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ORIGINAL COMMUNICATION

Therapeutic effects of psyllium in type 2 diabetic patients

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Objective: The aim of this study was to evaluate the effects of psyllium in type 2 diabetic patients.
Design: The study included three phases: phase 1 (1 week), phase 2 (treatment, 14 g fibre/day, 6 weeks) and phase 3 (4 weeks). At the end of each phase a clinical evaluation was performed after the ingestion of a test breakfast of 1824.2 kJ (436 kcal). Measurements included concentrations of blood glucose, insulin, fructosamine, $GHbA_{1c}$, C-peptide and 24 h urinary glucose excretion. In addition, uric acid, cholesterol and several mineral and vitamin concentrations were also evaluated.
Setting: The study was performed at the Department of Pharmacology, Toxicology and Nursing at the University of León (Spain).
Subjects: Twenty type 2 diabetic patients (12 men and 8 women) participated in the study with a mean age of 67.4 y for men and 66 y for women. The mean body mass index of men was 28.2 kg/m^2 and that of women 25.9 kg/m^2.
Results: Glucose absorption decreased significantly in the presence of psyllium (12.2%); this reduction is not associated with an important change in insulin levels (5%). $GHbA_{1c}$, C-peptide and 24 h urinary glucose excretion decreased (3.8, 14.9 and 22.5%, respectively) during the treatment with fibre (no significant differences) as well as fructosamine (10.9%, significant differences). Psyllium also reduced total and LDL cholesterol (7.7 and 9.2%, respectively, significant differences), and uric acid (10%, significant difference). Minerals and vitamins did not show important changes, except sodium that increased significantly after psyllium administration.
Conclusions: The results obtained indicate a beneficial therapeutic effect of psyllium (Plantaben®) in the metabolic control of type 2 diabetics as well as in lowering the risk of coronary heart disease. We also conclude that consumption of this fibre does not adversely affect either mineral or vitamin A and E concentrations. Finally, for a greater effectiveness, psyllium treatment should be individually evaluated.
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Introduction

Dietary fibre has significant gastrointestinal effects and it is a mainstay of treatment for constipation and haemorrhoids. Insoluble fibre is most effective for the treatment of these pathologies and an increased intake of soluble dietary fibre appears to benefit patients with diabetes mellitus (Gray, 1995).

The advantages of high-fibre diets for diabetic patients have been said to include lowering of serum lipids, assisted weight reduction and maintenance, and lowering of blood glucose levels (Kiehm *et al*, 1976; Anderson 1985a, b).

It is especially the gel-forming, water-soluble dietary fibre components such as guar gum, pectin and psyllium that have beneficial effects on carbohydrate metabolism (Jenkins *et al*, 1977; Chuang *et al*, 1992; Ellis *et al*, 1991; Fairchild *et al*, 1996; Gatenby *et al*, 1996; Wursch & Pi-Sunyer, 1997).

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Contributors: MS was mainly responsible for all stages of the study, including the study design, discussion and interpretation of results and writing of the paper. JJG participated in the discussion and interpretation of results and in the statistical analysis. NF and MJD were involved in the literature searches and data collection and entry and assisted with the preparation of the paper. APC carried out the analytical determinations and diet control. The Farmafibra Group was in charge of the medical management of subjects and sample collection and preparation.
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Psyllium or ispaghula husk (the husk of the seeds of *Plantago ovata*) is a mixture of neutral and acid polysaccharides with a rest of galacturonic acid. The polysaccharides are built up from the monomers D-xylose and L-arabinose, and ispaghula husk contains 67% pentosanes. Ispaghula husk is a gel-forming (water-soluble) fibre which has been used in treatment for constipation for many years. During the last two decades, several studies have been carried out to investigate whether ispaghula interferes with normal intestinal absorption of carbohydrate in healthy volunteers (Jarjis *et al*, 1984; Sierra *et al*, 2001) and in type 1 (Florholmen *et al*, 1982; Uribe *et al*, 1985) and type 2 diabetic patients (Sartor *et al*, 1981; Jarjis *et al*, 1984; Pastors *et al*, 1991). The effect of psyllium on fasting plasma cholesterol in hypercholesterolaemic patients has also been evaluated (Bell *et al*, 1989) and in obese and diabetic patients (Frati-Munari *et al*, 1983). The results obtained in these studies indicate that, in general, ispaghula administration yields to a decrease in glycaemia, insulinaemia and cholesterolaemia, but Jarjis *et al*, (1984) failed to detect significant glucose blunting.

In the present study we have evaluated the therapeutic effect of psyllium on glycaemic control in type 2 diabetic patients treated with glibenclamide and under dietary regulations. The effect on the total serum cholesterol concentrations and the distribution of serum cholesterol between the high-density-lipoprotein (HDL) and the low-density-lipoprotein (LDL) was also established. In addition, several hepatic, renal and haematological parameters were evaluated.

Subjects and methods

Patients

Twenty type 2 diabetic patients (12 men and 8 women) participated in the study. The mean age of the men was 67.4 y (range 50–80 y) and that of the women 66 y (range 54–79 y). The mean body mass index (BMI) of men was 28.2 kg/m^2 (range 25–29.6 kg/m^2) and of women 25.9 kg/m^2 (range 20–29.8 kg/m^2).

The duration of diabetes in all the volunteers eligible for the study was between 2 and 30 y (mean 10.4 y) in men and between 2 and 18 y (mean 7 y) in women. Diabetes was treated in all patients with a sulphonylurea (glibenclamide) and by conventional dietary restrictions. The diet followed by the volunteers was the same for all of them during the study. This diet is recommended to diabetic patients by the Program of INSALUD (National Institute of Health) and contains 55% of carbohydrate, 30% of fat (10% of saturated fat), 15% of protein and 25 g of fibre per day.

All subjects were questioned to assess subjective gastrointestinal side effects of the fibre, if any, but not one of the patients communicated any adverse effect. Each subject had normal stool consistence and frequency. Four patients who suffered from constipation showed a clear improvement during the treatment with fibre. All the volunteers successfully completed the study.

Study design

The study was conducted on an outpatient basis. The volunteers had no history of gastrointestinal disease and other major illnesses, and each subject served as his own control. The protocol was approved by the Human Ethical Committee of the University and INSALUD of Léon, Spain, and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each subject.

Patients were admitted to an open study for its entire duration. The study protocol included three different phases (phase 1, phase 2 (treatment) and phase 3) and at the end of each phase, the therapeutic and dietary accomplishment were evaluated by the patient and one of the investigators.

The study began with a 1 week period (phase 1) over which subjects followed a diet for diabetes and received the sulphonylurea. This was followed by the phase 2 (treatment phase, 6 weeks) over which patients continued with the diet and the sulphonylurea, and also received 3.5 g of psyllium (one dose of Plantaben®, orange flavoured, sugar-free, Madaus, S.A., Spain) four times a day: before breakfast, lunch, afternoon snack and dinner (14 g of psyllium/day). Subjects were instructed to mix each fibre packet in 250 ml of water, followed by 50 ml water for glass cleaning, and to drink the mixture before each meal. Phase 3 (4 weeks) was carried out after a 2-week washout interval. As in the phase 1, subjects followed the diet and received sulphonylurea. During phases 1 and 3, the patients received the same volume of water (300 ml) as in phase 2 without psyllium before meals in order to avoid changes in gastric emptying.

A clinical examination was performed at the end of each phase. On each occasion, and after overnight fast, they ingested a standard breakfast (Ebeling *et al*, 1988) of 1824.2 kJ (436 kcal; 53% carbohydrate, 26% protein and 21% fat), which consisted of 80 g low-fat boiled ham, two slices (60 g) of white bread and 200 ml low-fat milk with non-sweetened black coffee. Before breakfast, one dose of the fibre was given.

Blood samples (7 ml) were drawn through a butterfly cannula placed in the forearm at −15, 0, 10, 20, 30, 45, 60, 75, 90 and 120 min after breakfast ingestion for blood glucose estimation, and at −15, 0, 30, 60, 90 and 120 min blood insulin concentrations were also determined. The values calculated at −15 and 0 min were averaged to obtain glucose and insulin fasting values.

Blood samples obtained at time 0 were also used to determine several biochemical parameters (uric acid, total, HDL and LDL cholesterol) as well as different minerals (calcium, phosphorous, sodium, potassium, magnesium, iron) and vitamins (A and E) whose blood levels can be modified by the presence of fibre. In addition, other parameters related to patient status were also determined: glycosylated haemoglobin (GHbA$_{1c}$), fructosamine and C-peptide in serum as well as 24 h urinary glucose and C-peptide excretion. The urine was collected from ingesting the test breakfast until next morning.

Methods

Serum glucose was measured with the Schmidt method (Schmidt, 1961) using an autoanalyser (Hitachi, mod. 704, Tokyo, Japan). Insulin concentrations were determined with an immunoradiometric assay (IRMA assay kit, Biosource Europe, S.A., Nivelles, Belgium). Serum vitamin A and E were determined by high-pressure liquid chromatography (HPLC; Driskell *et al*, 1982). An enzymatic colorimetric method was used for the determination of cholesterol (Boehringer-Mannheim, GmbH, Mannheim, Germany). The HDL fraction was analysed after precipitation with magnesium chloride and dextrane sulphate (Finley *et al*, 1978). LDL cholesterol was calculated by the formula of Friedewald *et al* (1972). $GHbA_{1c}$ was determined by commercial ion-exchange chromatography (Quick-Step Fast Hemoglobin System®, Isolab Inc., Akron, OH, USA). Minerals and uric acid were determined by using an autoanalyser Hitachi, model 704 (Tokyo, Japan). Serum fructosamine was analysed in triplicate using the Cobas Fara II (Lloyd & Marples, 1984). Urinary glucose concentrations were evaluated by using an enzymatic method (Weatherburn & Logan, 1966). Finally, C-peptide was determined by RIA (Kuzuya *et al*, 1976).

During the study, except the 2 week washout interval, patients measured their diurnal blood glucose profile at home twice a week (on Tuesday and on Thursday). On these days six measurements were done (before and 90 min after breakfast, lunch and dinner) using Glucostix® (Miles Limited, Glamorgan, UK) test strips that were read with a Glucometer (Miles Laboratories Inc., Elkhart, IN, USA). The number of blood glucose determinations per patient was 132, during the three periods (12 in phase 1, 72 in phase 2, 48 in phase 3).

Statistical analysis

Arithmetic means and s.d.s were calculated from the results measured. The data obtained from the three phases were compared for statistical significance by Friedman's test, at $P < 0.05$ and, when the results were significant, Wilcoxon pairwise comparisons with Bonferroni correction were used, except for capillary glycaemia, where Kruskal–Wallis test and Mann–Whitney *U*-test were employed. All analyses were performed by using the Statgraphics Plus for Windows 2.0 (Manugistic Inc., Rockville, MA, USA).

Results

Serum glucose

The extent of glucose absorption decreased in the presence of psyllium when mean values were considered (Table 1 and Figure 1). Differences in mean concentrations at different sampling times were significant, except when the values obtained at time 0 for phases 2 and 3 were compared. Significant differences were also established for mean concentrations among subjects. C_{max} decreased nearly 10% in

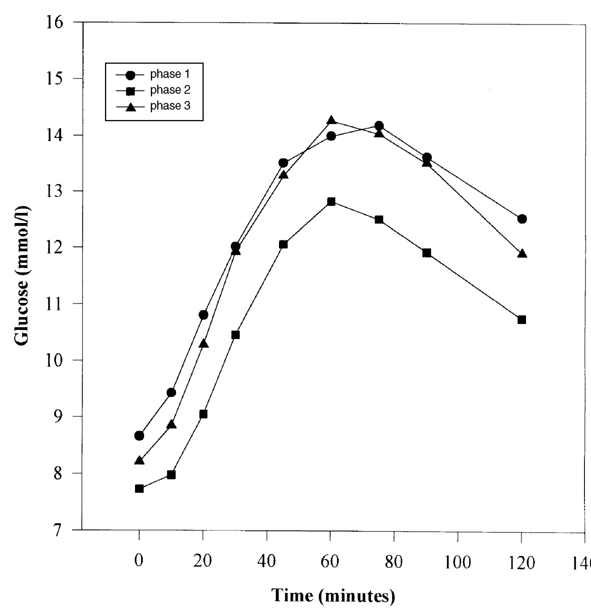

Figure 1 Mean serum glucose concentrations in 20 type 2 diabetic patients after test breakfast.

Table 1 Serum glucose concentrations (mmol/l) in 20 type 2 diabetic patients after a test breakfast

	Phase 1		*Phase 2*		*Phase 3*	
Time (min)	*$\bar{x} \pm$ s.d.*	*CV (%)*	*$\bar{x} \pm$ s.d.*	*CV (%)*	*$\bar{x} \pm$ s.d.*	*CV (%)*
0^{b}	8.66 ± 2.22^{c}	25.7	7.73 ± 1.98	25.6	8.21 ± 2.32	28.2
$10^{a,b}$	9.43 ± 2.29^{c}	24.3	7.98 ± 1.96	24.6	8.85 ± 2.45^{c}	27.7
$20^{a,b}$	10.81 ± 2.45^{c}	22.7	9.05 ± 2.01	22.2	10.29 ± 2.61^{c}	25.4
$30^{a,b}$	12.02 ± 2.82^{c}	23.5	10.46 ± 2.15	20.6	11.93 ± 2.59^{c}	21.7
$45^{a,b}$	13.52 ± 2.92^{c}	21.6	12.06 ± 2.21	18.4	13.29 ± 2.49^{c}	18.7
$60^{a,b}$	14.00 ± 2.67^{c}	19.1	12.83 ± 2.58	20.2	14.27 ± 2.93^{c}	20.5
$75^{a,b}$	14.19 ± 3.02^{c}	21.3	12.51 ± 2.81	22.5	14.04 ± 3.23^{c}	23.0
$90^{a,b}$	13.63 ± 3.12^{c}	22.9	11.93 ± 3.12	26.2	13.52 ± 3.63^{c}	26.8
$120^{a,b}$	12.54 ± 3.53^{c}	28.1	10.76 ± 3.43	31.9	11.91 ± 3.63^{c}	30.5

[a]Significant differences among phases (Friedman's test, $P < 0.05$).
[b]Significant differences among subjects (Friedman's test, $P < 0.05$).
[c]Significant differences with phase 2 (Wilcoxon modified test, for conditions see text).

the phase 2 (treatment) curve when compared with the values obtained in the phases 1 and 3. The rate of glucose absorption was similar during phases 2 and 3 ($t_{max} = 60$ min) and less than in phase 1 ($t_{max} = 75$ min).

The area under the serum glucose concentration–time curve (AUC) was 12.2% lower in the presence of fibre than that obtained at the end of phase 1 and 11.9% lower than that obtained at the end of the phase 3 (significant differences, Wilcoxon's test).

When accumulated areas (AUC_t, where t is the time over which AUC has been calculated) were considered, significant differences were also found between phases 1 and 3 data when compared with those obtained in the phase 2, except at 10 min between phases 2 and 3 (Wilcoxon's test).

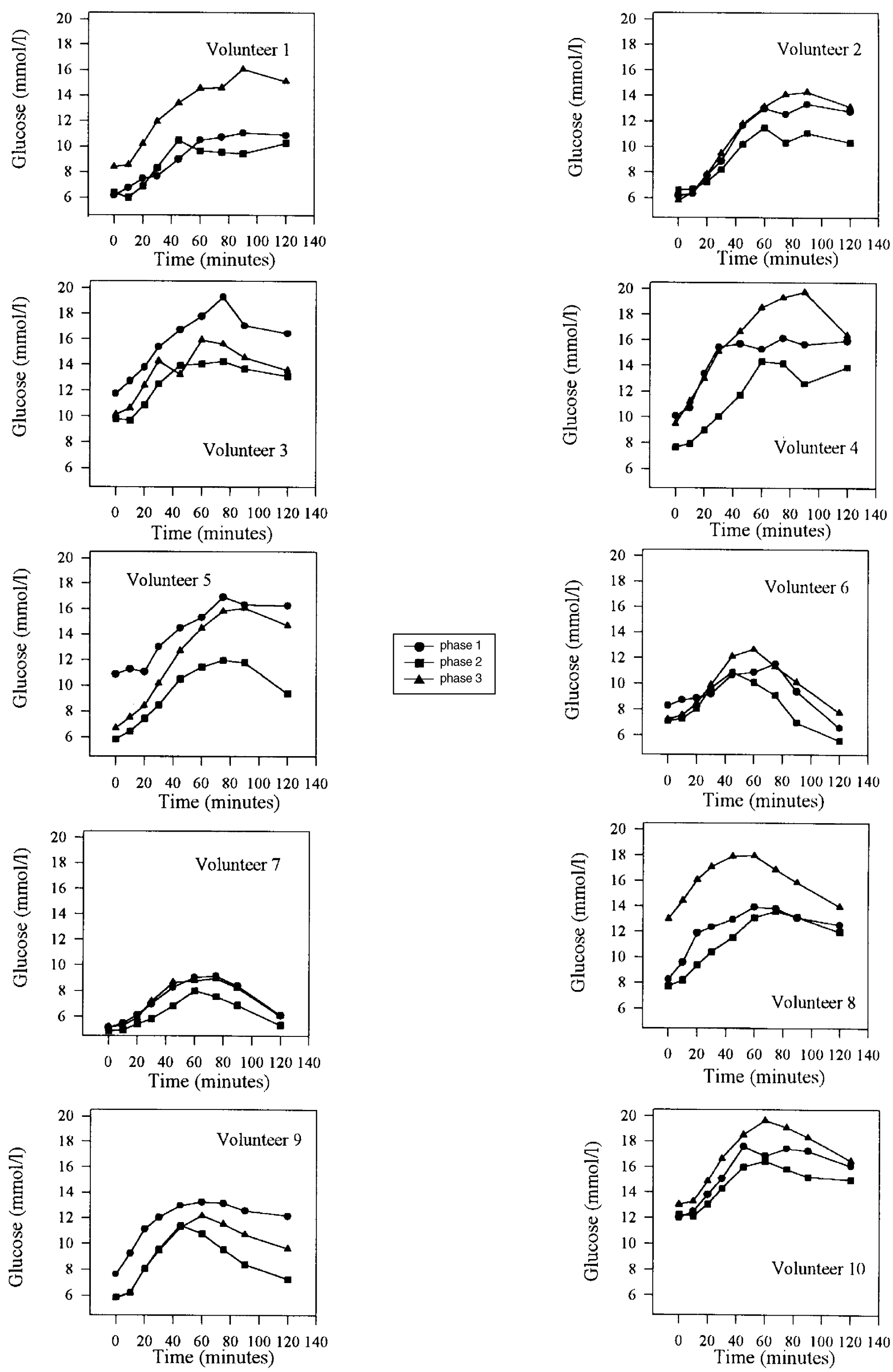

Figure 2 (a) Individual serum glucose-time curves in 10 type 2 diabetic patients after test breakfast.

Large interindividual variations were observed in glucose concentrations, with CV ranging from 18.7 to 31.9% (Table 1) and, because of this, it is important to evaluate individual curves (Figure 2a and b) in addition to mean curves (Figure 1). Thus, in 10 patients (numbers 1–10, Figure 2a), glucose concentrations and AUC values were clearly lower at the end of the phase 2 than at the end of phases 1 and 3, with AUC decreases

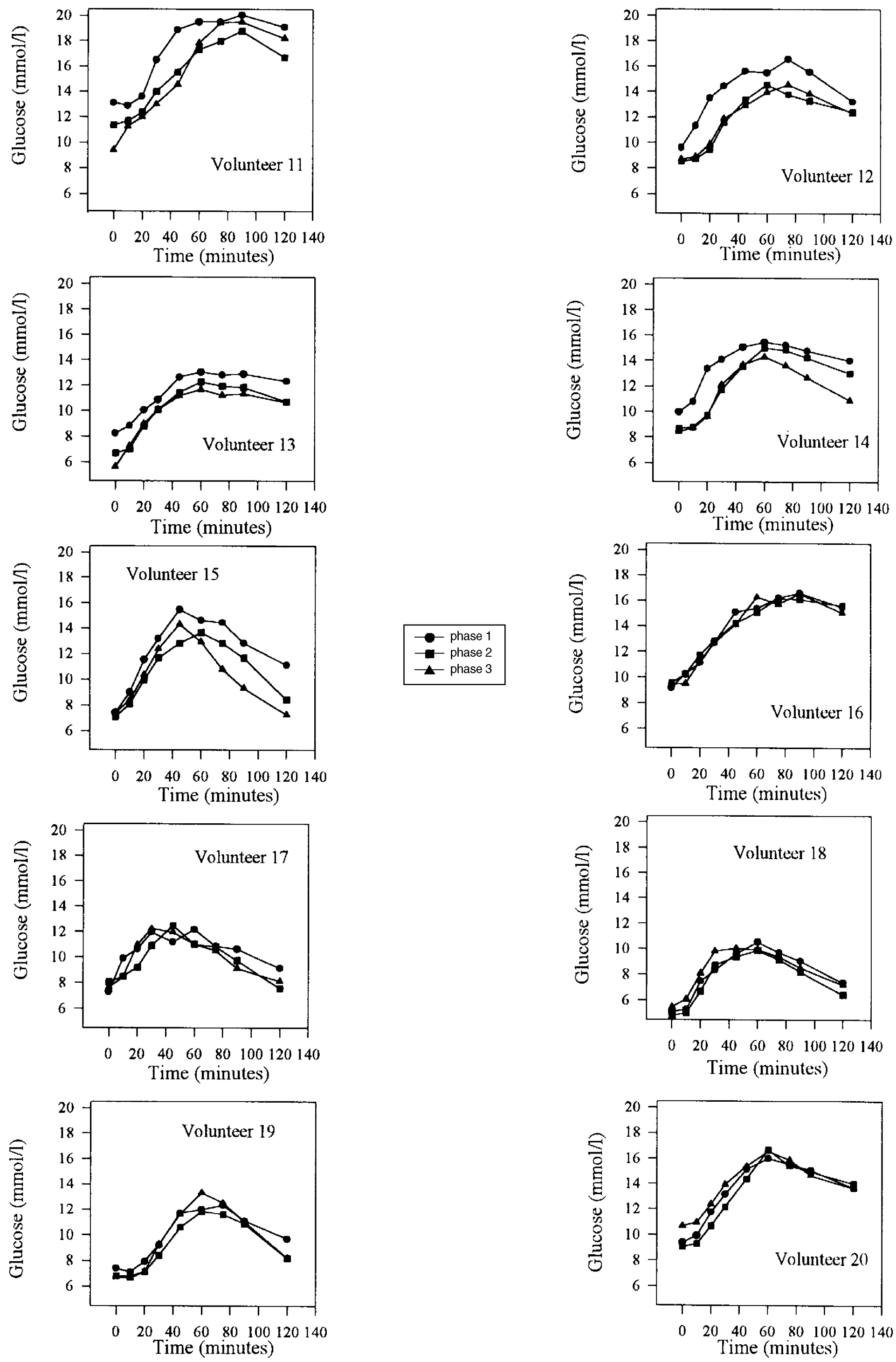

Figure 2 (b) Individual serum glucose-time curves in 10 type 2 diabetic patients after test breakfast.

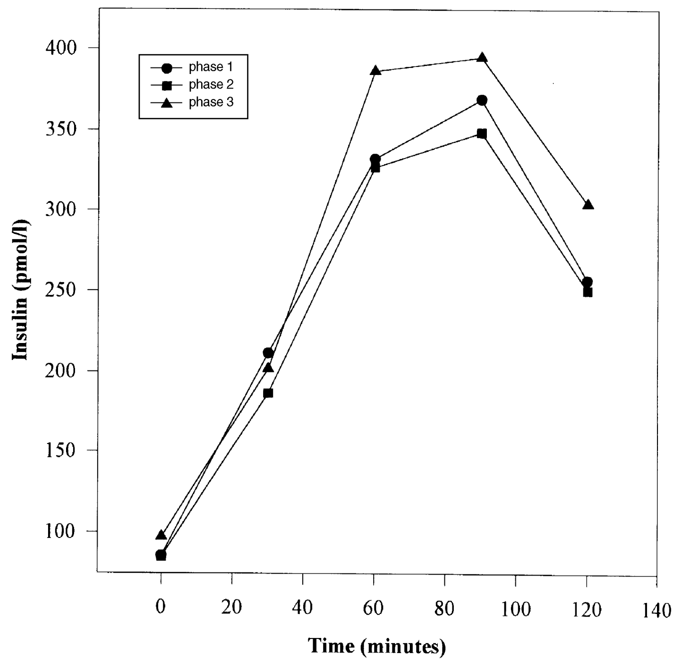

Figure 3 Mean serum insulin concentrations in 20 type 2 diabetic patients after test breakfast.

up to 34%. Five volunteers (numbers 11–15) showed higher values during the phase 1 than during phases 2 and 3, and in three of them (numbers 11–13), the curves obtained in phases 2 and 3 were very similar. Finally, in five subjects (numbers 16–20) the three curves were very similar.

Serum insulin

AUC decreased a 5% in phase 2 in comparison with the value obtained in phase 1, and it was 15% lower than in phase 3 (no significant differences, Friedman's test, at $P < 0.05$). Mean curve shapes (Figure 3) were similar in the three phases.

The value of C_{max} (Table 2) was lower in the presence of fibre (348.6 pmol/l) than in phases 1 (369.0 pmol/l) and 3 (394.8 pmol/l), but these differences were not significant.

The individual insulinaemic responses were very different, with CVs for the mean concentrations higher than those obtained for glucose. In our opinion, this fact reflects the different states of type 2 diabetes evolution in which patients can be. When phases 1 and 3 are compared, some patients show a high decrease in AUC mean values (up to 47.6%), while in others this value is scarcely modified or even increases (up to 45% in one patient).

Examining the corresponding curves it can be observed that nine patients showed low insulin concentration values. Five of them had high glucose levels (numbers 3, 4, 10, 11 and 16), reaching concentrations over 16.7 mmol/l; in four patients (numbers 9, 13, 14 and 20), the glucose concentrations were high, with values greater than 13.3 mmol/l; in the other volunteer (number 18), the glucose concentrations at the end of the curve were over the basal levels. Five volunteers (numbers 1, 5, 7, 8 and 19) show high insulin concen-

Table 2 Serum insulin concentrations (pmol/l) in 20 type 2 diabetic patients after a test breakfast

	Phase 1		*Phase 2*		*Phase 3*	
Time (min)	*$\bar{x} \pm$ s.d.*	*CV (%)*	*$\bar{x} \pm$ s.d.*	*CV (%)*	*$\bar{x} \pm$ s.d.*	*CV (%)*
0[a]	85.6 ± 46.3	54.0	85.1 ± 50.4	59.3	97.2 ± 40.0	41.1
30[a]	211.7 ± 126.6	59.8	186.5 ± 90.9	48.8	201.8 ± 110.2	54.6
60[a]	332.3 ± 225.7	67.9	327.0 ± 199.3	61.0	386.3 ± 255.1	66.0
90[a]	369.1 ± 277.4	75.2	348.7 ± 217.0	62.2	395.0 ± 289.6	73.3
120[a]	257.0 ± 203.3	79.1	250.8 ± 187.6	74.8	304.4 ± 225.1	73.9

Friedman's test ($P < 0.05$).
[a]Significant differences among subjects. No significant differences among phases were found.

Table 3 Capillary glycaemia (mmol/l) in 20 type 2 diabetic patients before and 90 min after meals

	Phase 1		Phase 2		Phase 3	
Time (min)	*x̄ ± s.d.*	*CV (%)*	*x̄ ± s.d.*	*CV (%)*	*x̄ ± s.d.*	*CV (%)*
Before breakfast[b]	7.72 ± 1.90	24.61	7.34 ± 1.88	25.59	7.46 ± 1.88	25.16
After breakfast[a,b]	11.58 ± 3.31[c]	28.59	9.98 ± 2.81	28.16	10.39 ± 3.13	30.14
Before lunch[b]	7.27 ± 2.64	36.24	6.69 ± 2.49	37.20	6.68 ± 2.33	34.86
After lunch[b]	9.67 ± 4.14	42.77	8.92 ± 2.76	30.91	9.56 ± 3.11	32.58
Before dinner[b]	6.73 ± 2.79	41.40	6.47 ± 2.56	39.49	6.43 ± 2.27	35.38
After dinner[b]	10.02 ± 3.28	32.74	9.20 ± 2.60	28.21	9.63 ± 2.83	29.35

[a]Significant differences among phases (Kruskall–Wallis's test, $P<0.05$).
[b]Significant differences among subjects (Kruskall–Wallis's test, $P<0.05$).
[c]Significant differences with phase 2 (Mann–Whitney *U*-test, for conditions see text).

trations during the administration of psyllium, and these values were generally higher than in phase 1 and lower than in phase 3. The three curves were similar in three patients (numbers 2, 6 and 15), except in the last times in two of them (numbers 2 and 6). Finally, in two subjects (numbers 12 and 17), the insulin concentrations decreased in the presence of fibre, when compared with those obtained in phase 1, and were similar to the values shown in the phase 3 curve.

Capillary glycaemia

A total of 120, 678 and 441 values of postprandial glucose concentrations were obtained, corresponding respectively to phases 1, 2 (treatment) and 3 of the study. The same number of preprandial data were evaluated. In general, there was a good compliance, but one patient only measured the glucose concentrations during phase 1; another patient forgot 2 days during phase 2 and, finally, one patient failed one day during phase 3.

Taking into account the mean values (Table 3), fasting blood glucose was slightly lower (4.5%) during phases 2 and 3 than during phase 1 (no significant differences, Kruskall–Wallis test, at $P<0.05$). The mean preprandial values corresponding to lunch and dinner were also slightly lower and differences were not significant (Kruskall–Wallis test, at $P<0.05$).

Mean postprandial glucose levels decreased during phase 2: 10.2% *vs* phase 1 and 5.3% *vs* phase 3 (significant differences, Mann–Whitney *U*-test).

The mean postprandial glucose concentrations corresponding to breakfast, lunch and dinner were always lower during phase 2 than during phases 1 and 3. The decreases in these values were 13.8% in breakfast, 7.8% in lunch and 8.2% in dinner (phase 2 *vs* phase 1), and 4.0% in breakfast, 6.7% in lunch and 4.4% in dinner (phase 2 *vs* phase 3). Significant differences were found between postprandial capillary glycaemia obtained after breakfast between phases 1 and 2. Important interindividual variations were also found in this parameter. In this way, some patients show decreases for postprandial glycaemia close to 30%, while in two subjects this parameter is scarcely modified.

Other parameters related to diabetes

Table 4 summarises several parameters related to diabetes. The treatment with fibre reduced slightly glycosylated haemoglobin ($GHbA_{1c}$; 3.8% *vs* phase 1 and 5.5% *vs* phase 3), although no significant differences were observed. Similar results were obtained with fructosamine (fell by 10.9% on fibre *vs* phase 1 and by 7.8% *vs* phase 3) and with blood C-peptide (fell by 14.9% on fibre *vs* phase 1 and by 10% *vs* phase 3). The statistical evaluation showed significant differences for fructosamine when we compared the value

Table 4 Mean values (± s.d.) of different parameters related to diabetes measured in 20 type 2 diabetic patients after a test breakfast

	Phase 1		Phase 2		Phase 3	
	x̄ ± s.d.	*CV (%)*	*x̄ ± s.d.*	*CV (%)*	*x̄ ± s.d.*	*CV (%)*
Fructosamine (mmol/l)[a,b]	3.0 ± 0.9[c]	29.6	2.7 ± 0.7	25.3	2.9 ± 0.7[c]	22.4
Blood C-peptide (nmol/l)[b]	0.91 ± 0.44	48.6	0.78 ± 0.34	43.8	0.86 ± 0.40	45.9
Glycosylated HbA_{1c} (%)[b]	6.8 ± 1.0	14.2	6.5 ± 0.9	13.6	6.9 ± 1.2	17.0
Urinary 24 h glucose excretion (mmol)[a,b]	20.7 ± 24.4	117.8	14.3 ± 20.8	145.4	16.3 ± 23.0[c]	140.8

[a]Significant differences among phases (Friedman's test, $P<0.05$).
[b]Significant differences among subjects (Friedman's test, $P<0.05$).
[c]Significant differences with phase 2 (Wilcoxon modified test, for conditions see text).

obtained in phase 2 with those recorded in phases 1 and 3. In these parameters important interindividual variations were observed.

Twenty-four hour urinary glucose excretion was 22.5% lower at the end of the treatment than in phase 1 and 14.6% than in phase 3, however, significant differences (Wilcoxon's test) were only found between the phases 2 and 3. In this case, interindividual variations were even greater.

Other parameters

Serum total cholesterol concentrations decreased significantly under psyllium treatment by 7.7% and by 6.2% in comparison

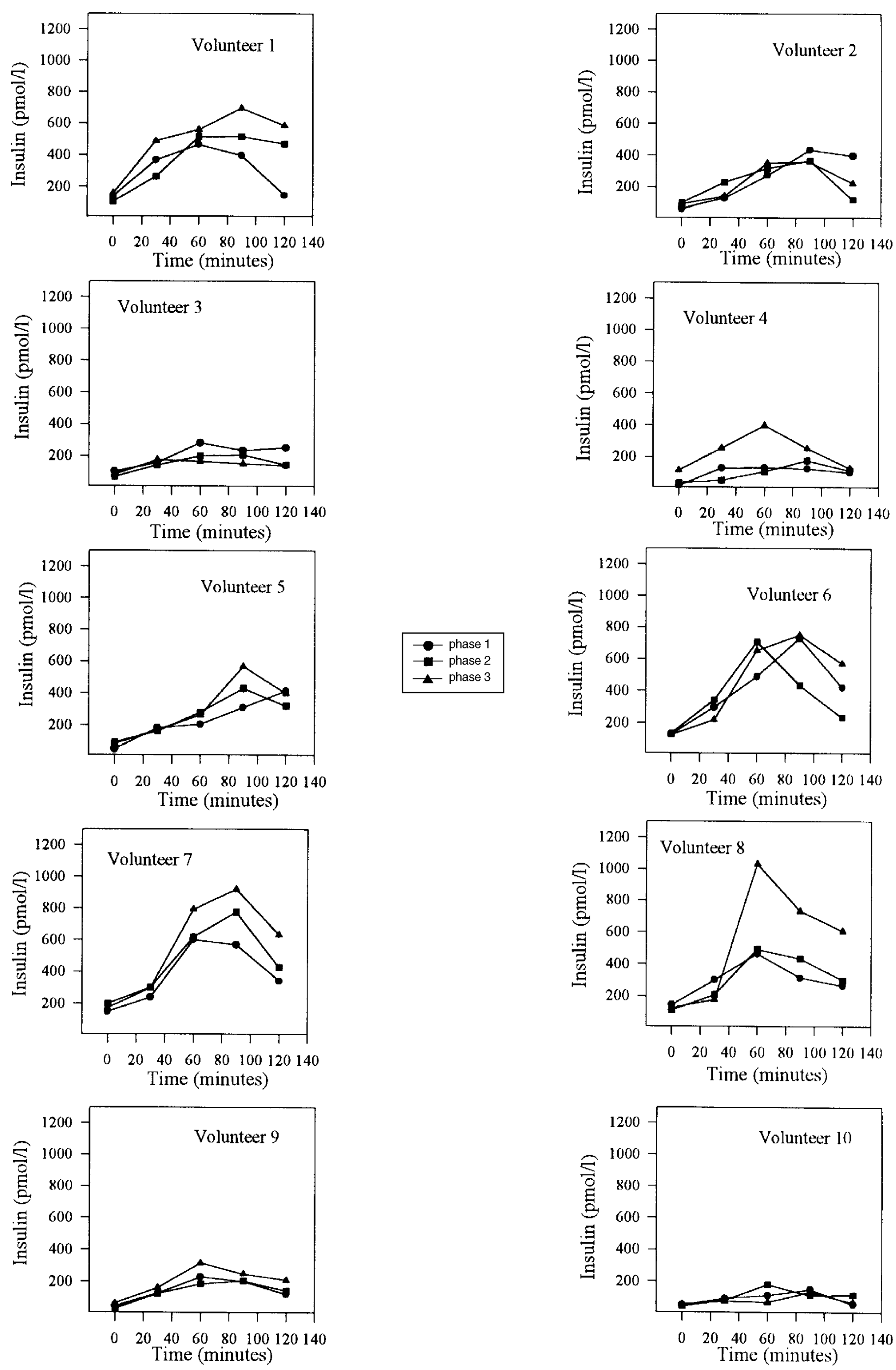

Figure 4 (a) Individual serum insulin-time curves in 10 type 2 diabetic patients after test breakfast.

with phases 1 and 3, respectively. In the same way, LDL cholesterol fell by 9.2 and 7.7%, respectively (significant differences, Wilcoxon's test). HDL cholesterol remained unchanged during phase 2 (no significant differences, Friedman's test, at $P < 0.05$). Psyllium administration also reduced uric acid (10%, significant difference, Wilcoxon's test).

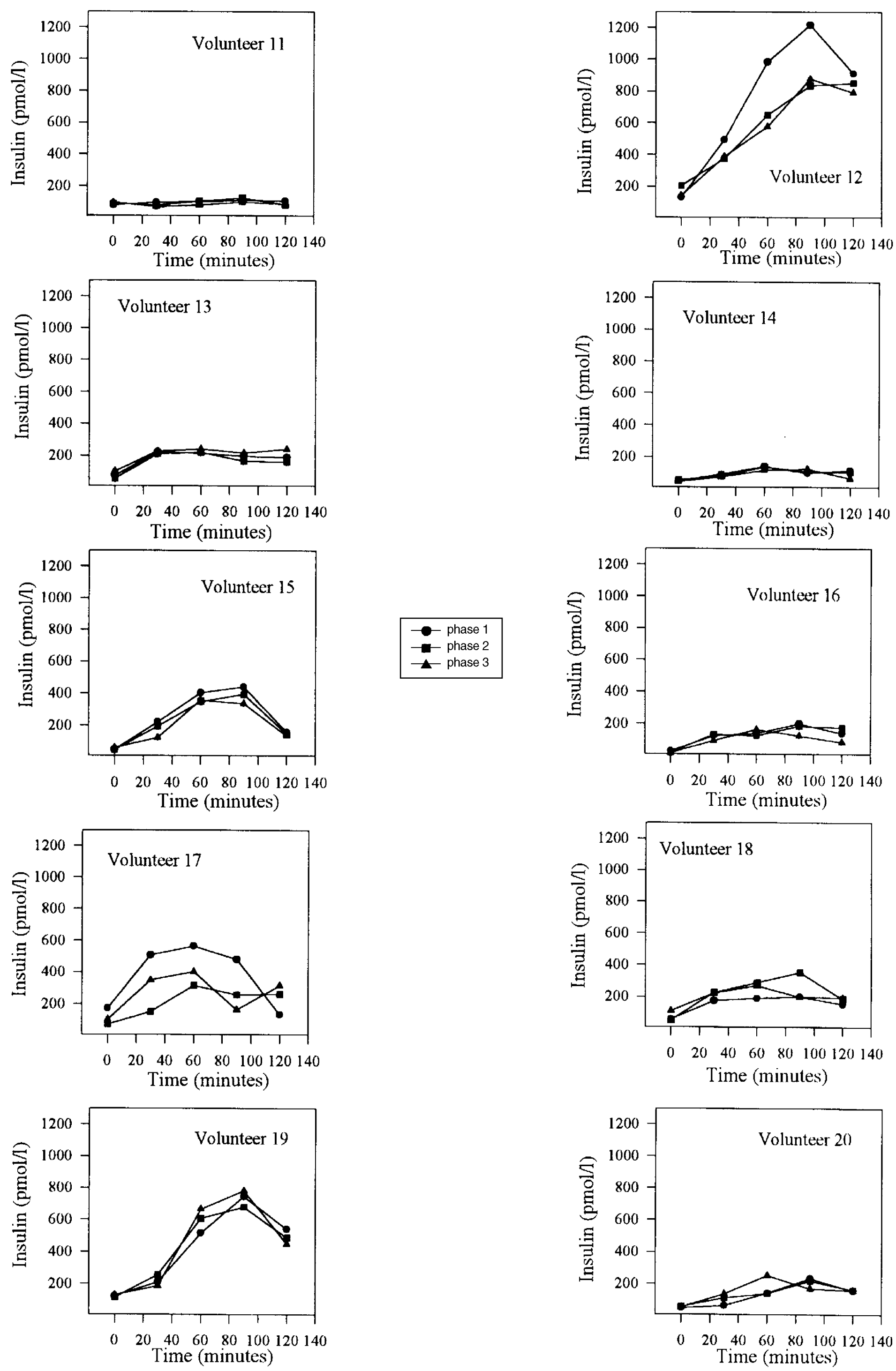

Figure 4 (b) Individual serum insulin-time curves in 10 type 2 diabetic patients after test breakfast.

Table 5 Minerals, vitamins and other biochemical parameters measured in 20 type 2 diabetic patients after a test breakfast

	Phase 1		Phase 2		Phase 3	
	$\bar{x} \pm$ s.d.	CV (%)	$\bar{x} \pm$ s.d.	CV (%)	$\bar{x} \pm$ s.d.	CV (%)
Uric acid (mmol/l)[a,b]	0.33±0.08[c]	24.2	0.30±0.07	24.7	0.33±0.07[c]	22.4
Total cholesterol (mmol/l)[a,b]	5.63±1.09[c]	19.3	5.2±0.84	16.1	5.54±0.93[c]	16.9
HDL cholesterol (mmol/l)[a,b]	1.31±0.34	25.7	1.31±0.24	18.1	1.48±0.32[c]	21.4
LDL cholesterol (mmol/l)[b]	3.84±0.38[c]	23.0	3.48±0.70	20.1	3.78±0.96	25.3
Ca (mmol/l)[b]	2.38±0.10	4.4	2.34±0.11	4.5	2.35±0.08	3.4
P (mmol/l)[a,b]	1.01±0.10	10.3	1.07±0.14	13.0	1.11±0.13	12.1
Na (mmol/l)[a,b]	142.6±4.7[c]	3.3	143.7±4.9	3.4	141.0±2.9[c]	2.0
K (mmol/l)[a,b]	4.6±0.4	9.1	4.4±0.4	9.2	4.3±0.4	8.6
Mg (mmol/l)[a,b]	1.3±0.7	54.1	1.3±0.7	54.2	1.4±0.7[c]	47.0
Fe (μmol/l)[b]	15.2±4.14	27.2	15.0±3.94	26.3	16.9±5.28	31.3
Vitamin A (μmol/l)[b]	2.44±0.35	21.5	2.09±0.70	26.9	2.79±0.72	27.0
Vitamin E (μmol/l)[a,b]	36.7±9.98	27.2	39.2±9.13	23.3	44.3±9.12[c]	20.6

[a]Significant differences among phases (Friedman's test, $P < 0.05$).
[b]Significant differences among subjects (Friedman's test, $P < 0.05$).
[c]Significant differences with phase 2 (Wilcoxon modified test, for conditions see text).

Finally, other variables, including potassium, calcium, phosphorous, iron and vitamin A, showed no significant changes during the three phases (no significant differences, Friedman's test, at $P < 0.05$). An increase in the levels of magnesium and vitamin E was found when data of phases 2 and 3 were compared (significant differences, Wilcoxon's test). Sodium levels also showed an increase between phase 2 and phases 1 and 3 (significant difference, Wilcoxon's test).

Discussion

As indicated by other authors (MacMahon & Carless, 1998; Rodríguez-Morán *et al*, 1998; Oliver, 2000), in this study psyllium was well tolerated without any significant adverse effects.

The effects of sustained fibre supplementation on glycaemic control in subjects with diabetes mellitus have been examined with considerable variations in results. The data are somewhat difficult to evaluate because of differences in population, fibre type, diet and study design (Weinstock & Levine, 1988).

The effect of fibre is related to its viscosity (Jenkins *et al*, 1978) and with the method of administration (Wolever *et al*, 1991).

Rendell (2000) indicates that improvement in glucose tolerance produced by consumption of viscous fibre is due to slower absorption of carbohydrate rather than malabsorption. Intimate mixing, allowing physical interaction between food and fibre, seems to be important in converting the carbohydrate to what might be termed a slow-release form.

Wolever *et al* (1991) demonstrated in normal and in type 2 diabetic patients that psyllium reduced the glycaemic response to a flaked bran cereal test meal when the fibre supplement was sprinkled onto the top of the cereal or incorporated into the flakes, but not when it was taken before the cereal. Despite this fact, in the present study the fibre was taken dispersed in water because psyllium incorporation in a meal (by sprinkling it) would make it, in most cases, unpalatable, and because this is the usual way any patient would prepare an oral treatment with a therapeutic fibre.

The mechanism of action of gel forming fibre is related to the ability to increase the viscosity of the gastrointestinal contents and thus interfere with motility and absorption (Hopman *et al*, 1988). Several authors (Holt *et al*, 1979; Sandhu *et al*, 1987) have demonstrated an inhibitory effect of dietary fibre on gastric emptying, but others could not prove it (Lawaetz *et al*, 1983; Lembcke *et al*, 1984). Hopman *et al* (1988) showed that glucomannan affects absorption within the intestine in a study carried out in patients with previous gastric surgery, and this is in agreement with the results obtained in several animal studies (Elsenhans *et al*, 1980,1981,1984; Johnson & Gee, 1981).

We found that psyllium, under the preparation used in this study, decreased significantly postprandial blood glucose concentrations in type 2 diabetic patients. It appears that this fact can show the best effect of psyllium. Earlier studies reported that psyllium reduced fasting serum glucose concentrations in individuals with type 2 diabetes (Fagerberg, 1982) and in type 2 diabetic patients with chronic portal-systemic encephalopathy (Uribe *et al*, 1985). Other studies demonstrated that different preparations of ispaghula husk lowered postprandial serum glucose concentrations in type 1 (Florholmen *et al*, 1982), in type 2 diabetic patients (Sartor *et al*, 1981; Pastors *et al*, 1991; Anderson *et al*, 1999), in healthy volunteers (Sierra *et al*, 2001) and in both healthy and type 2 diabetic subjects (Jarjis *et al*, 1984). Fibre doses used were different, ranging from 3.6 g administered with breakfast (Florholmen *et al*, 1982) to 35 g per day administered as a dietary supplement (Uribe *et al*, 1985). In contrast, no significant differences were found after a 50 g glucose load administered with 3.5 or 7 g fibre to healthy subjects (Jarjis *et al*, 1984).

The mean decrease of C_{max} obtained in this study after the administration of psyllium (10%) was similar to that reported by Sartor *et al* (1981) after a standardized breakfast (9%), and lower than the indicated by Pastors *et al* (1991) at breakfast (14%) and at dinner (20%), and by Sierra *et al* (2001) in healthy subjects after a glucose load (15.5%).

Results obtained with guar gum are variable. Several authors report no modifications in glycaemia or a modest improvement of glycaemic control (Botha *et al*, 1981; Carroll *et al*, 1981; Lim *et al*, 1990; Stahl & Berger, 1990), while others indicate significant decreases (Smith & Holm, 1982; Fuessl *et al*, 1987; Chuang *et al*, 1992; Fairchild *et al*, 1996; Gatenby *et al*, 1996; Brenelli *et al*, 1997), some of them similar to the value indicated in this paper (10.1%, Chuang *et al*, 1992a, b) and others higher (50%, Fuessl *et al*, 1987; 35%, Brenelli *et al*, 1997).

In relation to insulin, the mean decrease we have found when fibre is administered is not significant, although we think that this may be due to the fact that patients had had diabetes for different lengths of time. This result is similar to that obtained by Jarjis *et al* (1984) in healthy and in type 2 diabetic volunteers. Pastors *et al* (1991) found significant decreases for insulin after the administration of psyllium in type 2 diabetic patients, with a reduction (12%) higher than the reported in this study (5%). We have also found in a previous study (Sierra *et al*, 2001) carried out in healthy volunteers, a significant and higher reduction of insulin concentrations (36.1%) after the administration of ispaghula husk.

These differences observed in insulin concentrations after the administration of psyllium, have also been reported with guar gum: several authors found no significant (Groop *et al*, 1986,1993) or minimum (Stahl & Berger, 1990) changes while others indicate significant differences (Chuang *et al*, 1992; Fairchild *et al*, 1996; Gatenby *et al*, 1996).

In relation to other parameters related to diabetes ($GhbA_{1c}$, fructosamine, C-peptide concentrations in blood and in urine and glucose in urine), for all of them, we have obtained a decrease in their concentrations in the presence of fibre, which was significant for fructosamine. This last fact is important because, due to the relatively short duration of this study, fructosamine is a better marker than $GhbA_{1c}$. This reduction might be due to psyllium's ability to reduce hunger feelings and energy intake (Rigaud *et al*, 1998). We have no data available from other authors about how psyllium modifies these parameters. The results obtained with other soluble fibres such as guar gum are variable. Thus, Stahl and Berger (1990) found no significant differences in glycosilated haemoglobin after the administration of 15 g of guar gum daily during 3 months; Jones *et al* (1985), after the administration of 10 g/day during 2 months, obtained a significant fall in $GhbA_{1c}$ levels, without significant changes in 24 h urinary glucose excretion. Behall (1990) observed that guar gum significantly reduced blood C-peptide concentrations after the administration of 31.7 g fibre per day during 6 months and Holman *et al* (1987) obtained no significant changes in blood C-peptide and $GhbA_{1c}$ concentrations after the administration of 15 g/day during 8 weeks.

Mean reductions obtained in total and in LDL cholesterol (7.7 and 9.2%, respectively, significant differences) were slightly higher than those showed by Bell *et al* (1989) in hypercholesterolaemic patients (4.8% reduction in total cholesterol level and 8.2% in LDL cholesterol) after a treatment with 10.2 g psyllium daily during 12 weeks. The reduction observed for LDL cholesterol by Davidson *et al* (1998) in hypercholesterolaemic patients after being treated with 10.2 g psyllium per day during 24 weeks was also slightly lower (5.3%) than our value. On the other hand, our results were slightly lower than those found by Anderson *et al* (1999) in men with type 2 diabetes and hypercholesterolaemia after 8 weeks receiving 10.2 g psyllium daily. Romero *et al* (1998) observed that LDL cholesterol concentrations were reduced by an average of 22.6 and 26% after administering 1.3 g/day of psyllium to healthy volunteers. In the same way, other authors (Rodríguez-Morán *et al*, 1998; Segawa *et al*, 1998) found a significant reduction in total and LDL cholesterol.

In relation to HDL cholesterol, we did not found significant changes in this parameter after the administration of fibre. Similar results were shown by other authors (Davidson *et al*, 1998; Romero *et al*, 1998). However, Rodríguez-Morán *et al* (1998) observed a significant increase in this parameter after the administration of 15 g psyllium daily to type 2 diabetic patients.

Results obtained with guar gum are, again, contradictory. In this way, Jones *et al* (1985) found no changes in lipid levels after the administration of this fibre, while other authors obtained significant reductions in LDL cholesterol concentrations without changes in HDL cholesterol (Holamn *et al*, 1987) or with a significant decrease in total cholesterol (Blake *et al*, 1997).

It has been suggested that deficiencies of calcium, iron, trace metals, certain vitamins and possibly other nutrients may occur after prolonged periods of high fibre intake (Nuttall, 1983; American Diabetes Association, 1987).

The slight decrease observed in the mean level of uric acid at the end of the psyllium phase in relation to the other two phases is significant in both cases. We have no data obtained by other authors for comparison and we think that further studies are required in order to determine whether the use of psyllium would be advantageous for the treatment of hyperuricaemic patients.

Results obtained in the present study on mineral and vitamin levels indicate that psyllium does not significantly modify serum concentrations when mean phase 2 values were compared with those obtained in phase 1, except that sodium increases significantly during the administration of psyllium, although the differences in concentration are low. We have no data available from other authors about how psyllium modifies these parameters. Chuang *et al* (1992) found that sodium, potassium, chloride, magnesium and calcium levels showed no significant changes during the treatment with guar gum (8 weeks).

Behall (1990) did not detect apparent changes in mineral balance (calcium, magnesium, iron, copper and zinc), with the exception of a negative manganese balance, after carboxymethyl cellulose administration. In this study, carboxymethyl cellulose gum, karaya gum and locust bean gum were consumed by the patients during 4 weeks each (19.5 g of fibre per day). The author, in a second study (Behall *et al*, 1989), administered 31.7 g guar gum per day during 6 months and found that mineral balance was not affected for iron, copper, zinc, calcium, manganese or magnesium.

Taking into account the results obtained in the present study, those found in an earlier study carried out in healthy subjects (Sierra *et al*, 2001) and according to Chuang *et al* (1992), we conclude that psyllium treatment effectiveness should be evaluated individually in each subject with the purpose of establishing the most adequate dose and administration regime and a greater efficiency.

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