total). The control group ate muffins and bread substituted with whole-wheat flour.

**MAIN OUTCOME AND MEASURE** Attributable change in fasting lipid profile.

**RESULTS** Dietary flaxseed supplementation resulted in an attributable decrease of  $-7.35$  mg/dL ( $-0.19$  mmol/L) in high-density lipoprotein cholesterol (95% CI,  $-3.09$  to  $-11.60$  mg/dL [ $-0.08$  to  $-0.30$  mmol/L]; relative:  $-15\%$ , 95% CI,  $-24\%$  to  $-6\%$ ;  $P = .001$ ), an increase of  $29.23$  mg/dL ( $+0.33$  mmol/L) in triglycerides (95% CI,  $4.43$  to  $53.14$  mg/dL [ $+0.05$  to  $+0.60$  mmol/L]; relative:  $+26\%$ , 95% CI,  $+4\%$  to  $+48\%$ ;  $P = .02$ ), and an increase of  $+4.88$  g/d in dietary polyunsaturated fat intake (95% CI,  $+0.22$  to  $+9.53$ ; relative:  $+76\%$ , 95% CI,  $+3\%$  to  $+148\%$ ;  $P = .04$ ). Flaxseed had no attributable effects on total cholesterol ( $-8.51$  mg/dL [ $-0.22$  mmol/L]; 95% CI,  $-21.66$  to  $4.25$  mg/dL [ $-0.56$  to  $+0.11$  mmol/L]; relative:  $-4\%$ , 95% CI,  $-10\%$  to  $+2\%$ ;  $P = .20$ ), low-density lipoprotein cholesterol ( $-6.96$  mg/dL [ $-0.18$  mmol/L]; 95% CI,  $-16.63$  to  $2.71$  mg/dL [ $-0.43$  to  $+0.07$  mmol/L]; relative:  $-5\%$ , 95% CI,  $-12\%$  to  $+2\%$ ;  $P = .15$ ), body mass index z score ( $+0.002$ ; 95% CI,  $-0.147$  to  $+0.150$ ; relative:  $+0\%$ , 95% CI,  $-12\%$  to  $+12\%$ ;  $P = .30$ ), or total caloric intake ( $+117$  kcal; 95% CI,  $-243$  to  $+479$ ; relative:  $+8\%$ , 95% CI,  $-17\%$  to  $+33\%$ ;  $P = .52$ ). An attributable change in total and low-density lipoprotein cholesterol failed to exclude a potential benefit of flaxseed supplementation based on a prespecified minimum clinically important reduction of 10%. No concerns were noted regarding safety.

**CONCLUSIONS AND RELEVANCE** The use of dietary flaxseed supplementation, while safe, was associated with adverse changes in the lipid profile of children with hypercholesterolemia, although a potential benefit of low-density lipoprotein cholesterol lowering could not be excluded. The use of flaxseed supplementation in children with hypercholesterolemia might not be a viable option for lipid management in this population.

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Elevated lipid profiles in adolescents and young adults have been highlighted as a risk factor for the early development of atherosclerotic lesions and cardiovascular disease.<sup>1</sup> Therefore, managing lipid levels in youth is an important and effective means of addressing the prevalence of these conditions in adults. Clinical management of pediatric hyperlipidemia focuses on therapeutic lifestyle changes,<sup>2</sup> with pharmacologic interventions considered when lifestyle approaches fail to decrease low-density lipoprotein cholesterol (LDL-C) within acceptable ranges.<sup>3</sup> Ongoing controversy surrounding the safety and benefits of the long-term use of lipid-lowering drugs warrants greater research into possible alternative therapies.<sup>4</sup>

Flaxseed (*Linum usitatissimum*) is a functional food containing  $\alpha$ -linolenic acid, soluble fiber, and lignans, agents that have been shown to have hypolipidemic activity or other properties that may benefit cardiovascular health.<sup>5-7</sup> Increased dietary  $\alpha$ -linolenic acid (through flaxseed consumption) has been inversely associated with decreased primary cardiovascular events, as well as improved cardiovascular risk factors such as elevated serum LDL-C,<sup>8-12</sup> although results of human trials are inconsistent.<sup>13-15</sup> The effect of flaxseed on pediatric hypercholesterolemia remains unexplored. Additional study is warranted to define the role of dietary flaxseed in the management of pediatric hyperlipidemia. We sought to detect a 10% mean relative reduction in LDL-C levels attributable to daily consumption of dietary flaxseed supplementation in pediatric patients with moderately severe hypercholesterolemia compared with a placebo control.

## Methods

### Trial Design

The institutional research ethics board at The Hospital for Sick Children reviewed and approved the study protocol. All participants and their parents provided written informed consent prior to enrollment.

In this placebo-controlled, blinded, randomized, clinical trial, participants were randomly assigned to an intervention or placebo control group with a 1:1 allocation ratio. The intervention group received a 30-g/d, 4-week dietary flaxseed supplement in muffins and breads baked with ground flaxseed.

### Participants

Participants were included in the study based on age (8-18 years), elevated fasting serum LDL-C levels (135-193 mg/dL [3.5-5.0 mmol/L]; to convert to millimoles per liter, multiply by 0.0259), a positive first-degree family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease, and compliance with the National Cholesterol Education Program Step II diet for a minimum of 6 months prior to enrollment. Patients who had secondary causes for hyperlipidemia, had a major illness or surgery in the preceding 3 months, or were taking cholesterol-lowering drugs were excluded from participation. Also excluded were patients with known allergies to flaxseed or gastrointestinal tract prob-

lems. Inclusion and exclusion criteria were designed to allow generalizability of results to the broader population of pediatric patients with primary hypercholesterolemia who also adhere to a therapeutic diet and are not being treated with cholesterol-lowering pharmacologic agents—a specific patient group for which, to our knowledge, there are no previous data regarding flaxseed efficacy.

### Interventions

All patients of the lipid clinic at The Hospital for Sick Children, Toronto, Ontario, Canada, were screened for eligibility by medical record review. Eligible participants were approached by telephone and mail. Informed verbal consent was obtained by telephone, and those who consented were scheduled for preenrollment assessments in groups of 8 to 10. Consenting patients also were mailed 4-day food records to complete before their preenrollment visit. During the visit, each patient gave written informed consent and was immediately randomized to either the intervention or the control group. The dietitian (H.W.) collected the food records for dietary assessment, and each participant underwent a routine physical examination and fasting blood test. Before leaving the lipid clinic, patients were provided with a 4-week supply of either flaxseed muffins and bread or placebo muffins and bread, according to their randomized group assignment.

Participants in the intervention group were directed to consume 2 muffins and 1 slice of bread containing ground flaxseed daily, resulting in a daily intake of 30 g of dietary flaxseed throughout the study period. The control group was provided with identical muffins and bread, containing whole-wheat flour in place of flaxseed. Recipes for the intervention and placebo muffins and breads were designed by the study dietitian to be as closely matched in nutritional content as possible, with the exception of the contribution made by flaxseed. Nutritional information for muffins and breads is provided in **Table 1**. All participants were instructed to eat 1 muffin for breakfast, 1 muffin as an afternoon snack, and 1 slice of bread as an evening snack daily for a 4-week period. For the first week after randomization, participants were instructed to store all muffins and breads in the refrigerator. For the second, third, and fourth weeks of the trial, all muffins and breads were to be kept frozen, with the option of either defrosting a week's supply in the refrigerator at the start of each week or placing a daily supply in the refrigerator each evening to be consumed the next day. All muffins and breads supplied in the study were baked at a standardized kitchen separate from the study center. A second dietary assessment, physical examination, and fasting blood test were performed at the end of the 4-week period. The primary outcome measure was a change in fasting lipid levels.

### Compliance

No direct biologic measure of compliance was taken. However, participants were asked to keep an intake log, recording daily consumption of the study muffins and breads and to return any unconsumed muffins and breads. Compliance was expressed as the amount of muffins and breads reported as consumed (determined by the intake log and cross-

Table 1. Nutritional Content per Serving of Muffins and Breads Used in the Study

Variable	Flaxseed Muffin	Control Muffin	Flaxseed Bread	Control Bread
Calories, kcal	165.80	172.67	176.69	180.45
Total fat, g	7.38	7.24	7.43	7.28
Saturated fat, g	0.72	0.67	0.75	0.68
Polyunsaturated fat, g	3.37	2.12	3.38	2.13
Monounsaturated fat, g	2.87	3.99	2.88	4.00
Cholesterol, mg	17.65	17.83	17.83	17.83
Total carbohydrates, g	22.57	25.05	24.92	26.94
Dietary fiber, g	3.88	2.78	4.05	2.95
Sugar, g	10.93	9.90	11.76	10.25
Protein, g	3.78	3.66	4.26	3.82

referenced with returned muffins and breads) vs the amount that would have been consumed with 100% compliance during the study period.

### Sample Size

Sample size estimation was based on detecting a minimum 10% attributable reduction in LDL-C with 80% power. Hypothesizing that LDL-C lowering would be -10% in the flaxseed group (no change in the control group), with a  $\beta$  level of .80 and an  $\alpha$  level of .05, we estimated a required sample size of 11 patients per group, which increased to 15 patients to compensate for potential dropouts.

### Randomization Procedure

A random-number generator, using blocks of 6, was used to create a randomized assignment list. Randomization was carried out separately by the nurse practitioner (N.C.). This was done by blindly drawing patient hospital ID numbers from the pool of participants enrolled on that day and assigning consecutively drawn numbers to treatment groups according to the preset assignment list. The nurse practitioner then carried out the assignments by supplying the appropriate muffins or bread to each patient.

### Blinding

The trial was blinded for participants and measurement of the primary outcome. Blood testing to assess the primary outcome was conducted by laboratory technicians blinded to the group assignment of each patient. Participants and their families were also blinded as to the group assignments. Muffins and breads provided to the intervention and control groups were designed to be as similar as possible for size, texture, color, and taste to maintain the masking of the study participants. The patient nurse practitioner and dietitian responsible for recruitment and application of the study were unblinded as to the treatment group to which each patient belonged.

### Safety Monitoring

A complete physical examination, including an assessment of height, weight, and blood pressure, was performed on each participant at baseline and at the study end point. Height and weight measurements were used to calculate body mass index  $z$  scores, based on age-appropriate normal values. Any data

regarding signs of discomfort or adverse symptoms were collected and noted. Blood chemistry and complete blood cell counts were also assessed and compared at both time points. Participants were instructed to immediately contact study personnel if adverse effects were noted or if they developed serious illness, required surgery, or needed other pharmacologic treatment during the study period.

### Statistical Analysis

Data are reported as frequencies, medians with ranges, and means with standard deviations as appropriate. Characteristics at baseline and follow-up were compared between groups using the Fisher exact and  $t$  tests. Blood test results and changes in height, weight, and blood pressure were assessed with paired  $t$  tests for each group. Mean differences in the changes between the 2 groups were compared using  $t$  tests. Differences between groups in changes in lipid profile parameters adjusted for compliance were assessed with a general linear regression model. All analyses were performed on an intent-to-treat basis. All statistical analyses were performed using SAS version 9.3 (SAS Institute).

## Results

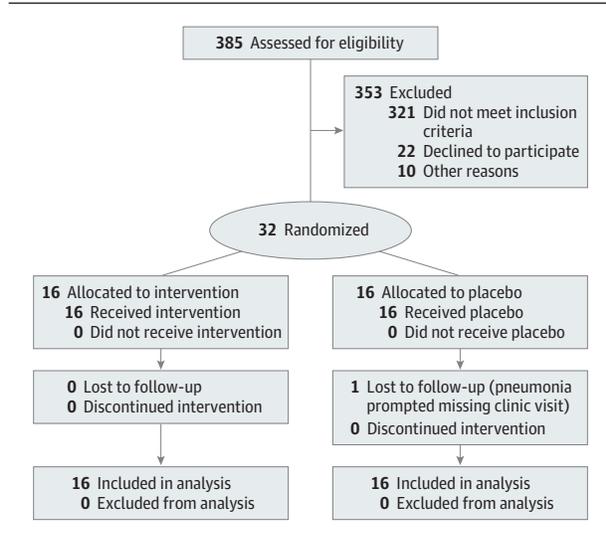
### Participant Flow

From October 2009 through October 2010, 32 participants were enrolled in the study and randomized to 1 of 2 groups of 16 subjects at the lipid clinic at The Hospital for Sick Children (Figure 1). One patient randomized to the placebo group became ill with pneumonia unrelated to the study intervention and was unable to return for the second clinic visit, constituting a loss to follow-up.

### Baseline Data

There were 17 male and 15 female patients in the study, and mean (SD) age at enrollment was 13.2 (2.3) years. All patients had a positive family history of first-degree relatives with hypercholesterolemia. Mean (SD) fasting lipid values at baseline were 208 (30) mg/dL (5.38 [0.77] mmol/L) for total cholesterol, 138 (25) mg/dL (3.56 [0.64] mmol/L) for LDL cholesterol, 49 (12) mg/dL (1.25 [0.31] mmol/L) for high-density lipoprotein (HDL-C), and 112 (47) mg/dL (1.26 [0.53]

Figure 1. CONSORT diagram



mmol/L) for triglyceride levels. No patient had hypertension, and all were judged to be sufficiently compliant with dietary goals. The distribution of patient characteristics between the 2 groups was not significantly different at baseline (Table 2), with the exception of higher monounsaturated fat intake in the placebo group ( $P = .05$ ) and higher fasting HDL-C levels in the intervention group ( $P = .05$ ).

**Outcomes**

Dietary flaxseed supplementation resulted in an attributable decrease of  $-7.35$  mg/dL ( $-0.19$  mmol/L) in HDL-C (95% CI,  $-3.09$  to  $-11.60$  mg/dL [ $-0.08$  to  $-0.30$  mmol/L]; relative:  $-15\%$ , 95% CI,  $-24\%$  to  $-6\%$ ;  $P = .001$ ), an increase of  $29.23$  mg/dL ( $+0.33$  mmol/L) in triglycerides (95% CI,  $4.43$  to  $53.24$  mg/dL [ $+0.05$  to  $+0.60$  mmol/L]; relative:  $+26\%$ , 95% CI,  $+4\%$  to  $+48\%$ ;  $P = .02$ ) (Figure 2), and an increase of  $+4.88$  g/d in dietary polyunsaturated fat intake (95% CI,  $+0.22$  to  $+9.53$ ; relative:  $+76\%$ , 95% CI,  $+3\%$  to  $+148\%$ ;  $P = .04$ ). Use of flaxseed had no attributable effects on total cholesterol ( $-8.51$  mg/dL [ $-0.22$  mmol/L]; 95% CI,  $-21.66$  to  $4.25$  mg/dL [ $-0.56$  to  $+0.11$  mmol/L]; relative:  $-4\%$ , 95% CI,  $-10\%$  to  $+2\%$ ;  $P = .20$ ), LDL cholesterol ( $-6.96$  mg/dL [ $-0.18$  mmol/L]; 95% CI,  $-16.63$  to  $2.71$  mg/dL [ $-0.43$  to  $+0.07$  mmol/L]; relative:  $-5\%$ , 95% CI,  $-12\%$  to  $+2\%$ ;  $P = .15$ ), body mass index z score ( $+0.002$ ; 95% CI,  $-0.147$  to  $+0.150$ ; relative:  $+0\%$ , 95% CI,  $-12\%$  to  $+12\%$ ;  $P = .30$ ), or total caloric intake ( $+117$  kcal; 95% CI,  $-243$  to  $+479$ ; relative:  $+8\%$ , 95% CI,  $-17\%$  to  $+33\%$ ;  $P = .52$ ) (Figure 2). The associations between cardiovascular risk and flaxseed were unaffected by including change in weight and caloric intake in regression models. The attributable change in total and LDL-C failed to exclude a potential benefit based on a prespecified minimal clinically important attributable difference of  $-10\%$ . No concerns were noted regarding safety other than the adverse effect on triglycerides and HDL-C levels.

**Compliance**

No significant differences were noted between groups regarding compliance throughout the study period. As determined

Table 2. Comparison of Baseline Characteristics<sup>a</sup>

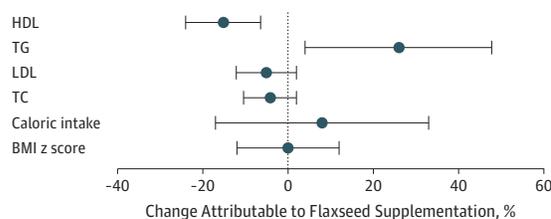
Variable	Flaxseed Group (n = 16)	Placebo Group (n = 16)
Sex, No.		
Male	7	10
Female	9	6
Age, y	13 (2)	13 (3)
Weight, kg	55 (15)	60 (30)
BMI	23.2 (5.3)	23.4 (6.6)
Dietary intake		
Calories	1310 (404)	1562 (373)
Fat, g/d	37 (13)	45 (16)
Saturated	11.9 (4.7)	13.9 (5.8)
Trans-saturated	0.62 (0.44)	0.55 (0.52)
Polyunsaturated	6.0 (3.9)	6.9 (3.3)
Monounsaturated	10.2 (5.5)	15.6 (8.0)
Total fiber, g/d	17.1 (8.8)	19.1 (7.4)
Soluble	2.4 (0.9)	2.4 (1.4)
Insoluble	6.6 (3.3)	8.9 (5.5)
Blood pressure, mm Hg		
Systolic	106 (11)	109 (12)
Diastolic	66 (10)	64 (8)
Fasting lipid profile, mg/dL [mmol/L]		
Total cholesterol	214 (25) [5.54 ± 0.65]	202 (34) [5.22 ± 0.89]
LDL-C	141 (22) [141 ± 22]	134 (27) [3.47 ± 0.71]
HDL-C	53 (12) [1.36 ± 0.3]	44 (12) [1.14 ± 0.32]
Triglycerides	104 (39) [1.17 ± 0.44]	119 (54) [1.34 ± 0.61]
C-reactive protein, mg/L	2.2 (2.2)	2.7 (3.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

<sup>a</sup> Unless otherwise stated, values are expressed as mean (SD).

Figure 2. Change in Outcomes



Change in outcomes attributable to flaxseed supplementation, including high-density lipoprotein cholesterol (HDL-C) ( $P = .001$ ), triglycerides (TG) ( $P = .02$ ), low-density lipoprotein cholesterol (LDL-C) ( $P = .15$ ), total cholesterol (TC) ( $P = .20$ ), caloric intake ( $P = .52$ ), and body mass index (BMI) z score ( $P = .30$ ).

from intake logs completed by participants during the study, compliance during the study period was a mean (SD) of 80% (18%) of expected in the placebo group vs 85% (12%) in the flaxseed group ( $P = .40$ ).

## Discussion

In a placebo-controlled, blinded, randomized clinical trial of flaxseed supplementation therapy in children with hypercholesterolemia, we found the intervention to have no significant benefit for cardiovascular risk in reducing lipid levels. Flaxseed supplementation was associated with a significant decrease in HDL-C level and an increase in triglyceride levels. On the basis of a 95% CI, we could not exclude a potential benefit of flaxseed supplementation based on a prespecified minimally clinically important reduction of -10% in LDL-C level.

Interest in flaxseed as a possible alternative therapy for treating hyperlipidemia is new, having gained acknowledgment only recently as a functional food.<sup>7</sup> The predominant mechanism by which flaxseed influences lipid profiles remains unknown.<sup>15</sup> Some promising results have been seen in animal and human trials and in studies on isolated nutritional components of flaxseed, such as  $\alpha$ -linolenic acid.<sup>8,16</sup> A recent meta-analysis of 28 clinical trials investigating the effects of flaxseed on blood lipid levels in adults supported a positive role for flaxseed in treating hyperlipidemia.<sup>17</sup> The dosage of flaxseed used in the reviewed trials ranged from 20 to 50 g/d,<sup>17</sup> encompassing the 30-g/d dosage used in our own study. Across the multiple trials, whole-seed flaxseed intervention resulted in a significant overall decrease in LDL-C levels but no change in HDL-C or triglyceride levels. However, despite an overall positive outcome, important discrepancies were noted between the results of individual trials, which seemed to correlate with differences in method and patient characteristics, such as age, sex, and baseline lipid levels.<sup>17</sup> Another explanation for the negative results seen in our study may be that palatable delivery of oral interventions is often more difficult in pediatric patients; it is possible that nutritional changes to ground flaxseed in our muffin and bread delivery method, necessary for palatability to pediatric patients, influenced the efficacy of the intervention vs standard methods used in adults, such as whole flaxseed<sup>18</sup> or purified lignans.<sup>8</sup> This finding of increased triglyceride and polyunsaturated fat intake with flax-

seed supplementation through palatable foods casts further doubt on possible benefits of flaxseed in children with hyperlipidemia; it is possible that any potential positive effects on cardiovascular risk factors in these children would be outweighed by this harm to their already elevated lipid profiles.

This study had several limitations. First, our study unexpectedly observed increases in body mass index (calculated as weight in kilograms divided by height in meters squared) and daily caloric intake in both study groups during the trial. We speculate that this observation may have resulted from patient ambiguity with respect to the intervention protocol, in which participants may have consumed the study foods in addition to their regular diet, rather than substituting them for part of daily meals and snacks. More detailed guidelines for consumption of study foods may help to prevent such trends in future trials. Also, our results may have been confounded by the inherent difficulty of confirming adherence and compliance to the study protocol since assessment of compliance was based on consumption reports from patient-completed intake logs. Compliance may have been affected by the unconfirmed palatability of the study breads and muffins, as well as the long period (4 weeks) between the pre- and posttreatment assessment visits. Accurate estimation of compliance would be improved by distributing flaxseed-supplemented foods to patients on a week-by-week basis, allowing for better tracking of consumption and possibly encouraging greater adherence. Finally, this study was limited by its small sample size ( $n = 32$ ), resulting in low study power for some secondary outcomes, as well as the short duration for which the intervention was tested (4 weeks). Both of these limitations may have compromised the generalizability of the study results.

In light of the results and limitations of our study, further research seeking longitudinal data from larger samples of patients is warranted to address the current discrepancy between evidence from adult and pediatric trials, as well as further elucidate the possible role of flaxseed in treating pediatric hyperlipidemia. Until its relevance is clearly understood, flaxseed supplementation remains an unverified strategy for the clinical management of cardiovascular risk factors in youth with hyperlipidemia.

### ARTICLE INFORMATION

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**Study concept and design:** Chahal, McCrindle.

**Acquisition of data:** Wong, Chahal.

**Analysis and interpretation of data:** All authors.

**Drafting of the manuscript:** All authors.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Manlihot, McCrindle.

**Obtained funding:** Wong, Chahal, McCrindle.

**Administrative, technical, and material support:** Chahal, McCrindle.

**Study supervision:** Chahal, McCrindle.

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