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ORIGINAL CONTRIBUTION

Inulin-enriched pasta affects lipid profile and Lp(a) concentrations in Italian young healthy male volunteers

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Abstract *Background* Inulin has been suggested to have beneficial effects on lipids, especially on triglyceridemia. Few data are available about the effects of inulin on Lipoprotein(a), a low-density lipoprotein-like particle considered as an independent risk factor for atherosclerosis. Adding inulin to pasta could be a preventive strategy for delaying the onset of atherosclerosis. *Aim of the study* was to evaluate the effects of inulin-enriched pasta on lipid profile and on Lipoprotein(a) in young healthy subjects. *Methods* Twenty-two young healthy male volunteers entered a randomized double blind cross-over study consisting of a 2-weeks run-in period, a baseline assessment, two 5-weeks study periods (11% inulin-enriched or control pasta), and an 8-weeks wash-out period in between. Serum lipid concentrations were evaluated by routine biochemical analyses and plasma Lipoprotein(a) concentrations by ELISA. The size of apolipoprotein(a) isoforms was determined by Western blot and immunodetection. *Results* Significant differences at baseline and in the treatment groups were found for HDL-cholesterol ($P = 0.004$), total cholesterol/HDL-cholesterol ratio ($P = 0.006$), triglycerides ($P = 0.04$), and Lipoprotein(a) ($P = 0.02$) concentrations (data analyzed by Friedman test). Dunn's multiple comparison test was used to assess the significance of differences between inulin-enriched pasta diet vs. baseline. HDL-cholesterol concentrations increased by 35.9%; total cholesterol/HDL-cholesterol ratio, triglycerides, and Lipoprotein(a) concentrations decreased by 22.2, 23.4, and 16.5% respectively. *Conclusions* Inulin-enriched pasta administration induced significant effects on lipid pattern parameters in young healthy volunteers, including a significant reduction in Lipoprotein(a) concentrations.

Key words atherosclerosis – blood lipids – diet – fiber – inulin – lipoprotein(a)

Introduction

Prebiotics are undigested dietary components that alter the intestinal flora and stimulate the growth of healthy bacteria [28].

Inulin, which belongs to a class of carbohydrates known as fructans is among the prebiotics that have been most widely studied, in relation also to presumed beneficial effects on lipid metabolism. Convincing lipid-lowering effects, especially for triglycerides, have been reported in animals, essentially due to a reduction in the number of plasma VLDL particles [8]. By opposite, reports in humans have been controversial: some authors reported no or poor effect on lipid metabolism [7, 11], whereas others reported some effects on triglycerides [21, 29] and/or, to a lesser extent, also on plasma cholesterol concentrations [37]. Actually, a recently performed meta-analysis of available studies to quantify the effects in humans of dietar inulin-type fructans [3] has shown that the intake of inulin significantly reduced serum triacylglycerol concentrations.

In literature, no studies but one, performed in mild hypercholesterolaemic individuals [11], have described the effects of inulin-type fructans on Lipoprotein(a) [Lp(a)], a plasma low-density lipoprotein (LDL)-like particle. A high Lp(a) concentration is an independent risk factor for coronary heart disease and peripheral vascular disease [36]. Plasma Lp(a) concentrations are associated with the highly polymorphic apo(a) gene. The variable number of apo(a) Kringle-IV coding domains determines about half of the Lp(a) variability: the number of Kringle-IV domains corresponds to apo(a) isoforms of different sizes (300–800 kDa). Apo(a) size and Lp(a) level are inversely related, even though the relationship is not linear and differs among populations [31]. Although plasma Lp(a) concentration is considered a quantitative genetic trait, a role is now emerging for non genetic factors, such as infections [4], therapeutic life-style changes [30], and diet [5, 11, 12, 15, 18, 27, 32–34, 38] in modifying this parameter.

The initial stages of atherosclerosis can occur early in life and Lp(a) concentrations, along with other established risk factors (e.g. low-density lipoprotein cholesterol, triglycerides, blood pressure, body mass index, and cigarette smoking habit), have now been reported to be implicated in the atherosclerotic risk even in young individuals [39]. Therefore, early dietary intervention in healthy subjects, using prebiotics, may be a reliable preventive approach to delay the onset and related complications of atherosclerosis [17, 20, 25].

Adding inulin to pasta may be a suitable strategy, since it would represent a minimal change in the diet of Italian population and it could be maintained for a long period. In this context, pasta has already been administered as vehicle for testing other substances, such as soy proteins [6].

Starting from these bases, aim of the present study was to evaluate the effects of enriching pasta with the prebiotic inulin on the lipid profile and lipoprotein Lp(a) in young healthy subjects.

Methods

Subjects selection

Students from the Istituto Tecnico Agrario "B. Caramia" in Locorotondo (BA), Italy, were considered for inclusion in this study. The Institute has a refectory and internal kitchen. Twenty-two healthy male volunteers were enrolled and 15 completed the study. The mean age was 18.8 ± 0.7 years, height 176 ± 6 cm, weight 73.7 ± 14.6 kg, body mass index (BMI) 22.8 ± 2.3 kg/m^2. They denied having dyspepsia or other gastrointestinal diseases and did not take any medication. Information on the healthy status of subjects was obtained at the moment of enrollment during an examination consisting of an interview on the current diet, lifestyle and medical history, and a physical examination. Exclusion criteria were: BMI outside the range 20–25 kg/m^2, alcohol intake above 30 g/day, smoking habit, hypertension, diabetes mellitus and other pathologies (e.g. systemic, endocrine, collagen-related diseases, familial hypercholesterolemia, and hypertriglyceridemia). Subjects had not taken vitamins, minerals, non-steroidal anti-inflammatory or prokinetic drugs, antibiotics, bismuth, antacids, H2-receptor antagonists, omeprazole, sucralfate or misoprostol in the 6 months prior to the examination and had no previous history of gastric or duodenal ulcers or gastric surgery. Gastrointestinal symptoms were assessed by a specific questionnaire and on food records. Appropriate biochemical analyses were performed to evaluate the metabolic profile.

The protocol was approved by the local Ethics Committee and all subjects gave informed consent to take part in the study.

Pasta making and pasta characteristics

The formulation of the inulin-enriched pasta administered was as follows: 86% semolina, 3% durum wheat vital gluten, 11% inulin. Inulin from chicory (Raftline HP-Gel) was supplied by Orafti (Tienen, Belgium). The average degree of polymerisation was >23 units of fructose or glucose. Standard pasta was composed of 100% durum wheat semolina. As to the pasta shape, each formulation was made up into long pasta (spaghetti) and short pasta (rigatoni) in a pilot pasta-making plant (Namad, Rome, Italy). Soluble,

Table 1 Chemical composition (% weight) and energy of control pasta and inulin-enriched pasta

	Control pasta	Inulin-enriched pasta
Moisture	12.5	11.8
Ash	0.90	0.59
Proteins	12.5	11.5
Fats	1.9	2.0
Dietary fibers		
Insoluble	2.3	3.1
Soluble	0.8	1.7
Total	3.1	4.8
Carbohydrates	67.7	58.3
Fructans	1.4	11.0
Energy per 100 g		
kcal	340	313
kJ	1,443	1,330

insoluble, and total dietary fibers were quantified by the enzymatic gravimetric procedure [22]. Analysis of moisture, ashes, lipids, and proteins was made by AACC standard methods [1]. Digestible carbohydrates were calculated by difference. Energy was calculated as kcal and kJ: proteins = 4 kcal/g (17 kJ/g); carbohydrates = 4 kcal/g (17 kJ/g); lipids = 9 kcal/g (37 kJ/g); dietary fibers = 0 kcal/g (0 kJ/g). Fructans = 1.5 kcal/g (6.3 kJ/g).

The chemical composition (% weight) and energy content of control pasta and inulin-enriched pasta are reported in Table 1.

Study design

The study featured a randomized double blind cross-over design consisting of a baseline assessment and two 5-weeks study periods (11% inulin-enriched pasta or control pasta diet: 100 g/day) and a wash-out period (8 weeks) in between, with a 2-weeks run-in period. Cross over design has been used by other authors in nutritional studies [2].

Throughout the study (run-in period and intervention periods), the subjects consumed a controlled diet and abstained from alcohol or heavy physical activity. All dietary instructions were provided by trained staff, who interviewed each subject before the study to obtain a report of the subject's usual diet to calculate their energy requirement. The diet provided 50% of total energy as carbohydrates (about 20% simple, mainly as fruit; about 30% complex, mainly as bread, potatoes, and pasta) and 35% fats (about 12% each of saturated, monounsaturated, and polyunsaturated fatty acids). The sources of saturated fatty acids were mainly butter, cheese, and meat. Food plants with a rich inulin content were excluded. The subjects consumed three meals per day. Foods, meals, and beverages were provided by the Institute kitchen.

To ensure compliance, meals and food intake were verified constantly by the refectory staff and dietary surveys were conducted during the last week of each diet period.

All the subjects in the study wrote down any extras in their diets. A questionnaire on gastrointestinal symptoms was administered before and after the two diets. The two diets differed only as regards the pasta composition.

Measurement of lipids and lipoprotein Lp(a)

Routine biochemical analyses were performed to evaluate serum lipid concentrations. Blood was drawn in the morning, with the subjects fasting for at least 12 h, collected in chilled bags and then stored at −80°C until laboratory analyses. Total cholesterol and high density lipoprotein fraction were measured by commercially available enzymatic assays. The LDL cholesterol was calculated using the Friedewald formula [10].

Plasma Lp(a) concentrations were determined in duplicate by ELISA using the Immunozym Lp(a) Kit (Progen Biotechnik GmbH, Heidelberg, Germany). The distribution of Lp(a) concentrations was examined for skewness [35].

Apo(a) phenotyping

Plasma samples were subjected to 0.1% SDS–1.5% agarose gel electrophoresis in reducing conditions [14]. Immunoblotting was performed with sheep antiserum against human Lp(a) (IMMUNO, Technoclone GmbH, Vienna, Austria) and a peroxidase-conjugated secondary antibody (ICN Biomedicals, Costa Mesa, CA), and the bands were revealed by enhanced chemiluminescence (ECL). The size of apo(a) isoforms was determined by reference to a human Lp(a) isoform standard (IMMUNO, Technoclone GmbH, Vienna, Austria).

Statistical analysis

The data were analyzed firstly using simple descriptive statistics of centrality and dispersion. Since not all the variables were normally distributed, data were expressed as medians and the range. The Friedman repeated measures analysis of variance on ranks with Dunn's post test were used to compare the effects of different dietary treatments. Relationships between Lp(a) and lipids concentrations were assessed using the Spearman correlation coefficient. To evaluate Lp(a) concentrations according to

Table 2 Daily dietary intake during the 2 diet periods

	Control pasta	Inulin-enriched pasta
Energy intake (kcal/day)	2,860 ± 685.0	2,840 ± 851.5
Proteins (% of energy)	15.1% ± 1.9	15.3 ± 2.3
Carbohydrates (% of energy)	48.6 ± 7.6	49.6 ± 8.7
Fats (% of energy)	30.9 ± 5.9	32.7 ± 6.9
Fibers (g/day)	32.1 ± 7.4	30.2 ± 6.4

The dietary intakes as calculated from the dietary surveys conducted during the last week of each diet period. Values are mean ± SD

apo(a) isoforms size, isoforms were dichotomized as low-molecular-weight (LMW, 11–22 Kringle-IV repeats) and high-molecular weight (HMW, >22 Kringle-IV repeats) [19] and subjects were subdivided into group one (subjects having two LMW isoforms) and group two (subjects having at least one HMW isoform). The Mann–Whitney non parametric test was performed to compare Lp(a) concentrations between subjects in group one and group two.

All the differences were considered significant at a 5% level. A specific statistical package for exact nonparametric inference (StataCorp. 2005. Stata Statistical Software: Release 9. College Station, TX) was used.

Results

Dietary intake

The dietary intakes, as calculated from the dietary surveys conducted during the last week of each diet period, are shown in Table 2. The total energy intake, the percent of total energy intake, and the daily intakes of fiber (excluding inulin intake during the inulin period) were not significantly different. All the subjects followed the diets without major exceptions. According to the questionnaires on gastrointestinal symptoms, no subject complained of side effects related to inulin administration, such as flatulence, meteorism or post-prandial fullness. Finally, no modification in bowel habit was recorded during the study.

Lipids and Lp(a) concentrations

Serum lipids and plasma Lp(a) concentrations at baseline and during the study diets are reported in Table 3. The distribution of Lp(a) concentrations showed the characteristic skewed profile; skewnesses were: 1.487 at baseline; 1.801 with the control pasta diet; and 1.658 with the inulin-enriched pasta diet.

Statistically significant differences between baseline, control pasta, and inulin-enriched pasta diets were found in HDL-cholesterol ($P = 0.004$), total cholesterol/HDL-cholesterol ratio ($P = 0.006$), triglycerides ($P = 0.04$), and Lp(a) ($P = 0.02$) concentrations (data analyzed by Friedman repeated measures analysis of variance). The all pairwise multiple comparison post-test assessed the significance of differences between the inulin-enriched pasta diet vs. baseline (Table 3). In response to inulin-enriched pasta, HDL-cholesterol concentrations increased by 35.9%, whereas total cholesterol/HDL-cholesterol ratio, triglycerides, and Lp(a) concentrations decreased by 22.2, 23.4, and 16.5% respectively, compared to baseline values.

No correlations were present between Lp(a) and lipids concentrations, either at baseline, or in response to diets (data not shown).

Table 3 Serum lipids and plasma Lp(a) concentrations in the study subjects ($n = 15$) at baseline and during the 2 diet periods

Variables	Baseline	Control pasta	Inulin-enriched pasta
Cholesterol (mg/dl)	a 159.0 (129.0–185.0)	a 169.0 (116.0–234.0)	a 154.0 (105.0–214.0)
LDL-ch (mg/dl)	a 89.0 (74.0–117.0)	a 101.2 (55.0–163.6)	a 85.6 (50.4–131.4)
HDL-ch (mg/dl)	a 39.0 (29.0–65.0)	ac 44.0 (31.0–61.0)	bc 53.0 (30.0–73.0)
Cholesterol/HDL-ch	a 3.6 (2.7–5.5)	a 3.5 (2.1–6.3)	b 2.8 (2.3–5.8)
LDL-ch/HDL-ch	a 2.1 (1.5–3.2)	a 2.1 (0.9–4.4)	a 1.6 (1.1–3.5)
TG (mg/dl)	a 88.8 (46.0–169.0)	ac 84.0 (35.0–134.0)	bc 68.0 (37.0–128.0)
Lp(a) (mg/dl)	a 13.3 (0.9–63.2)	ac 12.6 (0.8–55.0)	bc 11.1 (0.8–56.4)

Reported values are medians and the range (in parentheses). Statistical evaluations were performed by the Friedman one way repeated measures analysis of variance and Dunn's multiple comparison test. For each row, median values not sharing a common superscript differ significantly ($P < 0.05$)
Cholesterol total cholesterol, *LDL-ch* LDL-cholesterol, *HDL-ch* HDL-cholesterol, *TG* triglycerides

Table 4 Plasma Lp(a) concentrations (mg/dl) in relation to apo(a) isoforms dimension at baseline and during the 2 diet periods

Subjects	Baseline	Control pasta	Inulin-enriched pasta
Group one ($n = 6$)	a 29.8 (17.1–63.2)	ac 26.5 (14.6–55.0)	bc 23.7 (11.1–56.4)
Group two ($n = 9$)	a 8.5 (0.9–15.8)	a 8.4 (0.8–15.4)	a 7.5 (0.8–22.3)

Group one: subjects carrying both low molecular weight (LMW, 11–22 Kringle-IV repeats) apo(a) isoforms
Group two: subjects having at least one high molecular weight (HMW, 23 or more Kringle-IV repeats) apo(a) isoform
Values are reported as medians and the range (in parentheses)
Statistical evaluations were performed by the Friedman one way repeated measures analysis of variance and Dunn's multiple comparison test. For each row, median values not sharing a common superscript differ significantly ($P < 0.05$)

Apo(a) isoforms size and Lp(a) response

The median value of apo(a) isoform sizes was 23 Kringle-IV repeats (range: 14–34 Kringle-IV repeats) in the studied subjects. The apo(a) size was causative for the Lp(a) levels: as shown in Table 4, plasma Lp(a) concentrations were higher in subjects having two LMW apo(a) isoforms ($n = 6$) (group one) than in subjects having at least one HMW apo(a) isoform ($n = 9$) (group two), both at baseline ($P < 0.001$, Mann–Whitney test) and after the diets ($P < 0.001$, control pasta diet; $P < 0.01$ inulin-enriched pasta diet, Mann–Whitney test).

In addition, the responsiveness of Lp(a) concentrations to diets was different between subjects in group one and those in group two. Statistically significant differences between baseline, control pasta diet, and inulin-enriched pasta diet were present only in subjects belonging to group one ($P = 0.002$, Friedman test). The all pairwise multiple comparison post-test assessed the significant difference between inulin-enriched pasta diet vs. baseline concentrations. In response to inulin-enriched pasta, Lp(a) concentrations decreased by 20.5% (Table 4).

Discussion

There has been an increasing interest in the potential of prebiotics such as inulin, in modifying some of the metabolic risk factors for cardiovascular diseases [16]. As regards its ability to lower circulating lipids, more convincing data from animal studies [39] are counterpoised by conflicting results obtained in humans. This discrepancy has been in turn attributed to relatively inactive pathway of hepatic fatty acid synthesis in humans [29], way of administration as well as low doses used to avoid the appearance of gastrointestinal symptoms [16]. However, it has already been demonstrated that the dominant features of inulin administration in normolipidaemic subjects are the effects on serum triglycerides [37], as also established by a more recent meta-analysis of randomized controlled trials in literature [3]. The evaluation of 15 eligible studies from 1995 to 2005 confirmed that the dietary intake of inulin-type fructans may exert a significant reduction in triacylglycerols (−7.5%). In this context, data from present study show that the introduction of inulin-enriched pasta as the only intervention on the current diet significantly reduced triglycerides and increased HDL-cholesterol levels. Control of these variables might be useful in long-range primary prevention starting from young age, considering that atherosclerosis begins early in life [23] and even "normal" levels of triglycerides can pose a significant risk of heart disease. In an 18-year follow up study, Miller et al. [24] found that people with triglyceride levels equal to or higher than 100 mg/dl were 50% more likely than those with lower levels to suffer from coronary heart disease and related consequences. Additionally, the finding of increased HDL-cholesterol concentrations is in agreement with data previously obtained in vitro [26] and may show preventive value, since HDL-cholesterol concentration is negatively associated with atherosclerotic plaques [9].

As far as Lp(a) is concerned, the relationship between its plasma concentrations and diet has already been described in literature [5, 11, 12, 15, 18, 27, 32–34, 38]. Our study specifically investigated the effect of inulin-based dietary treatment on Lp(a) concentrations in healthy normolipidaemic young subjects. Adding inulin-enriched pasta in their habitual daily diet for 5 weeks significantly reduced plasma Lp(a) concentrations by 16.5% compared to baseline in the whole inulin-administered group. The mechanisms underlying dietary nutrient regulation of Lp(a) plasma levels are not well understood, although a peculiar individual response of Lp(a) concentrations to dietary intervention has already been demonstrated by Hermann et al. [12]. These authors classified their patients as "*responders*" and "*non-responders*" and postulated a role for genetics. Looking at individual changes in Lp(a), only subjects with both apo(a) isoforms of low molecular weight showed a statistically significant reduction of Lp(a) concentrations (by 20.5%) after inulin-enriched pasta administration. Therefore, borrowing the definition from Hermann et al. [12], we could refer to these subjects as "*responders*", whereas subjects having at least one large size isoform would be classified as "*non-responders*". The clinical implications for this evidence remain to be elucidated by further studies

focusing on the consequences of these genetic differences in the human response to diets.

Another important issue is the feasibility of using manufactured foods enriched with inulin in terms of practicability, palatability, and compliance.

The dietary intervention in present study was minimal since normal diet was maintained including the daily intake of pasta. Pasta servings were limited solely in terms of shape (spaghetti or rigatoni), quantity (100 g), and starch composition (with or without inulin). Other works have demonstrated that the substitution of only one meal per day is adequate to obtain and maintain the desired metabolic effects, at least in type 2 diabetic patients [13]. At the chosen dose of fiber, no side effects or gastro-intestinal symptoms were recorded, and compliance to the study scheme was very high.

In conclusion, 5-weeks administration of inulin-enriched pasta exerts slight but significant effects on the lipid profile and Lp(a) concentration also in healthy young subjects. Although it should be stressed that only a small number of healthy young male subjects over a relatively short period were studied, present preliminary findings encourage the research into new preventive strategies against atherosclerotic diseases, that can start from a young age. Studies of larger healthy populations, or patients with dysmetabolic syndrome, over longer periods of time are needed to confirm this evidence.

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