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Basic nutritional investigation

Could dyslipidemic children benefit from glucomannan intake?

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ABSTRACT

Objective: Primary dyslipidemias are major risk factors for cardiovascular disease and should be addressed early in life. The aim of this study was to evaluate, in children affected by primary hypercholesterolemia, the efficacy and tolerability of a short-term treatment with a dietary supplement containing glucomannan.

Methods: A double-blind, randomized, placebo-controlled, cross-over trial was conducted in 36 children (aged 6-15 years) affected by primary hypercholesterolemia. After a 4-week run-in period with dietary counseling, children received glucomannan or placebo twice-daily for 8 weeks, separated by a 4-week washout period. Lipid profile was assessed at baseline and after each treatment period.

Results: Glucomannan significantly reduced total cholesterol (TC) by 5.1% ($p = 0.008$), low-density lipoprotein cholesterol (LDL-C) levels by 7.3% ($p = 0.008$) and non-high-density lipoprotein cholesterol by 7.2% ($p = 0.002$) as compared with placebo. No significant differences were observed in high-density lipoprotein cholesterol, triglyceride, Apolipoprotein B, and Apolipoprotein A-I concentrations. According to sex, glucomannan significantly reduced in females, but not in males, TC (-6.1%, $p = 0.011$) and LDL cholesterol (-9%, $p = 0.015$). No major adverse effects were recorded and only few patients experienced transitory intestinal discomfort.

Conclusion: Treatment with glucomannan of children affected by primary dyslipidemia is well-tolerated and effectively lowers total and LDL cholesterol in females and non-high-density lipoprotein cholesterol, but not Apolipoprotein B in both males and females.

Introduction

Primary dyslipidemias are major risk factors for cardiovascular disease (CVD) [1]. The associated lipoprotein changes start early during childhood and remain throughout adulthood [2]; indeed, atherosclerotic lesions have been recorded in pediatric patients [3]. Therefore, increased attention is being paid to CVD prevention in childhood, through lipid-lowering strategies when applicable. The main approaches focus on lifestyle changes that chiefly concern diet and physical activity. When these approaches do not lead to a satisfactory reduction of low-density lipoprotein cholesterol (LDL-C) concentrations, the use of dietary supplements/functional foods is warranted, before prescription of hypolipidemic drugs [2].

Soluble fibers bind biliary salts and remove them from the enterohepatic circulation, thus representing an interesting example of dietary supplement aimed at cardiovascular prevention [4]. Several studies have focused on different soluble fibers such as glucomannan, oats, psyllium, pectin, and guar gum. Glucomannan, the main polysaccharide obtained from the tuber *Amorphophallus Konjac* (a member of the Araceae family, found in East Asia) is a palatable soluble fiber. In the East, people have being consuming glucomannan for thousands of years; its use also is increasing in the West. The chemical structure of glucomannan consists in a mannose:glucose 8:5 ratio, linked by β-glycosidic bonds. Glucomannan has the highest molecular weight and viscosity of any other known dietary fibers [5] and, like other soluble fibers, has been tested for its potential beneficial effects on risk for CVD, in particular because of its favorable effects on lipid profile [6].

Clinical trials have been carried out in adults to investigate the effects of fiber on body weight, blood pressure, fasting blood glucose, and lipid profile, yielding mixed results [7]. A meta-analysis of the efficacy of glucomannan in lowering LDL-C

OG was responsible for the study design and manuscript writing. FV was involved in the study and manuscript revision; FA with patient assistance; and PC with dietetic and technical assistance. This study was supported by grants from Turin University. No external funding was secured for this study.

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reported great variability among 14 studies conducted in adults and children [6]. More recently, inverse correlations between dietary [total, soluble, and insoluble] fiber intake and C-reactive protein, a sensitive marker of inflammation, were reported in healthy [8] and dyslipidemic [9] adults. In children, studies that evaluated the effect of water-soluble fibers on lipid profile show LDL-C reductions ranging from null to 30% [10–20]. Again, there is no concordance among the results of various trials [4,6].

This study had two main objectives: 1) to confirm the effects of glucomannan in lowering LDL-C in boys and girls and 2) to evaluate whether this dietary intervention modifies apolipoprotein B (ApoB).

Materials and methods

Patients

The study complies with the Declaration of Helsinki and was approved by the Local Ethics Committee. Written informed consent was obtained from patients and their legal guardians.

We recruited 36 hypercholesterolemic children among 42 outpatients followed by our Lipid Clinic since October 2011, who were screened for eligibility. Enrollment criteria included being ages 6 to 15 y with serum total cholesterol (TC) levels higher than their age- and sex-specific 90th percentile. Exclusion criteria comprised secondary dyslipidemias, overweight or obesity (body mass index [BMI] $\geq$ 85th and $\geq$ 95th percentile, age and sex matched, respectively), renal, endocrine, liver disorders, or chronic diseases requiring drug treatment (i.e., immunologic, neurologic, or oncohematologic disorders). Diagnostic criteria were based on accepted International standards [21]. As with familial hypercholesterolemia (FH) (n = 5), criteria included children with LDL-C $\geq$ 135 mg/dL, parental hypercholesterolemia with LDL-C $\geq$ 190 mg/dL, tendon xanthomas and/or CVD (phenotype IIA). Children showing TC and/or triglyceride (TG) above the 90th age- and sex-specific percentile, at least one parent affected by isolated hypercholesterolemia, hypertriglyceridemia, or both (IIA, IV, or IIB phenotype, respectively) with concomitant individual and familial lipid phenotype variability were diagnosed as familial combined hyperlipidemia affected (FCH) (n = 19). Children exhibiting LDL-C exceeding 90th percentile and a family history of hypercholesterolemia, but who did not fulfil the biochemical international criteria for inclusion in FH or FCH, were considered affected by undefined hypercholesterolemia (n = 12). All study participants were nonsmokers and no participants were on lipid-lowering treatment—including functional foods—for the 3 mo before the beginning of the study.

Study design

This double-blind, randomized, placebo-controlled, cross-over trial lasted 24 wk. Participants underwent four visits and were submitted three times to biochemical analyses (biochemical analyses were not performed at the start of the second half of the study). Moreover, food-intake evaluations were performed at baseline and at the end of each treatment (Fig. 1). This latter procedure was implemented to diminish the risk for attrition, which increases when children undergo frequent visits.

Children underwent a preliminary 4-wk run-in diet and were instructed by a trained dietitian not to change their standard low-saturated fat, low-cholesterol diet (i.e. the Step I diet) [22]. This first-level dietary approach consists of a normocaloric diet composed as follows: carbohydrate 55%, protein 15%, total and saturated fat 30% and 10%, of daily calories respectively. Cholesterol intake was less than 300 mg/d. Furthermore, children and their families were instructed not to modify children's physical activity. An external pediatrician randomly allocated the participants to receive either fiber or placebo. Randomly enrolled patients (N = 36) were assigned to consume either the dietary supplement or the placebo. Eighteen children started with the dietary supplement and 18 started with the placebo, for 8 wk each. At the end of the first treatment period, children underwent

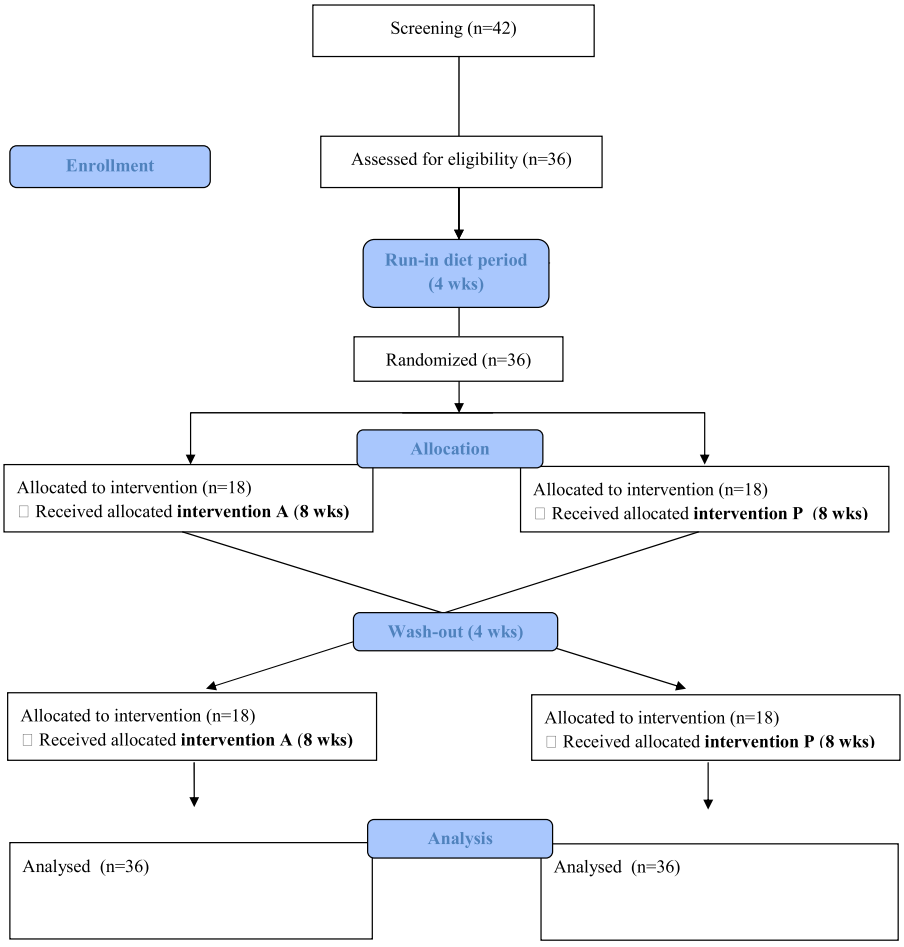

Fig. 1. Flowchart of the study. Intervention A: glucomannan; Intervention P: placebo.

a 4-wk washout and then switched treatment. At each visit, children underwent a physical evaluation that included weight, height, BMI, and blood pressure measurements. Tanner stage was also evaluated. At blood collection time, parents provided a weekly dietary diary to check for any potential deviation from the prescribed diet. Children and their parents completed the diary; dietitians then checked the records for accuracy. Furthermore, children's physical activity was evaluated at each visit. Finally, children and their parents were asked to report any symptoms, illness, or drug consumption that occurred during the trial.

The dietary supplement we used was formulated as oral gelatine capsules containing 500 mg of glucomannan (Propol KW, produced by Shimitzu Chemical Corporation, Hiroshima, Japan and distributed in Italy by Ca.Di.GROUP, Rome, Italy). The placebo mimicked the color and appearance of the supplement. Participants, parents, researchers, and staff were blinded to the treatment. The dose was two or three capsules twice a day (at lunch and dinner), based on children's weight (namely, <20 kg or >20 kg). Compliance was checked by counting the capsules returned by the patients and parents in relation to the number of capsules dispensed.

Biochemical analyses

Blood samples were obtained after an overnight fast. Standard assays for TC, high-density lipoprotein cholesterol (HDL-C), and TG were carried out by an automatic analyzer (Olympus AU 2700, Japan); plasma ApoB and apolipoprotein A-I (ApoA-I) concentrations were measured by immunoturbidimetry (Olympus AU 2700, Japan). LDL-C was estimated using the Friedewald formula. Non–HDL-C cholesterol was calculated as TC minus HDL-C.

Statistical analyses

A power calculation was performed to determine the required number of patients. It was predicted that a sample size of 36 children would be sufficient to detect a change of 10% in LDL-C with a power of 80% and $\alpha = 0.05$.

Variable distributions were examined to determine whether they were normal. Paired Student's t test or Wilcoxon rank-sum test were used to study differences between treatments. $P < 0.05$ was considered significant and 95% confidence intervals (CIs) also were calculated. Statistical analyses were performed using the SPSS 17.0 software (SPSS Inc, Chicago, IL).

Results

Glucomannan was well tolerated and no relevant adverse effects (AEs) were detected. Four children experienced adverse gastrointestinal effects such as flatulence, abdominal discomfort, and increased stool frequency. Two more children reported increased satiety. All these symptoms were transient and all patients completed the trial. No such effects were reported during placebo treatment period.

Patients' baseline characteristics are reported in Table 1. All children completed the trial; compliance, as assessed by capsule counting, was 92% and 90% for the supplement and placebo, respectively. During the study, children's compliance to the normocaloric, low-saturated fat, and low-cholesterol diet was adequate and there was no difference between the two trial treatment periods, as shown in Table 2. Furthermore, no variation of physical activity was recorded (data not shown). Height-weight growth, BMI, blood pressure, and Tanner stage did not show any variation along the trial (data not shown).

Table 1
Characteristic of the cohort at baseline and at the end of each treatment

Parameter	Baseline n = 36	Glucomannan n = 36	Placebo n = 36
Age, y	10.7 ± 2.1	10.9 ± 2.1	11 ± 2.1
Sex, M/F	16/20	16/20	16/20
Weight, Kg	38.6 ± 12.8	39.1 ± 13	39.1 ± 12.9
Height, cm	141.6 ± 13.8	142.5 ± 13.6	142.8 ± 13.7
BMI, Kg/m^2	18.8 ± 3.6	18.7 ± 3.6	19 ± 3.6
Sistolic blood pressure, mmHg	100.6 ± 10.1	104.6 ± 9.4	101.9 ± 8.3
Diastolic blood pressure, mmHg	65.2 ± 9	66.7 ± 7.3	64.3 ± 5.5

Table 2
Daily energy and nutrient intakes at baseline and at the end of each treatment period

Parameter	Baseline (n = 36)	Glucomannan (n = 36)	Placebo (n = 36)
Energy, kcal	1263.5 ± 257.6	1242 ± 236.3	1271.3 ± 183.2
Protein, % of energy	16.9 ± 2.3	15.9 ± 2.2	15.5 ± 1.6
Total Fat, % of energy	30.2 ± 2.3	30.7 ± 2.5	31 ± 2.2
Carbohydrate, % of energy	52.9 ± 2.3	53.4 ± 2.9	53.5 ± 2
Saturated fat, % of energy	10 ± 2	9.4 ± 2.3	10.3 ± 2.4
Monounsaturated fat, % of energy	15 ± 3.2	15.9 ± 2.7	16.3 ± 2
Polyunsaturated fat, % of energy	4.3 ± 1.4	3.9 ± 1.6	3.5 ± 1.2
Dietary fibers, g	9.6 ± 3.6	9.8 ± 3.2	8.9 ± 2.1
Cholesterol, mg	146.1 ± 43.5	134 ± 37.5	136.3 ± 41.2

Values are means ± SD, as calculated from 7-day food records during each treatment period.

Table 3 shows serum lipoprotein concentrations after treatments in each group. Compared with placebo, the dietary supplement significantly reduced, on average, TC by 10.8 mg/dL (95% CI, −18.5 to −3.1; $P = 0.008$), LDL-C by 10.1 mg/dL (95% CI, −17.4 to −2.9; $P = 0.008$), and non–HDL-C by 11.2 mg/dL (95% CI, −18 to −4.5; $P = 0.002$), which correspond to 5.1%, 7.3%, and 7.2% decreases, respectively. No statistically significant differences in TG, HDL-C, ApoA-I and ApoB levels between the two treatment periods were detected.

When comparison inside each treatment group was performed, no significant difference was observed. In the glucomannan treatment groups, the TC and LDL-C changes were −5.2 ± 12.40 mg % ($P = 0.135$) and −9.00 ± 18.66 mg% ($P = 0.123$), respectively.

Furthermore, when results were reanalyzed according to sex, we observed a TC decrease of 13.5 mg/dL (95% CI, −23.4 to −3.5; $P = 0.011$), 7.5 mg/dL (95% CI, −20.9 to 5.9; $P = 0.250$) and LDL-C decrease of 12.5 mg/dL (95% CI, −22.2 to −2.7; $P = 0.015$), 7.0 mg/dL (95% CI, −18.9 to 5.1; $P = 0.236$) in girls and boys, respectively. This change was significant in girls, but not in boys and corresponds to a percentage of 6.1 and 9.0 for TC and LDL-C, respectively, in the former group. Concerning HDL-C, values were increased (6.2%) when comparing the two treatments in males ($P = 0.045$). Non–HDL-C level reductions were detected in girls and boys: 10.9 mg/dL (95% CI, −20.2 to −1.5; $P = 0.025$) (6.8%) and 11.7 mg/dL (95% CI, −20.1 to −1.0; $P = 0.035$) (7.7%), respectively (Table 4).

Discussion

Treatment of inherited lipid disorders must start early to improve cardiovascular prognosis. A correct approach to such disorders should first involve dietary and lifestyle changes. Indeed, optimizing the intake of calories comprising total fats, saturated fats, and cholesterol lowers LDL-C concentrations from 8% to 15% in children [23]. The intake of fibers contained in cereals, fruits, and vegetables [24], as part of a correct dietary regimen, further ameliorates lipid profile [25]. In particular, fruit consumption appears to be inversely correlated to the carotid intima-media thickness (an established surrogate marker of CVD) in adults [26]. In children, fiber intake should conventionally correspond (in weight) to years of age plus 5 g/d [2]. However, this advice is very rarely heeded.

The use of glucomannan is a viable option to increase soluble fiber intake. Glucomannan acts by prolonging gastric emptying and increasing satiety, in turn reducing food ingestion. These activities modulate circulating cholesterol and glucose

Table 3
Serum lipids at baseline and at the end of each treatment period

Parameter (mg/dl)	Baseline		Glucomannan			Placebo			Mean absolute change (A-P) (95% CI)	P*
	Group 1 (n = 18)	Group 2 (n = 18)	Group 1 (n = 18)	Group 2 (n = 18)	P*	Group 1 (n = 18)	Group 2 (n = 18)	P*		
TC	227.7 ± 22.2	209.8 ± 23.2	216.1 ± 26.9	200.6 ± 15.8	0.135	231.8 ± 41.2	204.6 ± 23.8	0.053	−10.8 (−18.5; −3.1)	0.008
All (n = 36)	221.7 ± 23		210.4 ± 22.6			221.2 ± 34.6				
LDL-C	154.8 ± 23.1	128.6 ± 12.8	142.2 ± 27.0	124.6 ± 12.2	0.123	161.2 ± 37.2	125.0 ± 20.8	0.064	−10.1 (−17.4; −2.9)	0.008
All (n = 36)	147.6 ± 23		135.7 ± 22.1			145.6 ± 32.9				
HDL-C	52.4 ± 8.5	56.3 ± 9.0	55.2 ± 11.7	61.6 ± 9.4	0.951	54.6 ± 11.8	59.2 ± 10.0	0.391	0.4 (−2.1; 2.9)	0.739
All (n = 36)	56 ± 9.6		58.3 ± 11.9			57.9 ± 11.9				
TG	96.7 (43–231)	84.8 (32–164)	95.4 (45–241)	68.3 (43–235)	0.538	83.8 (43–134)	98.4 (35–118)	0.461	−3.8 (−17.4; 9.8)	0.399
All (n = 36)	80.5 (38–231)		69 (35–241)			74 (36–235)				
Apo B	100.1 ± 11.3	98.6 ± 10.5	106.6 ± 11.1	83.6 ± 7.5	0.707	99.0 ± 15.9	87.9 ± 12.1	0.980	3.5 (−0.6; 7.6)	0.092
All (n = 36)	101.2 ± 12.3		96.3 ± 14.7			93.9 ± 14.1				
Apo A-I	138.2 ± 11.5	149.7 ± 18.6	140.1 ± 22.2	140.3 ± 14.4	0.355	131.5 ± 16.0	139.9 ± 11.2	0.837	3.5 (−1.1; 8.2)	0.135
All (n = 36)	145 ± 17.5		141.3 ± 20.1			137.6 ± 16				
Non-HDL-C	174.2 ± 22.7	133.2 ± 14.9	160.5 ± 26.0	139.0 ± 12.9	0.096	177.6 ± 37.9	145.4 ± 23.2	0.165	−11.2 (−18; −4.5)	0.002
All (n = 36)	165.7 ± 22.9		152.1 ± 22.8			163.3 ± 33.2				

Values are mean ± SD or median (min-max). A: glucomannan; P: placebo
* Statistical significance for comparison between the treatments by paired *t* test or Wilcoxon rank-sum test.

concentrations, suppress hepatic cholesterol synthesis, increase fecal elimination of biliary acids, reduce postprandial hyperglycemia, and body weight [6]. Glucomannan does not exhibit AEs on the absorption of oligoelements such as iron, calcium, copper, and zinc, as demonstrated in adults [27,28] and children [29]. Indeed, in our study, the compliance to glucomannan was adequate: Children regularly took their capsules and no major AEs were reported. Minor AEs of glucomannan supplementation were irrelevant and discontinuous.

Preliminary studies in children aimed at assessing the efficacy of soluble fibers on LDL-C concentrations reported mixed results, ranging from no change to a 30% decrease [11–21]. Such variability might be conceivably attributed to participant selection and study designs, administered doses, and dietary regimens. The study design is particularly relevant and a cross-over study allows assessing intraindividual variabilities, in addition to intergroup changes also recorded in parallel trials. Carry-over effects could be excluded by the absence of significant differences when comparing the two groups of each treatment. In our study, biochemical analyses were not performed at the start of the second half of the intervention, but it should be noted that the effective period of glucomannan was contained within 4 wk (Table 3).

As far as we know, three cross-over trials in children have been published. A 16-wk trial [17] employed locust bean gum in six FH and five normal adolescents, and showed a significant 6% to 19% LDL-C decrease when comparing active and placebo groups. In a second study, limited to 11 borderline adolescents who consumed isabogol husk for 3 wk, a 7% LDL-C decrease was reported [16]. A third trial employed psyllium in 20 mild hypercholesterolemic children, with no significant effect [18]. It should be noted that very limited numbers of children—possibly with different types of hypercholesterolemia—were studied. Furthermore, fiber—including locust bean gum, isabogol husk, or psyllium—was added to food at variable daily dosages of 10 g to 20 g [17], 25 g [16], or 5 g [18]. All these variables could explain the differences in results, raising the question of whether fiber would be more beneficial to children with moderate or elevated hypercholesterolemia.

In this study, we observed a small, but significant reduction in TC and LDL-C, after 2 mo of glucomannan versus placebo treatment, specifically in girls. On the contrary, non–HDL-C decreased significantly in girls and boys.

The effectiveness of fiber supplementation in reducing TC and LDL-C in girls was previously reported in two studies [12,17], corroborating our results. Sex and hormonal status influence lipoprotein changes, as evidenced by the fact that men are at higher risk for CVD than women at younger ages, whereas postmenopausal women are at a higher risk than their younger counterparts [30,31]. In relation to the effect of fiber intake on men and women, one study reported that sex and hormonal status in adults influence the psyllium-induced responses to plasma lipids by increasing plasma TG concentrations in postmenopausal women, whereas a decrease in plasma TG in men and no change in premenopausal women were observed [32]. On the contrary, another study did not find any influence of sex and hormonal status on the psyllium and phytosterols effects on plasma lipids, suggesting that phytosterols might have

Table 4
Serum lipids at baseline and at the end of each treatment period, according to gender

Parameter (mg/dl)	Females (n = 20)				Males (n = 16)			
	Baseline	Glucomannan	Placebo	P*	Baseline	Glucomannan	Placebo	P*
TC	223 ± 24.5	213.1 ± 22.6	226.6 ± 35.5	0.011	220.1 ± 21.8	207 ± 22.8	214.5 ± 33.3	0.250
LDL-C	146.5 ± 25.7	136.3 ± 23	148.8 ± 34.4	0.015	149.1 ± 19.7	135.1 ± 21.8	142 ± 32.6	0.236
HDL-C	55.7 ± 8.9	57.7 ± 11.6	60.3 ± 11.5	0.062	56.3 ± 10.7	59.1 ± 12.5	54.9 ± 12	0.045
TG	98 (43-231)	90 (45–241)	74 (57–134)	0.794	67 (38–162)	58 (35–131)	74 (36–235)	0.105
Apo B	101.5 ± 13.8	98.6 ± 15.5	93.6 ± 12.7	0.112	100.9 ± 10.5	93.7 ± 13.7	91.9 ± 13.2	0.526
Apo A-I	147.1 ± 18	143 ± 18.3	141.3 ± 12.9	0.578	142.4 ± 17.1	139.4 ± 22.6	133.6 ± 19.1	0.136
Non-HDL-C	167.3 ± 24	155.4 ± 23.5	166.2 ± 34	0.025	163.8 ± 22.1	147.9 ± 22	159.6 ± 32.7	0.035

Values are mean ± SD or median (min-max)
* Statistical significance for comparison between the treatments by paired *t* test or Wilcoxon rank-sum test.

outweighed the effects of psyllium alone, as influenced by sex and hormonal status [33]. We currently have no exhaustive explanation for the observed difference between males and females, but we would like to underscore that the examined cohorts (from the present study and from other pediatric reports) include mainly peripubertal patients, where more marked discrepancies between gender have been observed: Hormonal variations could largely explain the results [34,35]. This issue is of particular interest and requires further, ad hoc investigations.

Among the surrogate markers of CVD, non–HDL-C and ApoB are well recognized and predictive ones [36] also in childhood [37], but they have not been currently evaluated by fiber trials in children [4,6]. In our study, the non–HDL-C reduction combined with the significant HLD-C increase represents the only efficacy marker detected in males. On the contrary, ApoB did not decrease significantly—neither in girls nor in boys—when comparing placebo with fiber. As ApoBs are transported by LDL particles in a 1:1 ratio, this observation suggests the formation of small dense LDL (sdLDL) fractions. sdLDL may be more susceptible to oxidation and have a lower clearance rate as the result of a reduced affinity for the LDL receptor [38]. This would represent a potentially noxious condition because these lipoproteins are thought to be pro-atherogenic [39,40]. To our knowledge, there are no reports evaluating changes in lipoprotein morphology and subclass distribution resulting from soluble fiber supplementation in children.

In dyslipidemic adults, fiber supplementation is beneficial. Oat fiber supplementation reduced sdLDL compared with wheat cereals in 36 obese adults [41] and the addition of barley to a healthy diet led to favorable changes in plasma lipids in both men and women [42]. In particular, larger LDL fractions and increased mean LDL particles were observed in postmenopausal supplemented women [42]. Furthermore, by combining fiber and phytosterol in 33 normal adults, one study obtained a decrease in ApoB, intermediate density LDL, and LDL fraction levels, and intermediate small LDL, although not a significant reduction of small and very small LDL lipoproteins [33]. The consumption of whole meal wheat foods for 3 wk reduced significantly plasma TC, LDL-C, and ApoB levels in healthy individuals, even though sdLDL fractions increased in the postprandial phase [25].

We should acknowledge that the small number of patients we recruited limited our study and that larger cohorts might provide more detailed information on the sex effects of glucomannan.

In conclusion, glucomannan supplementation for children affected by primary hypercholesterolemia significantly lowers TC, LDL-C, and non–HDL-C concentrations in girls. This treatment succeeded in reducing non–HDL-C and improving HDL-C levels in boys. ApoB levels were not influenced by glucomannan supplementation. Indeed, it appears as if the effects of glucomannan are limited to a modulation of serum lipid profile, conceivably consequent to a reduced fat and cholesterol absorption at the intestinal level. Our results do not moderate the need for statin therapy of high-risk children, but underscore the use of a correct and complementary dietary intervention aimed at optimizing the therapeutic approach. Finally, we confirm the usefulness of glucomannan as a feasible and effective mean to ingest soluble fiber that positively modulates plasma cholesterol.

Conflict of interest

The authors declare no conflict of interest.

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