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ORIGINAL ARTICLE

Primary hyperlipidemias in children: effect of plant sterol supplementation on plasma lipids and markers of cholesterol synthesis and absorption

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Abstract Plant sterols lower serum cholesterol concentration. Available data have confirmed the lipid-lowering efficacy in adults, while there is a relative dearth of data in children and almost exclusively restricted to subjects with familial hypercholesterolemia (FH). Aim of the present study was to evaluate the efficacy, tolerability and safety of plant sterol supplementation in children with different forms of primary hyperlipidemias. The effect of plant sterol consumption on plasma lipids was evaluated in 32 children with heterozygous FH, 13 children with Familial Combined Hyperlipidemia (FCH) and 13 children with Undefined Hypercholesterolemia (UH) in a 12-week open-label intervention study using plant sterol–enriched yoghurt. Plasma lipids and apolipoproteins were measured by routine methods. Markers of cholesterol synthesis (lathosterol) and absorption (campesterol and sitosterol) were measured by GC–MS. Tolerability and adherence to recommended regimen was very high. A significant reduction was observed in LDL-cholesterol in the three groups (10.7, 14.2 and 16.0% in FH, FCH and UH, respectively). Lathosterol concentrations were unchanged, reflecting a lack of increased synthesis of cholesterol. Of the two absorption markers, only sitosterol showed a slight but significant increase. Daily consumption of plant sterol dairy products favorably changes lipid profile by reducing LDL-cholesterol. To our knowledge, this is the first report of the use of plant sterols–enriched foods in treating children with primary hyperlipidemia such as FCH and UH, likely to be the most frequent form also in the young age in the western populations.

Keywords Plant sterols · Hyperlipidemia · Children

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Introduction

The impact of coronary heart disease risk factors on mortality is evident in all ages and is becoming especially strong in young persons [1]. Familial hyperlipidemia represents a major cardiovascular (CV) risk factor often occurring since pediatric age, when early atherosclerotic changes can already be demonstrated [2]. The relationship between hyperlipidemia and vascular events is unquestioned [3], and it is now clear that dietary and eventually drug treatment needs to be started as soon as possible [4]. Lowering of low-density lipoprotein (LDL) cholesterol below 160, 130 and 100 mg/dl, in low, medium and high risk subjects, respectively, is the target of the therapy in adults. In patients with diabetes, elevated triglyceride levels and low HDL-cholesterol levels become targets of therapy as well [5]. In children and adolescents, total plasma and LDL-cholesterol concentration are strongly influenced by age, gender, ethnicity and pubertal status. Acceptable levels are usually set below the 75th percentile, corresponding to <170 and <110 mg/dl for total and LDL-cholesterol, respectively [6]. Habitual dietary advice yields a 10–15% cholesterol reduction, not sufficient to reach the above reported goals in a large proportion of patients.

However, there is still some reluctance to start a lipid lowering drug therapy in pediatric age. As a consequence, many young hyperlipidemic patients who would need a substantial reduction of plasma cholesterol actually do not receive the appropriate treatment.

Phytosterols are plant components presenting a chemical structure similar to that of cholesterol [7–9]. They include mainly sitosterol and campesterol which are introduced with diet vegetable oils in amount corresponding to that of cholesterol (200–400 mg/die). Phytosterols compete with cholesterol for intestinal absorption and display cholesterol from micelles. Both cholesterol and phytosterols require the Niemann-Pick C1 Like 1 Protein (NPC1L1) to obtain entry in enterocytes. Non-esterified cholesterol and phytosterols are pumped back in the intestine lumen through the ABCG5 complex. Eventually, about 50% of cholesterol, but less than 5% of plant sterols, is absorbed [10–12].

It has been demonstrated that phytosterol supplementation is able to reduce LDL-C levels in adults with familial hypercholesterolemia (FH) by 10%, and the consumption of 2 g/day of phytosterols is part of the recommendation of NCEP [13]. Trials performed in FH children have confirmed their usefulness [14].

The clinical experience with phytosterols in pediatric subjects is virtually restricted to FH patients, a genetic disorder characterized by elevated cholesterol from birth. A number of children with hypercholesterolemia, however, have different disorders, like familial combined hyperlipidemia (FCH) or polygenic hypercholesterolemia (PH). Particularly FCH is a condition with increased risk of CV outcome in which LDL-C levels monitoring is mandatory.

Aim of the present study was to evaluate the efficacy, tolerability and safety of plant sterol supplementation in children with different forms of primary hyperlipidemias.

Methods

Patients

Fifty-eight outpatients affected by primary hyperlipidemia including 32 heterozygous FH (M/F,15/17), 13 FCH (M/F,6/7) and 13 children (M/F,6/7) with Undefined Hypercholesterolemia (UH) were recruited. The family tree was examined for two generations to clearly detect the disorder heritage. The diagnosis of FH was made according to the following criteria: LDL-cholesterol levels n >95th age- and sex-specific percentile [males and females (5–9 years) exceeding 129 and 140 mg/dl, respectively; males and females (10–14 years) exceeding 132 and 136 mg/dl, respectively]; dominant inherited hypercholesterolemia; family history of precocious cardiovascular events in parent or grandparent, tendon xantomata in parent or grandparent [15].

FCH was diagnosed in subjects with total cholesterol (TC) and/or triglyceride (TG) serum levels greater than 90th percentile of the reference population, with hypercholesterolemia and/or hypertriglyceridemia in at least one first-degree relative and intrafamilial variability [16]. Children were diagnosed as UH when showing LDL-C exceeding 90th percentile, with or without family history of dyslipidemia, and did not fulfill criteria for inclusion in FH or FCH group. Secondary forms of dyslipidemia were excluded, i.e. renal disease, liver disease, endocrinopathies, overweight and obesity, diabetes, immune-hematological disorders as well patients submitted to drug therapy such as anticonvulsants known to affect lipid metabolism.

Children in the age range 8–16 years were enrolled. They had to be on stable recommended Step 1 diet since at least 6 months and none of them was smoker or on a lipid lowering treatment in at least the past 3 months.

Study design

Enrolled children underwent a full clinical and biochemical examination (visit 0). Clinical and biochemical examination were repeated after a 12-week treatment with a yoghurt supplemented with phytosterols (visit 1). Yoghurt (100 ml) was monthly provided to children. The sterol content was 1.6 or 2.0 g per day, the higher content delivered to patients weighing n >40 kg.

To assess the adherence to diet, children were asked to provide a weekly diary at visit 0 and at visit 1 from which the nutrient intake was calculated. Tolerability was assessed by asking the patients and/or their guardians to daily record the assumption of the yoghurt, to record any intolerance and/or possible side effect.

Efficacy was evaluated through the modifications in blood lipids and apoproteins. Patients were arbitrarily classified in two groups (A and B) on the basis of LDL-C decrease at Visit 1 >5 or ≤5%, respectively. Safety was evaluated mainly through the variation in campesterol and sitosterol levels standardized for cholesterol concentration.

Ethics committee approved the trial and written informed consent was obtained from the legal guardians of the children and from the proband child. The study was conducted according to the declaration of Helsinki.

Analytical procedures

Blood samples for lipoprotein analysis were obtained after an overnight fast. Plasma cholesterol and triglycerides were measured by routine methods on a MODULAR

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