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Low dose chromium-polynicotinate or policosanol is effective in hypercholesterolemic children only in combination with glucomannan

Francesco Martino [a], Paolo Emilio Puddu [b,*], Giuseppe Pannarale [b], Chiara Colantoni [a], Eliana Martino [a], Tarcisio Niglio [c], Cristina Zanoni [a], Francesco Barillà [b]

[a] Lipid Research, Dipartimento di Pediatria e Neuropsichiatria Infantile, "Sapienza" Università di Roma, Rome, Italy
[b] Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, "Sapienza" Università di Roma, Rome, Italy
[c] Istituto Superiore di Sanità, Rome, Italy

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ABSTRACT

Objective: A low-fat, fiber-rich diet is the first step in the management for hypercholesterolemic children. Glucomannan (GM) is a natural fiber that has been demonstrated to lower total and LDL-cholesterol. The use of high-dose chromium-polynicotinate (CP) and policosanol (PC) has also shown cholesterol-lowering benefits. We aimed at investigating the effects of low-dose CP or PC and their GM combination in hypercholesterolemic children.
Methods: A double-blind trial was conducted in 120 children (60 M, 60 F, 9 ± 4 years, median 9.6 years, range: 3–16 years) randomly assigned to 5 neutraceutical and 1 placebo (only resistant starch) 8-week treatment groups. Fasting blood glucose (FBG), total cholesterol (CholT), triglycerides (TG), HDL and LDL cholesterol were considered.
Results: GM combination of low-dose CP or PC reduced CholT and LDL without changing HDL, TG and FBG. The highest post-treatment changes were seen after GM combination with CP (CholT 85 ± 3% and LDL 85 ± 5%, of pretreatment) which was significantly ($p < 0.01$) less than with low-dose CP or PC and starch. When GM was associated with starch, there was no lipid lowering effect, which was an unexpected finding as compared to previous data with GM and no starch. No adverse effects were reported.
Conclusion: This is the first report to show the cholesterol-lowering efficacy of GM combined treatment with low-dose CP or PC. Further studies are needed to investigate the best combinations and doses of nutraceutics to be added to the standard GM treatment. The potential negative association of GM and nutraceutics with starch is clearly shown.

1. Introduction

Atherosclerotic cardiovascular disease (CVD) is the most important cause of death in the Western world. Many studies have demonstrated the tracking evolution from the early intimal lesion (fatty streak) in childhood to adult atheroma [1–4]. Hypercholesterolemia is a well-recognized risk factor for developing atherosclerosis and an early increase of cholesterol may be a relevant factor in the progression of atherosclerosis in adults [3]. Consistently it has been reported that measurement of total cholesterol (CholT) and low density lipoprotein cholesterol (LDL) in childhood predicts the development of CVD in adults [2,3]. On the other hand, hypercholesterolemia in 6–14 years old children is not a rare condition if properly looked for [5,6]; at least in a Southern European region, based on age and gender specific quantile cholesterol distribution it may be as high as 5% [7]. Therefore, many authors advocated an early control of hypercholesterolemia in childhood to prevent CVD in adulthood [4–6]. However, the guidelines of the National Cholesterol Education Program (NCEP) [8] suggest not to use in children chemical drugs until the age of 8–10 years unless homozygous familial hypercholesterolemia is present. Therefore, the current management of children and adolescents with high LDL includes diet changes and increased physical activity [9].

* Corresponding author. Laboratory of Biotechnologies Applied to Cardiovascular Medicine, Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatrical Sciences, Sapienza, University of Rome, Viale del Policlinico 155, Roma 00161, Italy. Tel.: +39 06 49972659; fax: +39 06 4453891.
E-mail address: paoloemilio.puddu@uniroma1.it (P.E. Puddu).

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A low-fat and fiber-rich diet is the first treatment in all hypercholesterolemic children [10]. The quality of dietary fiber is important: water-soluble fibers such as pectin, gums and mixed-linked β-1,3- and 1,4-D-glucans have a significant cholesterol-lowering effect [11]. Glucomannan is a natural gel forming fiber extracted from *Amorphophallus konjac* tubers. There are many kinds of glucomannan but only the one with high viscosity is effective in the treatment of metabolic disorders, overweight and obesity [12]. This fiber may decrease serum levels of CholT and LDL, without changes in high density lipoprotein cholesterol (HDL). Previous studies demonstrated these positive effects in adults [12,13] and in children [14–16]. The action of high viscosity glucomannan in decreasing and maintaining the targeted cholesterolemia is also validated by the European Food Safety Authority (EFSA) report and many clinical trials [11–17]. Even though it has been reported that a glucomannan enriched diet may be effective in reducing LDL [11,17], in some patients its efficacy is limited. Therefore, other nutraceutics such as policosanol and chromium-polynicotinate were investigated in the treatment of lipid disorders showing cholesterol-lowering effects [16–18]. In particular, policosanol, a mixture of high-molecular-mass aliphatic alcohols isolated and purified from sugar cane, has been shown to inhibit cholesterol biosynthesis in the liver at a step before mevalonate generation [18], while chromium-polynicotinate, a niacin-bound trivalent chromium compound, has antioxidant properties and reduces the secretion of LDL particles [19]. Unfortunately, subjects taking high doses of these nutraceutics experienced adverse effects [20–23].

The aim of the present study was to investigate the lipid-lowering efficacy of low doses of policosanol and chromium-polynicotinate. These nutraceutics were given alone or in combination with glucomannan. To complement the capsules' mixture of policosanol and chromium-polynicotinate starch was included, which was also given in the control placebo group; accordingly, a combination of starch and glucomannan was also investigated, and 6 groups of hypercholesterolemic children were considered for randomization. A parallel comparison with children enrolled in a previous study and receiving glucomannan without starch [14] was also performed.

2. Methods

2.1. Subjects

One hundred and thirty-two hypercholesterolemic children (66 M, 66 F, 9.5 ± 3.5 years) were randomly enrolled from the population of pediatric patients referred to the Lipid Research Clinic, Department of Pediatrics, "Sapienza" University, Rome, Italy. The inclusion criteria of eligible patients were the following. 1) CholT greater than 170 mg/dl in two measurements before enrollment. 2) No drug treatment before enrollment. 3) No dietary treatment in the previous three months. All children had at least one of the additional criteria: one parent with CholT higher than 240 mg/dL or a family history of CVD in first- or second-degree relatives. The exclusion criteria were any other disease or any drug treatment affecting lipid plasma levels. All parents of the participating children gave their written informed consent before the beginning of the study. The study was approved by the local Ethical Committee.

2.2. Study design

A sample size of 19 was calculated to achieve 91% power to detect a mean of paired differences of 10.0 with an estimated standard deviation of differences of 10.0 and with a significance level (alpha) of 0.01000 using a two-sided paired *t*-test. The calculated size was increased by 15% in order to have a prudential approach and 22 individuals per group were considered. The study was a randomized double-blind six-arm parallel interventional trial. All subjects underwent a complete physical examination including anthropometric, heart rate and blood pressure measurements and, after a 1 week Step-One-Diet run-in period, were randomly allocated to six groups of 8-week treatment. Using the Frederickson's classification there were 50 of 120 children with either familial hypercholesterolemia of borderline hypercholesterolemia, which were distributed similarly among the treatment groups. There were:

- Control group = receiving capsules containing resistant starch 533 mg as placebo. Starch or amylum is a carbohydrate consisting of a large number of glucose units joined by glycosidic bonds. This polysaccharide is produced by all green plants as an energy store. It is the most common carbohydrate in the human diet and is contained in large amounts in such staple foods as potatoes, wheat, maize (corn), rice and cassava. Pure starch is a white, tasteless and odorless powder that is insoluble in cold water or alcohol. It consists of two types of molecules: the linear and helical amylase and the branched amylopectin. Depending on the plant, starch generally contains 20–25% amylose and 75–80% amylopectin by weight [24];
- GM + CP group = glucomannan 500 mg + chromium-polynicotinate 0.2 mg;
- CP group = chromium-polynicotinate 0.2 mg + starch 500 mg;
- GM + PC group = glucomannan 500 mg + policosanol 1.2 mg;
- PC group = policosanol 1.2 mg + starch 500 mg;
- GM group = glucomannan 500 mg + starch 500 mg.

Treatment lasted 8 weeks. Children aged up to 6 years received 2 capsules at lunch and 2 at dinner. Children aged over 6 years received 3 capsules at lunch and 3 at dinner. Parents verified daily the administering of capsules and they wrote a diary about food intake. Compliance with diet and treatment administration was confirmed by interview. At each visit the number of remaining capsules was checked. At each visit, subjects and their parents were asked to report any possible adverse effect that occurred during the treatment period.

2.3. Biochemical analyses

Before and after the 8-week treatment period all study subjects had a venous blood sampling for the assessment of plasma lipids. Blood samples (10 ml) were collected after an overnight fast into plain tubes and EDTA (1 mg/ml) containing tubes to separate serum and plasma, respectively, by centrifugation at 3000 rpm for 15 min. Fasting blood glucose (FBG), CholT, TG and HDL were measured using standard enzymatic-colorimetric procedures. LDL was calculated by the standard Friedewald formula.

2.4. Statistical analysis

After testing for normal distribution, differences between and within the 6 treatment groups were compared by the analysis of variance (ANOVA). The Dunnett's test was performed to compare all of the other means to the mean of the control group so that there are $k - 1$ comparisons. Dunnett's multiple comparison procedure gives an experiment wise error rate of α. Two-sided, simultaneous confidence intervals were provided for the difference between each treatment and the control. In addition, having delta percent changes of CholT and LDL (as compared to pretreatment values) as dependent variables, analysis of covariance among groups was performed considering: a) gender and age along with baseline