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ORIGINAL CONTRIBUTION

Effects of a diet with inulin-enriched pasta on gut peptides and gastric emptying rates in healthy young volunteers

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Abstract
Aim Our group has previously shown that the administration of pasta enriched along with the prebiotic inulin induces a significant reduction in triglyceride and glucose levels with a significant delay in gastric emptying (GE) rates. This protective effect may occur by affecting the release of a number of gut peptides involved in the control of gastrointestinal motility. The aim of the present study was to evaluate the effects of inulin-enriched pasta on the circulating levels of neurotensin (NT), somatostatin (SS), and corticotropin-releasing factor (CRF) in relation to the GE time in young healthy subjects.
Methods Twenty healthy young male volunteers completed a randomized double-blind crossover study consisting of a 2-week run-in period and two 5-week study periods (11% inulin-enriched/control pasta), with an 8-week wash-out period in between. Gut peptide concentrations were evaluated by radioimmunoassay. GE time was evaluated by ultrasonography.
Results The prebiotic treatment significantly increased the area under the curve (AUC) values of both NT and SS ($p < 0.05$ Dunn's post-test). With regard to gastric motility, along with a significant delay in both the final time and $T_{1/2}$ gastric emptying time, a positive correlation was found between $T_{1/2}$ and SS AUC values ($r = 0.57$, $p = 0.009$) in the inulin-enriched pasta group.
Conclusion These results support the hypothesis that inulin plays an active role in mechanisms affecting the release of these gut peptides, which may modulate the gastric emptying of digesta.

Keywords Corticotropin-releasing factor · Diet · Fibre · Gastric emptying · Gut peptides · Inulin · Metabolic syndrome · Neurotensin · Somatostatin

Introduction

The term metabolic syndrome refers to a constellation of risk factors including elevated plasma glucose concentrations, dyslipidemia, hypertension, and abdominal obesity [1]. In association with current pharmaceutical strategies, the prevention and treatment of metabolic syndrome may be significantly improved not only by changes in lifestyle but also with nutritional interventions including condition-specific dietary supplements such as dietary fibre [2]. According to Spiller [3], the term dietary fibre refers to the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Many types of soluble fibre may benefit individuals with metabolic

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syndrome, through their effects on appetite, body weight, and blood lipid and glucose levels [4]. Their protective effect may also occur via effects on gastrointestinal (GI) motility. Fructans, including inulin, are able to modify lower GI motility, improving relaxation and increasing stool frequency in constipated subjects. In addition, they may modulate upper GI motility by inducing relaxation of the proximal stomach, as well as delaying gastric emptying (GE) via short chain fatty acids (SCFAs) and/or GI peptides [5–7]. Therefore, inulin may retard or impede the absorption of specific macronutrients in the form of glucose and fats, and, hence, positively affect both glucose and lipid (in particular triglycerides) levels [8]. Control of these variables might be useful in long-range primary prevention starting from a young age, given that metabolic disorders begin early in life [9] and that even "*normal*" levels of triglycerides can pose a significant risk of heart disease, as demonstrated by Miller et al. [10]. In this context, previous studies by our group have demonstrated that inulin-enriched pasta administration to young healthy male volunteers causes a significant reduction in triglyceride and glucose levels, an increase in HDL levels [11], and a significant delay in GE rates [12].

In gastric motor processes, a significant role is played by a number of gut peptides. Increased levels of these substances can result in gastric dysmotility [13]. Of these, considerable importance has been attributed to neurotensin (NT) [14], somatostatin (SS) [15], and the corticotropin-releasing factor (CRF) [16–19].

To our knowledge, the effects of inulin on gut peptides and GE rates in healthy subjects have not previously been investigated, and it could be of some interest to evaluate its properties when added to pasta. Against this background, the aim of the present study was to evaluate the effects of the daily consumption of inulin-enriched pasta on the release of a number of gut peptides (namely NT, SS and CRF) in relation to GE rates in a group of healthy young male subjects.

Methods

Subject selection

Students from the Istituto Tecnico Agrario ''B. Caramia'' in Locorotondo (BA), Italy, were enrolled in this study. Twenty-two healthy male volunteers were enrolled and 20 completed the study. The mean age was 18.8 ± 0.7 years, height 176 ± 6 cm, weight 73.7 ± 14.6 kg, and body mass index (BMI) 22.8 ± 2.3 kg/m^2. They denied having dyspepsia or other GI diseases and were not taking any medication. Information on the healthy status of the subjects was obtained at the time of enrolment during an examination consisting of an interview about their current diet, lifestyle and medical history, and a physical examination. GI symptoms were assessed using a specific questionnaire and food records. 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. 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, and 11% inulin. Inulin from chicory (Raftline HP-Gel) was supplied by Orafti (Tienen, Belgium). The average degree of polymerization was >23 units of fructose or glucose. Standard pasta was composed of 100% durum wheat semolina. In terms of 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, insoluble, and total dietary fibres were quantified by the enzymatic gravimetric procedure [20]; fructans are not included (fructo-oligosaccharides) or partially included (inulin) within compounds determined by enzymatic gravimetric procedure [21, 22]. Fructans were determined according to AACC Method 32-32 [23]. 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 fibre = 2 kcal/g (8 kJ/g) (Commission directive 2008/100/EC); fructans = 1.5 kcal/g (6.3 kJ/g) [23, 24]. 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 crossover design consisting of a baseline assessment and two 5-week study periods (inulin-enriched pasta or control pasta diet: 100 g/day = 11.0 and 1.4 g/day of fructans, respectively) with a wash-out period (8-weeks) in between, and a 2-week run-in period. 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

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 fibre		
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	346	323
kJ	1,468	1,368

interviewed each subject before the study to obtain a report of the subject's usual diet and thus 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. Food, 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. The two diets differed only with regard to the pasta composition.

Gastrointestinal hormones

After overnight fasting, basal blood samples were obtained from subjects in the study. Moreover, sequential blood samples were obtained at 15′, 30′, 60′, 120′, and 180′ after the supply of a mixed solid/liquid standard meal consisting of 55% carbohydrates, 30% protein, and 15% fat (caloric content 513 kcal). This was consumed within 15 min.

Blood samples were collected in ice-chilled tubes containing 500 KIU/ml of Aprotinin (100,000 KIU-MP Biomedicals, LLC, Ohio, USA) and 1.0 mg EDTA/ml blood. The samples were centrifuged at 1,600×g for 15 min at 4 °C and the separated plasma stored at −70 °C until assayed. One millilitre of plasma was acidified with 1 ml of 1% trifluoroacetic acid (TFA, HPLC grade) and then centrifuged at 3,000×g for 20 min at 4 °C. The supernatant was loaded onto the pretreated C18 column (200 mg, Sep-columns, Peninsula Laboratories Inc., Belmont, California, USA). The eluant was evaporated to dryness using a centrifugal concentrator and then lyophilized. The plasma levels of NT, SS, and CRF were measured by radioimmunoassay (RIA) using commercial kits (Peninsula Laboratories Inc., Belmont, California, USA).

Gastric emptying study

Both antral distension and gastric emptying (GE) were estimated by real-time ultrasonography, a highly reproducible technique that can accurately estimate fasting antral content and determine the GE time [25]. The ultrasound examinations were always performed by the same investigator (MC) using a real-time apparatus (UF4000, Fukuda-Denshi Co. Germering, Germany) equipped with a 3.5 MHz convex probe. Tests were performed in the morning after an overnight fast. Measurements of the antrum were taken before the administration of the above described standard meal and subsequently at regular 30-min intervals until complete emptying of the stomach.

The probe was positioned at the level of the transpyloric plane for simultaneous visualization of the antrum, superior mesenteric vein, and the aorta. The antral measurements were always taken from the outer profile of the wall. Since the cross-section of the gastric antrum, corresponding to the sagittal plane passing through the superior mesenteric vein, is elliptical in shape, its area can be calculated by measuring the longitudinal (L) and antero-posterior (AP) diameters and applying the formula πLxAP/4. In each subject, the emptying time (in minutes) was expressed as the half-emptying time ($T_{1/2}$, corresponding to the time at which the cross-sectional area of the antrum had an intermediate value with respect to the basal value) and the final time (*FT*: the time at which the antral area corresponds to the fasting area). $T_{1/2}$ was calculated by linear regression analysis from the linear part of the emptying curve.

Statistical analysis

The total integrated response was calculated as the area under the curve (AUC) to obtain overall values for the gastric parameters and GI hormones over time. To avoid the assumption of normal distribution, data were expressed as medians and ranges, and non-parametric tests were performed using a specific software package (StataCorp 2005; Stata Statistical Software: Release 9, College Station, TX, USA). The Friedman repeated measures analysis of variance on ranks was used to compare the effects of different dietary treatments. When a difference was found, non-parametric multiple comparisons were performed (Dunn's post-test) to determine the groups between which there was a significant difference. Correlations were

investigated using the Spearman correlation test. All differences were considered significant at the 5% level.

Results

Dietary intake

The dietary intakes, as calculated from the dietary surveys conducted during the last week of each diet period, are reported in Table 2. The total energy intake, the percentage of total energy intake, and the daily intakes of fibre (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 GI symptoms, no subject complained of side effects related to inulin administration, such as flatulence, meteorism, or post-prandial fullness. Finally, no change in bowel habit was recorded during the study.

Gastrointestinal hormones

Table 3 reports the basal plasma values of NT, SS, and CRF at baseline and during consumption of the study diets. The Friedman repeated measures analysis of variance on ranks found statistically significant differences ($p < 0.05$) between the basal values of NT and SS, which were higher in the inulin-enriched pasta group compared to the baseline and control pasta group. The all-pairwise multiple-comparison post-test assessed the significance of differences between the inulin-enriched pasta diet vs. baseline and control pasta. In contrast, CRF basal levels did not significantly differ between groups. Figure 1 shows the AUC values of NT, SS, and CRF, representing the total release of these peptides over the time of observation after a standard meal, in the subjects at baseline and after the two study diet periods (control pasta and inulin-enriched pasta). Inulin-enriched pasta had no effect compared to control pasta for all peptides, although AUC values were significantly higher than baseline for NT and SS ($p < 0.05$ Dunn's post-test).

Table 2 Daily dietary intakes 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
Dietary fibre (g/day)		
Insoluble fibre	22.3 ± 4.7	21.1 ± 3.9
Soluble fibre	9.3 ± 2.5	8.7 ± 1.9
Total fibre	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

Table 3 Basal plasma values of GI hormones at baseline and during the study diets

	Baseline	Control pasta	Inulin-enriched pasta
NT	6.41[a]	8.78[a]	10.62[b]
	(1.62–20.87)	(1.34–16.25)	(5.92–13.82)
SS	13.04[a]	12.66[a]	15.43[b]
	(0.88–30.09)	(1.23–32.55)	(2.5–34.33)
CRF	17.70[a]	16.40[a]	17.73[a]
	(1.46–35.81)	(7.78–27.39)	(1.18–37.82)

Values not showing a common letter differ significantly. Data are expressed as pg/ml (medians and the range)

NT Neurotensin, *SS* Somatostatin, *CRF* Corticotropin-releasing factor

Gastric motility data

At baseline, none of the subjects showed delayed GE. Figure 2 reports the profiles of GE in the three groups of subjects, expressed as antral areas at each observation time. No significant difference was found between groups, although the antral area profile in the inulin pasta group was lower than that shown by subjects at baseline, without reaching statistical significance.

By analysing the ultrasound parameters (Table 4), a significantly longer GE time (as both *FT* and $T_{1/2)}$ was found in the group that consumed inulin-enriched pasta compared to control pasta diet and baseline ($p < 0.05$ Dunn's post-test). The fasting antral area was higher in the inulin-enriched pasta group compared to the baseline and control diet, although without reaching statistical significance. Finally, by correlating GE times (both FT and $T_{1/2}$) with the hormonal AUC values in the three groups, a positive correlation was found only between the $T_{1/2}$ and the SS AUC values in the group of subjects consuming inulin-enriched pasta (Fig. 3; Spearman test, $r = 0.57$, $p = 0.009$).

Discussion

There has been increasing interest in the potential of diets enriched with prebiotics, such as inulin, to modify some of the risk factors for metabolic syndrome, since recent observations have implied that gut microbiota profiles have an additional influence on this condition. Although metabolic syndrome typically occurs during middle age or later in life [26], it is possible, with increasing childhood obesity, that it may affect young adults and even adolescents and children [27]. Therefore, the precocious control

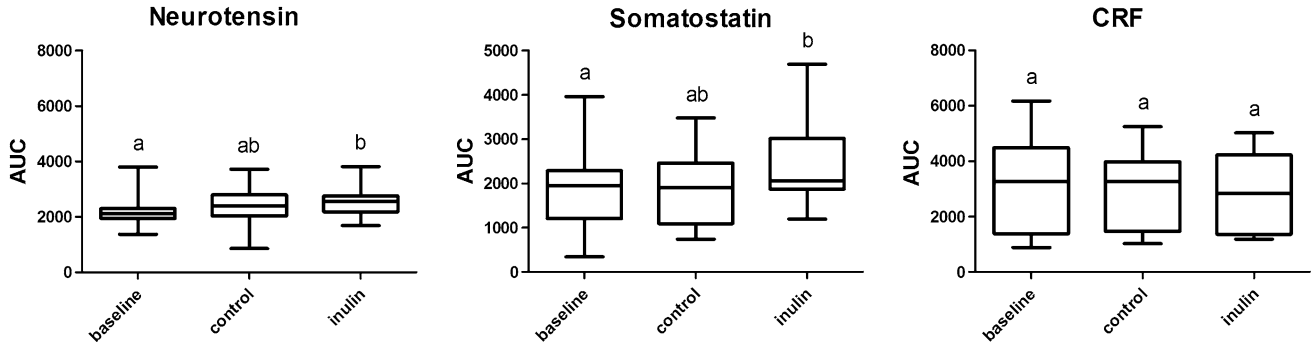

Fig. 1 The *box* and *whiskers* plot represent the total release of each hormone over the time of observation as area under the curve (AUC) in subjects at baseline and after consuming control pasta or inulin-enriched pasta. The box extends from the 25th percentile to the 75th percentile with a horizontal line at the median (50th percentile). The whiskers show the range of the data. *Boxes* not showing a common letter differ significantly

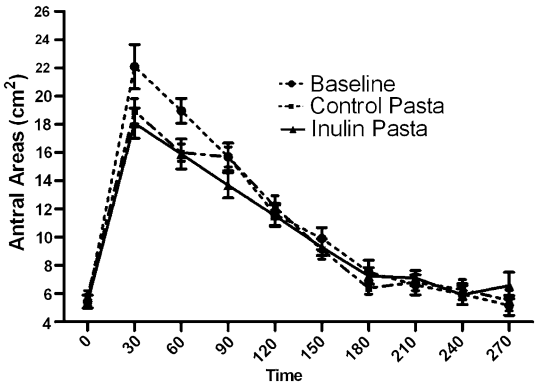

Fig. 2 Gastric emptying curves expressed as antral areas in subjects according to diets. Data are expressed as mean ± SEM

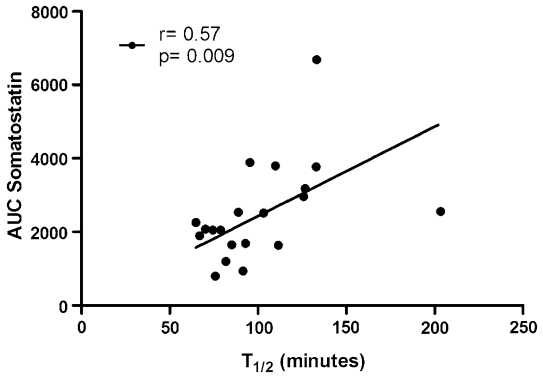

Fig. 3 Positive correlation between $T_{1/2}$ and the SS AUC values in the group of subjects consuming inulin-enriched pasta (Spearman test. $r = 0.57$, $p = 0.009$)

Table 4 Ultrasound gastric emptying parameters: comparison among basal condition, control diet, and inulin diet

	Baseline	Control diet	Inulin diet
FT (min)	210[a]	210[a]	240[b]
	(180–270)	(180–270)	(180–300)
$T_{1/2}$ (min)	90.7[a]	92.1[a]	99.0[b]
	(63.3–148.7)	(63.5–152.5)	(65.8.3–168.1)
Fasting antral area (cm^2)	4.9[a]	5.2[a]	5.3[a]
	(3.6–11.4)	(4.0–9.6)	(3.3–7.9)

FT: the time in which the antral area corresponds to the fasting area
$T_{1/2}$: value corresponding to the time in which the cross-sectional area of the antrum has an intermediate value with respect to the basal value and the maximum recorded after a meal. Repeated measures analysis of variance on ranks (Friedman Test with Dunn's post-test). Data are expressed as median value and the range. Values not showing a common letter differ significantly

of metabolic variables involved in this syndrome, also using prebiotics, might be useful in long-range primary prevention starting from a young age. The prebiotic effect of inulin-type fructans has been extensively confirmed. An inulin dose of 5–8 g/d should be sufficient to elicit a positive effect on the gut microbiota. More interestingly, prebiotics, possibly in association with the gut endocrine system, may exert effects far away from the colon, e.g. by contributing to a decrease in appetite or affecting GI motor processes.

Our results on healthy young volunteers show that the introduction of 100 g of 11% inulin-enriched pasta as the only intervention in the current diet for 5-weeks affected the release of important gut peptides involved in the control of gastric motor functions (namely NT and SS) and significantly delayed GE time. In particular, inulin-enriched pasta induced a greater antral area and a slower outflow of gastric effluent, as demonstrated by the significantly higher *FT* and $T_{1/2}$ values in comparison with baseline and control pasta values. With regard to gut peptides, inulin-enriched pasta increased the basal plasma values of circulating NT and SS, which were significantly elevated after inulin diet in comparison with baseline and control pasta concentrations. In contrast, CRF circulating concentrations were not significantly affected by dietary intervention.

These results suggest an effect by prebiotics like inulin, in mechanisms involving the release of those gut peptides

that, in response to a variety of stimuli in gastric chyme, modulate the gastric emptying of digesta. It has already been suggested that prebiotics may delay GE times and/or shorten transit time in the small intestinal tract. This may be via SCFAs produced from the oligosaccharides in the colon. SCFAs may be involved in the so-called "*ileocolonic brake*", which refers to GE inhibition by nutrients reaching the ileo-colonic junction. In the large bowel, infusion of SCFAs has been shown to inhibit peristaltic activity and stimulate tonic activity as well [6]. In turn, ileal and colonic SCFAs, through a humoral pathway involving different peptides, may modify upper motility by either inducing relaxation of the proximal stomach and lower oesophageal sphincter or delaying GE rates [5].

Different gut peptides have been implicated in GI motility process. Among them, NT and SS have been demonstrated to strongly affect gastro duodenal motility by lowering GE rates [13–15]. In the present study, AUC values of the three GI peptides in the inulin-enriched pasta group were not significantly different from those in control pasta group**.** However, in the group of subjects consuming inulin-enriched pasta, a positive correlation between $T_{1/2}$ and SS AUC values was observed. This evidence suggests that inulin may exert its delaying effects on GE mainly by influencing SS levels. In a recent study carried out in mice fed with a high fat diet (HFD), the role of SS in the progression of metabolic syndrome was investigated. Following HFD intake for 38 days, a decrease in the plasma levels of SS was observed, while there was an increase in ROS production, body weight, and lipid parameters. Simultaneous administration of octreotide (an analogue of SS) to HFD-fed mice significantly improved all of the above adverse changes, suggesting the involvement of this peptide in the progression of metabolic syndrome [28]. With regard to CRF, inulin-enriched pasta did not exert the same significant effects on its release as for the other peptides in this study. It is likely that the link between CRF and GE processes is not as straightforward. Previous research has indicated a role for this peptide essentially in intestinal permeability rather than gastroduodenal motility, as well as active involvement in stress-induced changes in gut motility and intestinal mucosal function [29].

To our knowledge, this is the first report of a clear effect of inulin administration on gut peptides that are involved in GE in healthy subjects. Metabolically, slower GE rates can induce slower absorption of nutrients, reducing the postprandial elevation of blood glucose and so maintaining better glucose homeostasis, not only after acute administration but also as a result of the chronic administration of fibre. In this context, previous studies by our group [11, 12] and others [30] reported a significant lowering effect on both glucose and lipid parameters. In addition, a recent meta-analysis of available studies to quantify the effects in humans of dietary inulin-type fructans showed that the intake of inulin significantly reduced serum triacylglycerol concentrations [8]. In this framework, the present study suggests further consideration of the use of inulin-enriched pasta as a possible tool for tackling dysmetabolic disorders. As a matter of fact, it is conceivable that early dietary intervention in healthy subjects, also using prebiotics, may represent a reliable preventive approach for delaying the onset and related complications of metabolic syndrome. Another important issue is the feasibility of using manufactured foods enriched with inulin in terms of practicability, palatability, compliance, and duration of administration. At the chosen dose of fibre, no side effects or GI symptoms were recorded, and compliance to the study scheme was very high. The dietary intervention in the present study was negligible since the normal diet was maintained, including the daily intake of pasta.

In conclusion, the 5-week administration of inulin-enriched pasta exerted significant effects on both GE rates and the release of gut peptides such as NT and SS in healthy young subjects. It should be emphasized that the present findings are preliminary, since only a small number of healthy young male subjects were studied over a relatively short period. Notwithstanding, the results are promising and encourage further research in this direction in the form of studies on both larger healthy populations and patients with metabolic syndrome, over longer periods of time.

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