Dietary fibre and diabetes mellitus

Citation for published version (APA):

Sels, J-PJE. (1991). *Dietary fibre and diabetes mellitus*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.19910322js>

Document status and date:

Published: 01/01/1991

DOI:

[10.26481/dis.19910322js](https://doi.org/10.26481/dis.19910322js)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

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Dietary fibre and diabetes mellitus

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PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus, Prof. Mr. M.J. Cohen,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen
op vrijdag, 22 maart 1991 om 16.00 uur

door

Jean-Pierre Joseph Emile Sels

Promotores: Prof. Dr. A.C. Nieuwenhuijzen Kruseman
Prof. Dr. J.A. Flendrig

Beoordelingscommissie: Prof. Dr. P.B. Soeters (voorzitter)
Prof. Dr. P.J. Brombacher
Dr. W. Van Dokkum (TNO-CIVO)
Prof. Dr. W.H.M. Saris
Dr. E.F.M. Wouters

CIP GEGEVENS KONINKLIJKE BIBLIOTHEEK DEN HAAG

Sels, Jean-Pierre Joseph Emile

Dietary fibre and diabetes mellitus / Jean-Pierre Joseph

Emile Sels. - Maastricht : Datawyse. - Ill.

Thesis Maastricht. - With ref. - With a summary in Dutch.

ISBN 90-5291-047-2

NUGI 742

Subject headings: dietary fibre / diabetes mellitus

Productie en Layout: Datawyse Maastricht, Ruud Leliveld

Omslagontwerp: Datawyse Maastricht, H. Haafkens

Dit proefschrift is tot stand gekomen met ondersteuning van TNO en Diabetes Research Fonds.

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Introduction

Diabetes mellitus is an endocrine disorder characterised by hyperglycaemia with polydipsia, polyuria and weight loss, and is caused by an absolute (type 1 diabetes) or relative (type 2 diabetes) deficiency of insulin. In particular in type 2 diabetes the lipid metabolism is also disturbed, which is an important additional risk factor for the development of late vascular complications.

Dietary fibre is a constituent of practically every food product. It consists of polysaccharides and lignin, which are not digested by the human small intestinal enzymes.

Dietary recommendations are still of ultimate importance in the management of patients with diabetes mellitus to avoid large fluctuations of blood glucose values through the day as well as hyperlipidaemia. In the last decades the dietary recommendations for diabetic patients have evolved from carbohydrate restriction to carbohydrate enrichment and fat restriction (1,2). To overcome hyperglycaemia, which may result from high-carbohydrate meals, complex carbohydrates in combination with extra dietary fibre are usually prescribed. Addition of dietary fibre is supposed to result in a delay of enzymatic digestion and intestinal absorption of carbohydrates which contributes to a smoothening of postprandial blood glucose excursions. An additional advantage of dietary fibre may be that lipid metabolism is influenced as well, independent of its effects on carbohydrate absorption. Several reports have, however, revealed that the advantageous effects of complex carbohydrates can partly be annulled if consumed in daily meals with normal quantities of fat and proteins (3,4). These nutrients also exert effects on carbohydrate digestion and absorption and appear herein more important than the complexity of the carbohydrates. The same may to some extent apply to dietary fibre. For this reason the studies with dietary fibre described in this thesis were undertaken. More specifically, the aim of this thesis is to investigate whether incorporation of the water soluble dietary fibre guar into ready-made food products such as bread or spaghetti with an acceptable taste has a beneficial effect on carbohydrate and lipid metabolism in diabetic patients.

In chapter 1 the significance of dietary fibre in the management of diabetic patients is reviewed. To increase daily intake of dietary fibre two modes are possible, i.e. an increase of high-fibre food in daily meals or supplementation of dietary fibre to the food (5). In the studies described in this thesis we followed the fibre supplementation approach as large diet changes to increase the fibre content of meals are usually difficult to follow and rarely continued for longer periods. As fibre supplement we selected the soluble fibre guar-gum for several reasons. Guar is recognised by the FDA as a GRAS (Generally Recognised As Safe) product and is widely used in food as a solidifier and gelling agent. However, when hydrated guar is sticky and unpalatable. To be effective it has to be mixed thoroughly with the food. The best way to overcome these difficulties is to incorporate guar into the food products. We therefore decided to incorporate guar into bread (75 g guar/kg flour), as bread is an important component of the Dutch daily food. In chapters 2 and 3 studies with type 1 and type 2 diabetic patients are described regarding the effects of this guar-bread consumed as part of their daily meals for periods of 6 weeks and 3 months on metabolic control. As loaf quality and taste make it difficult to incorporate large quantities of guar into bread, which may have consequences for the efficacy of the dietary fibre, additional short-term experiments were performed with guar-spaghetti testmeals. Higher quantities of guar (up to 200 g guar/kg flour) can be incorporated into spaghetti without seriously affecting the palatability. These studies, described in chapter 4, were conducted in healthy volunteers and type 2 diabetic patients who ingested complex guar-spaghetti meals prepared from two species of wheat, i.e. soft (*Triticum aestivum*) and hard (*Triticum durum*) wheat. These wheat forms have a different hardness of the starch granules. As grinding damages starch granules of hard wheat more than granules of soft wheat, food prepared from hard wheat may be more susceptible to enzymatic digestion. In chapter 5 *in vitro* experiments are described which were conducted to study the effects of guar incorporated into these spaghetti forms on the enzymatic digestion of the starch and diffusion of oligosaccharides through the food bolus. This thesis concludes with a reconsideration of the dietary recommendations for diabetic patients.

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CHAPTER 1

Dietary fibre in the management of diabetes mellitus

A review

JPJE Sels, ThJL Postmes, BHR Wolffenbuttel, AC Nieuwenhuijzen Kruseman
The Netherlands Journal of Medicine: in press

SUMMARY

The role of nutritional habits in the emergence of certain diseases in the western world enhanced the interest in nutrition. As a consequence, the importance of what is now called dietary fibre has changed from an unnecessary constituent of plant food to an essential element of healthy nutrition. Several diabetes associations now advice to include a defined amount of dietary fibre in an up-to-date dietary treatment of diabetes mellitus. However, there are still many controversies and unanswered questions. This paper reviews briefly the problems of definition and determination of dietary fibre. The possible mechanisms of action are discussed, and a survey of data in the literature that deal with the effect of long-term ingestion of increased amounts of dietary fibre on carbohydrate and lipid metabolism, safety and applicability is presented.

INTRODUCTION

Dietary treatment is a mandatory element in the therapeutic concept of any form of diabetes mellitus. Two aspects are important in the dietary landscape: the so-called fast- and slow-releasing or lente carbohydrates and dietary fibre.

Food products with the same carbohydrate content may produce quite different glucose response curves or glycaemic indexes. Some starches are quickly digested (fast-releasing carbohydrates), while others take a long time to release their glucose (slow-releasing or lente carbohydrates). Examples of fast-releasing carbohydrates are boiled potatoes, white bread and processed foods such as potato crisps, whereas lentils and many leguminous foods belong to the category of slow-releasing carbohydrates. In particular if food is composed of fast-releasing carbohydrates dietary fibre plays an essential role in transforming these into slow-releasing carbohydrates.

The favourable effect of dietary fibre and a high content of carbohydrates in the food goes back to Aretaeus of Cappadocia (second century A.D.), who told his patients: "As food use milk and with it use cereals, starch, groats and gruels, a stringent wine, undiluted, as a tonic for the stomach" (1). Already in 1935, Himsworth demonstrated the beneficial effects of high carbohydrate intake on glucose tolerance (2). Later on this was confirmed by others (3-5).

For these reasons and in line with the recommendations of the American Diabetes Association (ADA) of 1971 (6) and 1979 (7) the food prescribed to diabetic patients usually should provide at least 50 energy% carbohydrates, 20 energy% proteins, 30 energy% fat and contains about 25 g/1000 Kcal dietary fibre. A much lower daily dietary fibre intake (approx. 14 g/1000 Kcal) in a general concept of healthy nutrition for the total population is however advised by the Dutch Nutrition Council in 1986 (8). In a critical note this Council said that advices on daily requirements of dietary fibre are hampered by the lack of a clear dosis-response relationship between dietary fibre and its presumed effects and therefore do not support the high fibre intake as recommended by the ADA. Nevertheless, dietary fibre appears to be essential when a high carbohydrate diet is prescribed. In this situation dietary fibre prevents the worsening of glucose control and increase of serum lipoproteins, in particular triglycerides, which occur when high carbohydrate meals are consumed without additional dietary fibre (9-11).

This paper will discuss the physiological implications of dietary fibre in human nutrition. Furthermore, it reviews clinical trials carried out with various high-fibre, high-carbohydrate diets in diabetic patients.

DEFINITION AND NATURE OF DIETARY FIBRE

In general, dietary fibre can be defined as the component of nutrition not digested in the human small intestinal tract, due to absence of specific enzymes (e.g. cellulose) or the inability of present enzymes for complete digestion (changed physical and/or chemical structure). However, which nutrients should be included in this definition of dietary fibre still raises much discussion among food scientists (12-14). Trowell (15) defines dietary fibre as "The remnants of plant cells resistant to hydrolysis by the alimentary enzymes of man". This botanical definition is rather restrictive. Undigestible polysaccharides not related to the cell wall like gums and mucilages are usually included in the dietary fibre concept and are difficult to differentiate analytically from cell wall polysaccharides. For these reasons a chemically more precise definition is nowadays used including undigestible polysaccharides and lignin (16). This concept of dietary fibre is thus not completely congruent with plant cell wall constituents (Table 1). During processing of food some starches are transformed into resistant starch (RS), which means that they become undigestible in the small intestine and hence can be classified as dietary fibre as well, although this has been disputed by some (12-14). This RS discussion still remains unsettled due to differences in analytical methods to quantitate fibre in nutrients. In particular the enzymatic gravimetric method of the Association of Official Analytical Chemists (AOAC) does measure RS as well.

Table 1. Difference between plant cell wall and dietary fibre. The plant cell wall contains substances that do not belong to dietary fibre. On the other hand, dietary fibre includes other compounds than plant cell wall constituents.

Plant cell wall	{	Proteins	{	Dietary fibre
		Lipids		
		Inorganic constituents		
		Lignin		
		Cellulose		
		Hemicellulose		
		Pectins		
		Gums		
		Mucilages		
		Algal polysaccharides		
		Modified cellulose		

Table 2. Fractionation of dietary fibre. Dietary fibre can be divided into soluble and insoluble forms. These forms can be subdivided according to their chemical composition, eg the nature of the polysaccharides.

Total dietary fibre	Non-starch polysaccharides (NSP)	Non-cellulosic polysaccharides (NCP)	Other polysaccharides	soluble fibre
			Pectin	(in)soluble fibre
			Hemicellulose	
		Cellulose	Cellulose	insoluble fibre
	Lignin	Lignin	Lignin	

Dietary fibre can be chemically fractionated in lignin, a phenylpropane polymer, and non-starch polysaccharides, containing cellulose, hemicellulose, pectins, mucilages and algal polysaccharides (Table 2).

From a physiological point of view dietary fibre can be divided into water-soluble non-starch polysaccharides on the one hand and water-insoluble fibre non-starch polysaccharides and lignin on the other. The soluble fibres include gums (e.g. guar), mucilages, pectines and some hemicelluloses. These are degraded in the colon to short-chain fatty acids (SCFA) or volatile fatty acids (VFA) and contribute little to bulk formation of the faeces. The insoluble fibres include cellulose and some hemicelluloses. Together with lignin these contribute to a large extent to bulk formation. The quality and properties of dietary fibre are not only dependent on the chemical composition, but also on plant species, the where and when of harvesting, physical structure (17,18) and particle size (19,20). Processing also affects the fibre structure. This alters the physico-chemical properties and thus changes the physiological effects of dietary fibre (21-23).

ANALYSIS OF DIETARY FIBRE

All analytical methods for dietary fibre analysis depend on an efficient removal of starch. Several methods are in use. They can be divided in two groups: 1) gravimetric methods in which dietary fibre is weighed after removal of other components by the use of detergents (neutral detergent fibre (NDF) or acid detergent fibre (ADF) method) or enzymes (AOAC method). 2) fractionation methods in which dietary fibre monomers are specifically assayed. The AOAC method (24) uses 3 enzymes, a heat stable alpha-amylase, a protease for degrading the cell proteins, and an amyloglucosidase with amylolytic activity. After enzymatic digestion, ethanol is added, the precipitate washed with alcohol-aceton, and total dietary fibre is then weighed and corrected for undigested protein and ash. Soluble and insoluble fibre can be isolated by slightly different washing, precipitating and drying procedures. A fractionation method is described by Englyst *et al.* (25), which starts with starch digestion followed by acid hydrolysis. The resulting monosaccharides are determined by gas liquid chromatography (GLC) (25) or high-performance liquid chromatography (HPLC) (26) and uronic acid, another component of dietary fibre particularly pectines, by colorimetry. The AOAC method separates dietary fibre more in physiological entities, whereas the Englyst method gives a more detailed description of the chemical composition of the analyzed fibre.

MECHANISMS OF DIETARY FIBRE ACTION

Dietary fibre has effects on gastro-intestinal motility, food digestion, absorption of nutrients and bowel function e.g. stool transit.

Stomach

Time for chewing food and gastric filling are prolonged during consumption of a high-fibre meal compared to low-fibre meals (27), whereas the water binding of the various dietary fibre components causes swelling of the gastric content. As a consequence of this slower gastric filling, increased volume and higher viscosity of the food, the gastric emptying is delayed both in man and animal (28-30), although this has not been confirmed by all studies (31). These discrepancies may be due to differences of design such as the use of hypertonic solutions, application of gavage techniques and perhaps different effects on

gastric emptying short- and long-term experiments (31). Dietary fibre also alters buffer capacity of the gastric secretions and reduces gastric acidity (32), perhaps by reduced gastrin secretion (33). However, all these effects appear to be of no importance for the reduction of postprandial blood glucose and serum insulin levels (34,35).

Small intestine

Dependent on the nature of the dietary fibre, human studies have shown that the transit of digested fibre-rich food from mouth to caecum can be delayed (31,36), is unchanged (37), or even shortened (38). Intestinal transit time is usually measured indirectly by determination of hydrogen in the breath generated by fermentation of lactulose. This is a synthetic disaccharide which is not absorbed in the small intestine. It is fermented by colonic bacteria, generating hydrogen which is expired in breath. The time between ingestion of lactulose and the expiration of hydrogen is a measure of gastric emptying and small intestinal transit velocity. Guar-gum prolongs transit time, whereas it is shortened by wheat fibre. Pectin and methylcellulose appear to have no effect on intestinal transit time at all (39).

Hypothetically, a prolonged intestinal transit time may result in an increase of absorption of nutrients. However, a number of factors prevents such a simple absorption equation. When the viscosity of the food increases, in particular with water-soluble dietary fibre, intestinal movements to mix food decrease, which delays absorption of nutrients(40). Enzyme-fibre interactions (41), leading to enzyme-trapping and dilution of enzymes by water binding of dietary fibre, result in a diminished absorption as well. Furthermore, some dietary fibres contain enzyme-inhibitory activities (42). As a consequence, the digestion of high-fibre food is delayed, despite normal or even elevated pancreatic enzyme secretion (30,43). Adsorption of minerals by dietary fibre could also influence the mineral balance.

After digestion of high-fibre food, absorption of monosaccharides and neutral amino acids is impaired, due to an increased unstirred water-layer resistance at the surface of the mucosa (44,45) induced by dietary fibre. It is still controversial whether dietary fibre increases (46), decreases (47,48) or exerts no effect (49) on brush-border enzyme concentrations and its activity.

Viscous fibre may also increase faecal excretion of bile acids and cholesterol (50,51). This leads to compensatory stimulation of bile acid and cholesterol synthesis by an increase of enzyme activity of the pentose-phosphate shunt

[glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase] and the Krebs cycle enzyme malate dehydrogenase. These provide NADPH necessary for fatty acid and cholesterol synthesis. In these situations, extra substrate for fatty acid synthesis is supplied by glycogenolysis via increased levels of 6-phosphofructokinase (52). However, since Pedroso *et al.* (53) found decreased levels of G6PD and malate dehydrogenase this has been controversial.

A variety of experiments with dietary fibre as a nutritional stimulus have revealed histological changes of the small intestinal surface, in particular greater length and leaf-like shapes of villi (54), raised goblet cell activity and increased mucine production (55). In animals, increased mucosal crypt cell proliferation and epithelial cell turnover is demonstrated (48,56). These histological changes may be induced by an increased cell turnover due to an adaptive enlargement in response to a reduced absorption of nutrients.

Large bowel

Bulking of the stool stimulates peristalsis of the colon and leads to a shortening of caecum-anal transit time. The fact that soluble fibre has practically no effect on bulk formation of the stool can be explained by the digestion of these fibres in the large bowel by microbial fermentation. This fermentation results in reduced colonic pH, reduced bile absorption and in the formation of short-chain ('volatile') fatty acids (SCFA or VFA), which include acetate (60%), propionate (20%) and butyrate (16%). Approximately 70% of these acids is absorbed in the colon. Acetate is the only substance not completely cleared by the liver and therefore detectable in the systemic circulation. In large amounts, butyrate serves as an energy source for the colonic mucosa. The VFA have relevant extra-intestinal metabolic effects. Acetate and butyrate are transformed into acetyl-CoA which stimulates gluconeogenesis by activating pyruvate carboxylase. They increase the hepatic citrate concentration, which reduces phosphofructokinase activity and hence the glycolysis. Propionate has the opposite effect. As its impact on carbohydrate metabolism overrules the effect of acetate, the net result is a promotion of glycolysis and a decreased hepatic gluconeogenesis (57). Propionate also inhibits the enzyme HMG-CoA reductase, the rate-limiting enzyme in the synthesis of cholesterol. Next to the interruption of the enterohepatic cycle, this is the second mechanism by which dietary fibre may reduce plasma cholesterol levels (58). Short-chain fatty acids generated from soluble dietary fibre also reduce peripheral lipolysis, resulting

in a decrease of fasting free fatty acids (59). Finally, the short-chain fatty acids provide no substantial contribution to energy availability in western type diets (60).

Metabolic effects

Addition of dietary fibre to food causes a flattening of the postprandial glucose response in healthy people as well as in diabetic patients. The largest effects are found with guar, although these effects do not occur when hydrolyzed non-viscous guar is used (39). The reduction of blood glucose response for each fibre substance correlates well with its viscosity. The most viscous dietary fibre is guar, while methylcellulose has the lowest viscosity. Comparable reductions in postprandial blood glucose values are found, when naturally occurring fibre-rich nutrients are incorporated into meals (61,62).

Numerous studies have shown that use of dietary fibre results, parallel to blood glucose reduction, in lower postprandial insulin and C-peptide levels. In acute studies, these lower levels can be explained by a slower rate of intestinal absorption of carbohydrates and an attenuated glucose stimulus on insulin secretion. In long-term studies, an increase in insulin binding and sensitivity have been found in addition to decreased insulin responses due to delayed carbohydrate absorption (63-65). Apart from an effect on insulin secretion, dietary fibre is found to constitute effects on other peptides involved in glucose homeostasis as well, in particular glucagon, gastric inhibitory polypeptide (GIP) and somatostatin. The K-cells of the proximal small intestine secrete GIP, which inhibits gastric motility and stimulates insulin secretion. The stimulus for GIP is glucose entering the K-cell from the luminal side of the small intestine. Reduction of glucose diffusion in the small intestine by dietary fibre attenuates GIP secretion (66,67). After ingestion of dietary fibre pancreatic glucagon levels are reduced (68,69), whereas somatostatin levels are increased (70,71). All these hormones involved in glucose homeostasis have a complex inter-relationship, which varies with blood glucose levels and thus also with daily dietary fibre ingestion (72). The importance of these hormonal alterations for long-term diabetes control are however uncertain.

LONG-TERM STUDIES IN DIABETES MELLITUS

In the dietary treatment of patients with diabetes mellitus guar is one of the best examined dietary fibres. Guar is a galactomannan polymer with a molecular weight of approximately 220,000 dalton and a ratio of mannose to galactose of about 2:1. The main source of guar is the endosperm of the seed of the Indian cluster bean (*Cyamopsis Tetragonaloba* (L) Taub). It is available as a white powder which quickly swells in water. It can be incorporated in crispbread crackers, bread (up to 5%) or pasta (up to 20%). Higher concentrations affect food texture and taste and may cause gastrointestinal complaints (73). Guar may also be administered as a granulate with a protective layer of protein. The favourable role of guar in the food on long-term metabolic control in diabetic patients has first been demonstrated by Jenkins and coworkers (74). In a 52-weeks study with insulin dependent (IDDM) and non-insulin dependent (NIDDM) diabetic patients a daily intake of 14-26 g guar incorporated in crispbread resulted in a better metabolic control as estimated by a decrease in glucosuria and a reduction of the required insulin dose. In other studies, addition of soluble fibres different from guar also caused lower postprandial glucose and insulin responses. A number of studies reported thereafter failed to demonstrate an improvement of metabolic control in diabetes mellitus with extra dietary fibre in the food. To obtain a compiled impression of the effects of dietary fibre on the glucose regulation in diabetic patients, we evaluated published investigations, in which at least 5 patients were studied and a substantial increase of daily fibre consumption for at least 2 weeks was prescribed (5,10,74-106). In 24 of these studies (74-97), the effects of supplementation of dietary fibre to the food on metabolic control were studied. The other 11 studies (5,10,98-106) concerned investigations of metabolic effects of high-fibre meals. Six of these studies applied high-carbohydrate diets.

Carbohydrate metabolism

Tables 3 and 4 summarize the effects of additional dietary fibre on blood glucose control. Most studies concern the administration of guar (Table 3). In only four studies (75-78) a significant improvement of blood glucose control is reported. All other studies show no improvement in long-term diabetic control, as assessed by HbA_{1c} measurements. Only one study in NIDDM patients (75) reports a significant reduction of fasting blood glucose. These disappointing effects of dietary fibre on blood glucose control can not be explained by

Table 3. Studies in IDDM and NIDDM patients employing fibre supplemented diets in which the effects of dietary fibre were estimated on HbA₁ or HbA_{1c} changes

Author	Ref	Fibre type	Type diab	Number pat.	Fibre g/day	Study weeks	ΔHbA ₁ (%)	ΔFasting glucose (%)
Tagliaferro	75	guar	NIDDM	10	16	6	- 7*	-10*
Jones	76	guar	IDDM+NIDDM	20	10	8	-10*	+ 3
Huth	77	guar	NIDDM	17	15	26	-14*	nr
Jones	78	guar	NIDDM	11	10	7	-22*	+ 5
Kyllastinen	79	guar	NIDDM	14	16	8	0	- 8
Holman	80	guar	NIDDM	29	15	8	+ 3	0
Uusitupa	81	guar	NIDDM	39	15	13	- 6	- 2
Uusitupa	81	guar	NIDDM	39	15	55	+ 4	+ 5
Ehrhart-Schmelzer	82	guar	NIDDM	21	10-20	3	ns	ns
Ebeling	83	guar	IDDM	9	20	4	- 5	nr
Sels	84	guar	NIDDM	13	8	6	+ 5	ns
Sels	85	guar	NIDDM	12	9	13	+ 2	+ 2
Sels	85	guar	IDDM	16	12.7	13	- 3	- 8
Beattie	86	guar*	NIDDM	24	30+15	8	ns	ns
Hagander	87	beet fibre	NIDDM	12	27	8	- 3	- 5

* $p \leq 0.05$ vs pretreatment; ns = reported non significant; nr = not reported; * guar + cereal fibre; ref 83 is the only randomized, double blind, placebo controlled study.

differences in intake of dietary fibre, since in the studies showing no effect intake of dietary fibre was even higher (17.8 ± 10 vs. 12.7 ± 3.2 g/day) than in the studies which reveal efficacy of dietary fibre.

Two of the 6 studies on high-carbohydrate high-fibre (HCHF) diets (table 4, ref 5,98) show a significant HbA₁ decrease, but only in NIDDM patients. The standard carbohydrate high-fibre diets (SCHF) show no effect. In contrast, fasting blood glucose values decreased in the majority of HCHF studies and in 2 SCHF studies. However, in long-term studies HbA₁ rather than fasting blood glucose levels are representative for metabolic control. Thus, the effect of dietary fibre as a supplement or incorporated in a high carbohydrate meal on long-term diabetes control is disappointing.

Table 4. Studies in IDDM and NIDDM patients employing high-fibre diets, in which the effects of dietary fibre were estimated on HbA_{1c} or HbA_{1c} changes.

Author	Ref	Diet* type	Type diab	Number pat.	Fibre g/day	Study weeks	ΔHbA _{1c} (%)	ΔFasting glucose (%)
Simpson	98	HCHF	NIDDM	18	96.6	6	-11*	-15*
Simpson	5	HCHF	NIDDM	14	78	6	-11*	-13*
Simpson	98	HCHF	IDDM	9	96.6	6	2	-27*
Simpson	99	HCHF	IDDM	11	78	6	0	-36*
Hollenbeck	100	HCHF	NIDDM	6	26.7**	4	ns	+9
Ney	101	HCHF	NIDDM	20	70	16	-22 \$	nr
Kinmonth	102	SCHF	IDDM	10	60	6	ns	-35*
Scott	103	SCHF	NIDDM	33	35	26	+6	+16*
Hagander	104	SCHF	NIDDM	14	43.7	8	+2	-6*

*: HCHF: high-carbohydrate (50%) high-fibre diet. SCHF: standard-carbohydrate (40%) high-fibre diet; **:expressed as gr/ 1000 Kcal.; \$: significantly changed compared to initial value but not changed compared to control group with control diet; * p ≤ 0.05 vs pretreatment.

Lipid metabolism

More positive effects of dietary fibre have been shown on lipid metabolism. In the majority of studies a reduction of total plasma cholesterol is observed (tables 5-6). Only in eight studies (Table 5) such a reduction is not found. In these studies, daily intake of dietary fibre was the same compared to that used in the studies showing reduced cholesterol levels. Data on LDL-cholesterol are given in 12 studies only. A decrease comparable to the changes in total cholesterol is usually reported. HDL-cholesterol appears not to be altered by dietary fibre. The effects of dietary fibre on plasma triglycerides (TG) are more divers: some studies report a decrease in TG, while other show an important increase or no effect at all.

The results with a high-carbohydrate, high-fibre diet (HCHF) are similar (Table 6). Reductions of total and LDL-cholesterol are similar in IDDM and NIDDM patients on HCHF, whereas usually no effect on HDL-cholesterol is observed. HCHF diets may increase plasma total and VLDL-triglyceride levels (107), although some studies have shown that the fibre content of these diets

Table 5. Changes in serum lipids in IDDM and NIDDM patients, employing fibre supplemented diets.

Author	Ref	Fibre type	Type diab	Nr. pat.	Fibre g/day	Study weeks	Δ TC (%)	Δ LDL-C (%)	Δ HDL-C (%)	Δ TG (%)
Jenkins	74	guar	NI+IDDM	11	14-26	52	-10*	-19*	+ 8	+ 8
Kyllästinen	79	guar	NIDDM	14	16	8	-13*	nr	+10	- 3
Tagliaferro	75	guar	NIDDM	10	16	6	-11*	-19*	- 2	-11
Smith	88	guar	NI+IDDM	17	20	13	-14*	nr	nr	- 3
Uusitupa	81	guar	NIDDM	39	15	13	-14*	nr	- 2	+13
Uusitupa	81	guar	NIDDM	39	15	55	- 7*	nr	+ 4	0
Ehrhart-Schmelzer	82	guar	NIDDM	21	10-20	3	-10*	-10*	nr	ns
Najemnik	89	guar	NIDDM	41	15	4	-25*	nr	nr	-14*
Najemnik	89	guar	NIDDM	38	15	4	-25*	nr	nr	- 7*
Ebeling	83	guar	IDDM	9	20	4	-21*	-27*	0	- 3
Gatti	90	guar	NIDDM	5	10-15	2	-17*	nr	nr	-18*
Sels	85	guar	IDDM	16	12	13	- 9*	-14*	- 4	+18
Sels	85	guar	NIDDM	12	8.3	13	- 9	-13*	- 7	+ 2
Mc Ivor	91	guar	NIDDM	8	30	16	+ 4	nr	nr	+73
Aro	92	guar	NIDDM	9	21	12	-15*	-17*	- 2	+11
Holman	80	guar	NIDDM	29	15	8	nr	-11*	0	+ 7
Jones	76	guar	NIDDM	20	10	8	- 2	- 4	0	+ 5
Klimm	93	guar	NIDDM	8	15	26	-7 +4	nr	nr	-10→-31 \$
Mc Ivor	94	guar	NIDDM	16	24-40	26	+ 3	-15 (M-22*) ##	-10	+89*
Jones	78	guar	NIDDM	11	10	7	+ 4	+ 3	0	0
Beattie	86	guar°	NIDDM	24	30	8	0	nr	nr	ns
Ray	95	guar#	NIDDM	12	20+10	8	-31*	nr	nr	-56
Bosello	96	wheat bran	NIDDM	14	20	13	- 9*	nr	nr	-18*
Hagander	87	beet fibre	NIDDM	12	27	8	- 2	2	+ 2	- 3
Sharma	97	fenu seeds	NIDDM	5	25	3	-12*	nr	nr	nr

TC: total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; * $p \leq 0.05$ vs pretreatment; ns = reported non significant; nr = not reported; # guar + wheat bran. ## in male participants as a separate group a significant decrease of 22% LDL-C was found; \$: in 2 consecutive periods with guar changes in triglycerides levels varied from -10 to -31%. ref 83, 92 and 94 are randomized, double blind, placebo controlled studies; ° guar + cereal fibre.

Table 6. Changes in serum lipids in IDDM and NIDDM patients, employing high-fibre diets

Author	Ref	Diet* type	Type diab	Number pat.	Fibre g/day	Study weeks	Δ TC (%)	Δ LDL-C (%)	Δ HDL-C (%)	Δ TG (%)
Simpson	98	HCHF	IDDM	9	96.6	6	-15*	-15	-16*	ns
Simpson	98	HCHF	NIDDM	18	96.6	6	-15*	-19*	-11	ns
Anderson	10	HCHF	ID+NIDDM	14	64	2-5	-32*	nr	nr	-11
Anderson	10	HCHF	ID+NIDDM	11	64	2	-4 ^{\$}	nr	nr	-22*
Anderson	105	HCHF	ID+NIDDM	20	65	2	-29*	nr	nr	-2
Simpson	99	HCHF	IDDM	11	78	6	-11*	-25*	0	-10
Simpson	5	HCHF	NIDDM	14	78	6	-14*	-8	-13	-6
Hollenbeck	100	HCHF	NIDDM	6	26.7**	4	+5	+10	+10	+8
Hagander	104	SCHF	NIDDM	14	43.7	8	-4*	-5*	+3	-9
Scott	103	SCHF	NIDDM	33	35	26	0	nr	0	0
Karlström	106	SCHF	NIDDM	14	42.4	3	+2	-5*	+3	+12

TC: total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein; HDL-C: high density lipoprotein; * $p < 0.05$ vs pretreatment; ns = reported non significant; nr = not reported; *: HCHF: high-carbohydrate (50%) high-fibre diet; SCHF: standard-carbohydrate (40%) high-fibre diet; **: expressed as gr/1000 Kcal; \$: -4 comparing HCHF to HCLF diets but -22* compared to control diet.

prevent a rise of TG induced by the high carbohydrate. The number of published SCHF studies is too limited to draw firm conclusions on the effects of these diets on lipid metabolism.

ACCEPTABILITY AND SAFETY OF DIETARY FIBRE

Intake of large quantities of dietary fibre may give rise to unpleasant side effects, as nausea, flatulence and abdominal discomfort. Guar is rather sticky when hydrated, which makes consumption difficult. Incorporation of guar in food products may alleviate this problem. However, there are limitations to the amount of guar that can be incorporated. An increase of dietary fibre intake can more easily be reached by using high-fibre food products. However, high-fibre diets mainly composed of legumes are not bearable for everyone on long-term resulting in less compliance.

An increased consumption of dietary fibre may decrease absorption of trace elements. Although several authors reported negative mineral balances (108,109) Van Dokkum (110) demonstrated that increasing wheat bran consumption decreases availability of minerals, but this does not affect mineral balance considerably. No changes are found in nutritional status, hematologic and hepatorenal function after long-term ingestion of guar (91). Nevertheless, it is possible that use of diets with large amounts of insoluble fibre provoke impaired absorption of calcium, iron and zinc in susceptible individuals. The influence of high fibre diets on other minerals such as manganese and chromium is not known.

Although mucosal cell proliferation in small intestine and colon mucosa has been described (48,56), epidemiological data point to a protective role against colon cancer. Different mechanism can be involved: dilution of carcinogens by the water holding capacity of dietary fibre, reduction of colon transit time reducing exposure of colon mucosa to carcinogens, reduction of dehydroxylation of bile salts and of nitrosamine formation, and the protective action of the formed butyrate. Due to the multifactorial aetiology of large bowel cancer the literature is controversial on this subject.

RECOMMENDATIONS FOR APPLICATION OF DIETARY FIBRE IN DIABETIC PATIENTS

With the current advices to diabetic patients to limit fat and protein intake, carbohydrate content of the food will be raised to 50% of the daily energy intake. This regimen leads to higher blood glucose and insulin levels and triglycerides without any beneficial effect on lipid levels (107). As diabetes is an independent risk factor for coronary heart disease (111), one may question the general recommendations for high-carbohydrate diets. In practice, addition of dietary fibre may prevent the moderate increase of blood glucose levels that occurs with these high-carbohydrate diets and will in addition lower plasma cholesterol levels. The advice of the Dutch Nutrition Council concerns the general population. Today, no differences persist any more between advice on healthy nutrition for a general population and diabetic patients. Therefore, the advice of the Dutch Nutrition Council of 14 g dietary fibre per 1000 kcal is applicable. This general advice has to be adapted to the own food choice and habits of each patient to obtain long-term compliance. Realisation of this goal can only be successful if the increase of fibre intake is gradually established. Practical application demands a careful selection of foods high in fibre content.

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CHAPTER 2

The influence of guar-gum bread on the regulation of diabetes mellitus type 2 in elderly patients

JPJE Sels, JA Flendrig, ThJL Postmes
Published in: Br J Nutr 1987;57:177-183

SUMMARY

The effect of a high-fibre bread mixed with guar-gum (75 g/kg flour) on blood glucose, serum connecting peptide (C-peptide), haemoglobin A₁ (HbA₁), high density-lipoprotein-cholesterol (HDL-cholesterol) and triglycerides was examined in fourteen elderly patients with diabetes mellitus type 2. The mean daily consumption of guar-gum was 8.1 g. Gastrointestinal disorders were not observed. Consumption of guar-gum bread resulted in a significant decrease of C-peptide values on the first day and blood glucose values after 3 weeks (both measured 90 min after breakfast). C-peptide values remained low, while an unaccountable 'rebound' phenomenon was seen in the blood glucose values 90 min after breakfast at the end of the study. No significant change was seen in respect to HDL-cholesterol and triglycerides. However, a small significant increase in HbA₁ was noted.

INTRODUCTION

Criticism of the use of oral antidiabetic agents by patients with diabetes led to efforts to find other methods of treatment (1). An example is therapy by dietary fibre as developed by Trowell and Burkitt (2-10). Dietary fibre delays the absorption of carbohydrates in the small intestine.

Of all the known dietary fibres, guar-gum probably has the greatest effect on slowing the absorption of carbohydrates. Guar-gum is extracted from the endosperm of the Indian bean *Cyamopsis tetragonolobus* and is a non-absorbable galactomannan polymer. It is a tasteless, light-brown powder, very viscous in solution and therefore used in the food industry as a solidifying agent. If the retarding effect of guar-gum on the absorption of carbohydrates is to be used for the treatment of diabetes, the gum should be presented in a desirable form.

Jenkins *et al.* (11-12) were the first to make an edible product with guar-gum in the form of 'crisp bread'. As bread is an important element of the Dutch diet, it is obvious to mix guar-gum with bread. In cooperation with the Institute for Cereals, Flour and Bread of TNO, Wageningen, a brown bread of good quality and taste was made in accordance with the directions of Apling & Ellis (13) (Plate 1). In the present paper the effects of this guar-gum bread on the regulation of diabetes in elderly patients with diabetes mellitus type 2 are reported.

SUBJECTS AND METHODS

With the approval of the Medical Ethical Committee of the University Hospital, Maastricht, fourteen patients with diabetes mellitus type 2 from the Klevarie Clinic participated in this study. The age range of the patients was between 53 and 96 years. Details of the subjects, including medical information, is given in table 1. Only patients with blood glucose values between 5 and 20 mmol/l at 90 min after breakfast and after lunch took part in this pilot study.

Study design

Bread meals were taken in the morning and in the evening. As guar-gum bread contained less energy per unit weight than the control bread (7730 vs 9660 kJ (1840 vs 2300 kcal)/kg respectively), the quantity of bread consumed during the guar-gum bread period was changed in such a way as to keep the energy value

(a) Normal high-fibre bread and (b) a high-fibre bread containing guar-gum.

of each bread meal per patient constant. The bread meals were consumed in 20 min. The exact daily intake of bread was supervised by the dietician and the nurses of the wards. The midday meals were not changed and therefore did not contain any additional fibre.

During the control period (1 week), normal brown bread was eaten. A period of 3 weeks with high-fibre bread was interposed, followed by a 6-weeks period with guar-gum bread (fig.1). This regimen allowed adaptation to the difference in taste between normal brown bread and guar-gum bread and, at the same time, assessment of the influence of dietary fibre without guar-gum on the regulation of diabetes mellitus.

All bread meals were isoenergetic during the different periods for each patient. The high-fibre bread contained 42 (g/kg) dietary fibre (neutral-detergent fibre (NDF)). Guar-gum bread contained 40 (g/kg) dietary fibre (NDF) and 40 guar-gum (guar kwal CSAA-M200, Meypro B.V., Zaandam) on a wet weight basis. The guar-gum content can also be expressed as 75 g/kg flour.

Table 1. Details of elderly patients participating in the study.

Sex	Age	Body-wt(kg)		Blood glucose (screening) (mmol/l)		Energy intake (MJ/d)	Drugs(g/d)
		initial	final	after breakfast	after lunch		
F	53	58.2	61.3	11.5	12.1	4.8	Rastinon 1.5
F	83	60	64	6.8	6.4	4.2	Rastinon 1.0
F	88	60.5	61.3	8.2	7.8	5.0	Rastinon 1.5
M	85	72.5	73.8	9.3	9.6	7.0	Rastinon 2.5
F	77	44	46.5	8.4	7.3	5.7	
F	96	71.8	73	7.5	9.5	5.0	Rastinon 1.5
F	87	57	56	10	8.2	4.8	Rastinon 3
							Glucophage 1
F	68	57.7	58.3	16.8	23.6	5.8	Diamicron 0.16
							Rastinon 2
F	74	54.3	57.7	12	10.7	7.3	Rastinon 1
F	71	70.5	71.4	7.8	7.7	4.5	Rastinon 1.5
M	81	55	53	5.5	5.6	6.1	
F	86	51.5	54	8.0	6.8	5.4	
F	73	61	60	7.2	11.9	4.4	Rastinon 1.5
F	65	77.7	74.3	9.9	8.4	5.6

Figure 1. Scheme of the experimental study of 10 weeks in which the effects of high-fibre bread and guar-gum bread were evaluated vs control period. ↓ indicates blood sampling.

The following indices were determined: body-weight; blood glucose (glucoquant kit no. 245178, Boehringer Mannheim, FRG) after an overnight fast, 90 min after breakfast and 90 min after the midday meal; serum connecting peptide (C-peptide), as an indicator of insulin secretion, with a RIA-kit (Hoechst) using blood samples taken 90 min after breakfast; haemoglobin A₁ (HbA₁), percentage with a thiobarbituric acid (TBA) assay according to Postmes *et al.* (14); plasma high-density-lipoprotein (HDL)-cholesterol by a precipitation method according to Allen *et al.* (15), using the CHOD PAP method by a test comb cholesterol kit (no. 172626, Boehringer Mannheim, FRG); and plasma triglycerides (Triglyceride Rapid Test kit no. 0710865, Roche, Switzerland). Blood samples were taken at the start of the study, on the 1st day of the high-fibre-bread period, on the 1st day of the guar-gum-bread period and after 3 and 6 weeks on guar-gum bread.

Statistical analysis was based on a paired t-test.

RESULTS

At the end of the study it appeared that on average most patients had gained 1 kg in body weight (table 1).

Blood glucose

During the whole period of the study (10 weeks) there were only small variations in the blood glucose values in the samples taken before breakfast. The mean blood glucose level change for each patient was 1.7 (SD 1.1) mmol/l.

After 3 weeks on guar-gum bread, a significant decrease was found in the blood glucose value 90 min after breakfast (fig. 2(a)) compared with the control week (mean -8.6%, $p < 0.05$). The difference between the start of the guar-gum bread period and the start of the 4th week of the guar-gum bread period (fig. 2(b)) was also significant (mean -12.1%, $p < 0.05$). The blood glucose value after 3 weeks on guar-gum bread showed a significant difference compared with the high-fibre bread period (mean -13.8%, $p < 0.005$). At the end of the guar bread period no significant changes were found compared to the control or the high-fibre period.

The blood glucose values 90 min after the isoenergetic midday meals (without guar-gum) in the various experimental periods were not significantly different.

Figure 2. Blood glucose values 90 min after breakfast measured after 3 weeks on a diet containing guar-gum bread (●) compared (a) with the control week (○) and (b) with the 1st day on guar-gum bread (■). After 3 weeks on guar-gum bread the blood glucose value decreased significantly ($p \leq 0.05$) when compared to the control week when normal bread was eaten and in comparison with the 1st day of guar-gum bread.

C-peptide

All C-peptide measurements were done on plasma samples taken 90 min after breakfast. The consumption of the high-fibre bread did not lead to changes in the C-peptide value compared with that of the control week. The use of guar-gum bread, on the other hand, resulted in a significant decrease in the C-peptide value compared with that of the control week (fig. 3 a,b,c) on the 1st day and after 3 and 6 weeks on the guar-gum bread. Mean values were -19.8, -21.9 and -27.8% respectively. Compared to the high-fibre bread period the mean values were -22.8, -24.7 and -28.1%. Remarkably, the maximum decrease was achieved on the 1st day of the guar-gum bread period. Prolonged consumption of

Figure 3. Plasma C-peptide concentrations after consumption of normal brown bread (control) and high-fibre bread containing guar-gum. When compared with the control week (O) the C-peptide concentrations (determined 90 min after breakfast) appeared to have decreased significantly (a) on the 1st day (■), (b) after 3 weeks (●) and (c) after 6 weeks on guar-gum bread (▲).

guar-gum bread did not lead to a further decrease in the C-peptide value. No correlation was found between the decrease in C-peptide and the quantity of guar-gum consumed daily, nor in relation to the daily energy intake. The average daily consumption of guar-gum was 8.1 (SD 1.8, range 5-12) g.

HbA₁

During the whole study the HbA₁ values appeared to increase rather than decrease. Statistical analysis showed a significant increase during the high-fibre and guar-gum bread periods in relation to the control week, varying from +7.8 to +28.4%. At the end of the study, however, there was a decrease in comparison with the value after 3 weeks on the guar-gum bread (mean -5.53%). With respect to the entire guar-gum period, the HbA₁ value remained constant.

HDL-cholesterol and triglycerides

These values remained constant through the whole study period.

DISCUSSION

In order to obtain a decrease in blood glucose, guar-gum must be well mixed with the food (16). It must be in a palatable form to promote faithful application of the therapy and a ready-made product has to be available, e.g. in the form of a 'crisp bread' (11-12) or bread (13,17). Our experience shows that the treatment of diabetes mellitus entirely depends on the faithfulness in the application of the therapy. According to Ellis *et al.* (17), there is apparently a dose-effect relation between the quantity of guar-gum and the blood glucose diminishing effect. In a preliminary study we found that bread containing 75 g guar-gum/kg flour was accepted. The average hedonic score was 3 on a scale ranging from 0 to 5. This is comparable to the bread prepared by Ellis *et al.* (1981). Bread containing 100 g guar-gum/kg flour appeared to be unacceptable. In our study, bread containing 75 g guar-gum/kg flour was accepted by all the patients during the 6 weeks study. Moreover, no one suffered from any gastrointestinal trouble.

The effect of guar-gum bread, brown bread and white bread on the levels of glucose, C-peptide and insulin was investigated in healthy persons by Pikaar *et al.* (18). In their study breakfast was standardized: the starch component was fixed while the quantity and type of dietary fibre was varied. Lunch contained various kinds of starch. Various combinations of breakfast and lunch allowed investigation of the effect of breakfast and lunch on a number of selected

indices with a small number of persons and within a short period of time. Guar-gum bread appeared to have the greatest influence on the peak concentration and 'area under the curve' of blood glucose, plasma C-peptide and insulin values. Only with guar-gum bread did a 'second meal' effect appear.

Our investigation is similar to that of Pikaar *et al.* (18). However, there is a difference: in elderly patients frequent blood sampling is a practical problem, therefore only a limited number of measuring points were used, which rendered it impossible to plot curves. In addition, nothing can be said about the 'second meal' effect, as lunch was not standardized.

The blood glucose values (determined before breakfast) showed no change during the guar-gum bread period, although supper also contained bread with guar-gum. This contradicts the findings of Ray *et al.* (19). The blood glucose at 90 min after breakfast showed a significant decrease after 3 weeks on the guar-gum bread, which was not maintained, as after 6 weeks there was no further difference compared with that of the control week (rebound phenomenon?). After lunch there was no significant decrease in the blood glucose value. As reported previously these meals were isoenergetic but not standardized as to composition.

The influence of guar-gum bread on the C-peptide values is remarkable. The maximum decrease was achieved after the first breakfast with guar-gum bread and in the course of the experiment the C-peptide values stabilized. Contrary to the findings of Ellis *et al.* (17) we found no relation between the quantity of guar-gum consumed and the decrease in the C-peptide values when 5-12 g guar were consumed daily. Another remarkable fact is that the decrease in the C-peptide values occurred on the very 1st day of the guar-gum bread period, while the blood glucose value, determined 90 min after breakfast, decreased significantly only after 3 weeks. This could indicate an uncoupling between blood glucose and C-peptide. The same phenomenon occurred after 6 weeks on guar-gum bread: blood glucose 90 min after breakfast increased to a value not significantly different from that of the control week, while the C-peptide remained low. In this small group of patients, three out of thirteen showed a striking increase in C-peptide values while on guar-gum bread (fig. 3). However, at the end of the study, only one patient had elevated C-peptide values compared with the control week. We therefore investigated different factors that might explain these results, especially to characterize possible 'non-responders'. Blood glucose, daily energy intake, total dietary fibre consumption,

drugs, weight gain or daily guar-gum intake could not be used to predict the individual's response to guar-gum bread. Hence, we have started a study with a greater number of patients and over a longer period, during which this problem will be investigated thoroughly again.

The HbA₁ value reflects the mean blood glucose value during the last 2-3 months. A period of 6 weeks is rather short to eliminate variations in HbA₁ levels resulting from the previous period. Nevertheless, in our test the HbA₁ value showed a significant increase which could perhaps partly be explained by the increase in the blood glucose during the high-fibre bread period. It is strange, however, that the HbA₁ value did not decrease when the blood glucose decreased significantly after 3 weeks on guar-gum bread.

Information on the effect of dietary fibre on lipids is rather contradictory. Some authors reported a decrease (20-22) while others found no change (23, 24). The results of the present study indicate no effect on the HDL-cholesterol and triglyceride values when 5-12 g guar-gum was consumed daily for 6 weeks.

The effect of dietary fibre is explained in the literature in various ways: delayed emptying of the stomach (19,25), increased viscosity in the small intestines, resulting in delayed diffusion through the unstirred layer of the small intestinal mucosa (26,27), diminished gastric inhibitory polypeptide (GIP) secretion (28), increased sensitivity to insulin (29-31), and decreased glucagon secretion (32,33).

Our short-term study shows that a guar-gum-flour mixture can be made into a palatable bread with an evident effect on blood glucose and C-peptide values. Guar-gum bread is an acceptable way to slow the resorption of carbohydrates. Further investigations should comprise a long-term study with particular reference to entero-hormonal patterns.

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CHAPTER 3

Comparative effects of guar-gum bread and high-fibre diet in the treatment of patients with type 1 and type 2 diabetes mellitus

JPJE Sels, ThJL Postmes, F Nieman, R Ebert *, BHR Wolffenbuttel, AC Nieuwenhuijzen Kruseman

*Dept. of Medicine, Division of Gastroenterology and Metabolism
University of Göttingen

Submitted for publication

SUMMARY

In a randomized cross-over study we compared the long-term effects of guar bread and high-fibre bread on blood glucose control, lipid and hormonal profiles in 16 patients with type 1 and 12 patients with type 2 diabetes mellitus. High-fibre bread and guar bread were prepared from the same flour batch. The guar bread contained 40 g dietary fibre (neutral detergent fibre (NDF)) per kg bread and 75 g guar per kg flour. The high-fibre bread contained 42 g dietary fibre (NDF) per kg bread. In both types of diabetes patients no changes in blood glucose control, as assessed by the levels of fasting and postbreakfast blood glucose, HbA₁ and serum fructosamine levels, were observed. In type 1 diabetic patients total and LDL-cholesterol levels were lower during the guar period (4.95 ± 1.0 vs. 5.42 ± 1.1 mmol/l, and 3.29 ± 1.0 vs. 3.81 ± 1.1 mmol/l, both $p < 0.01$). HDL-cholesterol and triglycerides concentrations remained unchanged. In the type 2 diabetic patients total and HDL-cholesterol and trigly-

ceride levels did not change, whereas levels of LDL-cholesterol were lower (3.77 ± 0.6 vs. 4.33 ± 0.9 mmol/l, $p < 0.001$) after 3 months of guar consumption. Lipoprotein(a), as well as C-peptide, glucagon and GIP levels remained unchanged during the different experimental periods in both patient groups. It is concluded that addition of guar to a high-fibre bread has no important effect on blood glucose control in both type 1 and type 2 diabetic patients, but effectively lowers serum lipids concentrations, in particular those of total and LDL-cholesterol. This may have consequences for the development and progress of vascular complications.

INTRODUCTION

The treatment of patients with diabetes mellitus is directed to obtain as near as normal blood glucose control in order to reduce morbidity and to prevent the development of micro- and macrovascular complications. Diet still is the cornerstone of therapy in all types of diabetes. Dietary intervention has attracted again much attention since Trowell and Burkitt launched their theory of dietary fibre (1). Improvement of blood glucose control by slowing postprandial glucose absorption may be achieved by adding viscous fibre to the diet. Some, but not all investigations demonstrated effectiveness of the dietary fibre guar-gum, which is an extract of the Indian Cluster bean *Cyamopsis Tetragonolobus*, to improve carbohydrate metabolism in patients either with type 1 (2,3) or type 2 (4,5) diabetes. Beneficial effects of dietary fibre on lipid metabolism are however more pronounced (6). As guar itself is quite unpalatable and good mixing with the food is a prerequisite for an optimal effect, different forms have been proposed such as granulates, or incorporation in bread, pasta and biscuits.

In a previous short-term study we found only moderate improvement of blood glucose control during the use of guar bread (5). The aim of the present study was to explore the effects of guar-gum bread on blood glucose control, lipid and hormonal profiles in patients with diabetes, and to compare these with the effects of a high-fibre diet during a 3-month trial period.

SUBJECTS AND METHODS

Subjects

Sixteen patients with type 1 diabetes (6 women, 10 men, mean age 44.5 (range 25-85) years, body mass index ($\pm$ SD) 24.2 ± 2.9 kg/m²), and 12 patients with type 2 diabetes (6 women, 6 men, mean age 62 (range 45-77) years, body mass index ($\pm$ SD) 25.8 ± 3.5 kg/m²) participated in the study, which was approved by the hospital Ethical Committee. Mean known duration of diabetes was 14 (range 2-34) years in the type 1, and 11 (range 1-23) years in the type 2 diabetic patients. Eleven patients with type 2 diabetes were treated with sulphonylureas. All subjects were in good general health without clinical or biochemical evidence of renal, hepatic or vascular disease, and on a constant blood glucose regulating regimen for the last 4 months prior to the study. During the study diabetic treatment was not changed.

Study design

A 3-months period cross-over design was used. The patients were randomized into two diet regimens. The first regimen consisted of guar bread meals at breakfast and dinner, and the second regimen comprised high-fibre control bread meals. After a run-in period of 2 weeks, 8 type 1 and 5 type 2 diabetic patients started with the first regimen, whereas 8 type 1 and 7 type 2 diabetic patients started the second regimen. The meals at lunch time were left unchanged and did not contain any additional fibre. After 3 months patients switched to the alternate regimen. Type 1 diabetic patients were prescribed a weight-maintaining diet containing 40 per cent carbohydrates, 40 per cent fat and 20 per cent protein. The energy content varied from 3591 to 10227 kJ (855 to 2435 kCal) per day. Energy content of the diets of type 2 patients varied from 3267 to 9345 kJ (778 to 2225 kCal) per day with the same distribution of carbohydrates, fat and protein.

The high-fibre control bread and the guar bread were prepared by the Institute for Cereals, Flour and Bread TNO (Wageningen, The Netherlands) using the same flour batch for both bread preparations. The guar bread contained 75 g guar/kg flour (guar kwal: CSAA-M200, Meypro BV, Zaandam, The Netherlands). The quantity of bread in each guar bread meal was adapted to compensate for the reduced caloric content of the guar bread compared to the

control bread (7730 vs 9660 kJ (1840 vs 2300 kcal)/kg). All patients were seen the first day and at 4-weeks intervals in each study period in the outpatient clinic. At each visit body weight was recorded, and blood was drawn in the fasting state for the determination of blood glucose, glycosylated haemoglobin (HbA₁), serum fructosamine and plasma lipids. At each visit blood was also taken 1.5 hours after breakfast for determination of blood glucose, plasma C-peptide (in type 2 diabetic patients only), glucagon and gastric inhibitory polypeptide (GIP).

Analytical methods

Blood glucose was determined with an automated hexokinase method on the Cobas Bio analyzer. HbA₁ was determined with a thiobarbituric assay (normal values 4-7%). Serum fructosamine was determined according to the method of Johnson *et al.* (7) after alkalisation and reduction with nitroblue tetrazolium (Sigma) on the Cobas Bio analyzer. The standard was calibrated on 1-desoxy-1-morpholino-fructose (Sigma) in an albumin solution (overall cv 4%). The reference values (0.62-1.22 mmol/l) for this assay are lower than values reported in the literature, due to the use of different standard and reducing agents, and show a significant correlation with a commercially available assay (Hoffman-La Roche, Switzerland; $r=0.98$, $y=1.16x+2$). Total cholesterol (normal values 4.1-6.4 mmol/l) was determined using the CHOD-PAP method (Boehringer Mannheim, Mannheim, FRG) on the Cobas-Bio analyzer with an interassay cv of 1.2% and 1.5% for 5.6 and 3.3 mmol/l respectively. HDL-cholesterol (normal values 0.6-1.9) was determined after precipitation with polyethylene glycol (8). Triglycerides (normal values 0.8-1.9 mmol/l) were determined using the Triglycerides Rapid Test (Hoffmann-La Roche, Switzerland). Low-density-lipoprotein (LDL)-cholesterol was calculated with the Friedewald-formula. Lipoprotein(a) was determined by commercially available RIA (Pharmacia Diagnostics AB, Uppsala, Sweden). Plasma C-peptide (normal values 0.2-1.2 nmol/l) was determined by radioimmunoassay (Mallinckrodt, Dietzenbach, FRG). For the range of 0.8 to 1.8 nmol/l intra- and interassay cv were 5.6 and 7.5%, respectively. Glucagon was determined by radioimmunoassay with a double antibody separation step (Medgenix, Fleurus, Belgium), with intra- and interassay cv of 5% and 15%, respectively. GIP was assayed using radioimmunoassay technique as described by Creutzfeldt *et al.* (9) with the GÖ 5/76/9 antibody. The sensitivity of the assay allowed detection of 30 pg/ml difference. The intra- and inter-assay cv are 7.9% and 16.1%, respectively.

Statistical analysis

Data are expressed as mean $\pm$ SD or as median values and range if appropriate. A MANOVA repeated measurements analysis was performed with the SPSS/PC statistical software package (SPSS Inc., Chicago, IL, USA) using the following factors: period, treatment and subgroup effects (plus all interactions between the factors). Wilcoxon paired rank order test was used to test the effect of the first guar bread meal. P-values less than 0.05 were considered statistically significant. To simplify the presentation of the results, only significant differences are reported.

RESULTS

Guar consumption

During the study period the patients consumed 11.2 ± 2.5 g guar per day, divided over the 2 meals. No patient withdrew from the study because of specific side effects. The majority of the patients reported early satiety, bloated sensations, increased flatulence and a moderate increase of stool volume and frequency of evacuation during consumption of the guar meals. No such complaints were reported during consumption of the control bread meals. Palatability of the guar bread was reported to be acceptable or good.

First meal

Table 1 summarizes the postprandial blood glucose, plasma C-peptide, glucagon and GIP concentrations obtained after the first guar bread meal in comparison to the same variables collected after the breakfast eaten at baseline. In both patient groups blood glucose and plasma glucagon levels were the same when guar bread was given compared to the normal meals. Plasma GIP levels significantly decreased in type 1 diabetic patients, but not in type 2 patients. In type 2 patients the plasma C-peptide levels after this first bread meal increased from 0.58 (baseline) to 0.79 (guar) nmol/l ($p < 0.02$).

Table 1. Postbreakfast blood glucose and plasma C-peptide, glucagon and GIP values after the breakfast at baseline compared to levels after the first guar bread meal in 16 type 1 and 12 type 2 diabetic patients.

Postbreakfast		type 1 diabetes		type 2 diabetes	
blood glucose (mmol/l)	baseline	11.4 ± 4.1	ns	12.4 ± 5.0	ns
	guar	13.3 ± 5.6		13.0 ± 4.2	
plasma C-peptide (nmol/l)	baseline	n.d.	p<0.02	0.58 (0.27-1.29)	p<0.02
	guar	n.d.		0.79 (0.34-2.13)	
plasma glucagon (pmol/l)	baseline	19 (6-30)	ns	32 (6-67)	ns
	guar	16 (6-32)		26 (6-78)	
GIP (pmol/l)	baseline	55 (32-169)	p≤0.05	64 (31-123)	ns
	guar	53 (28-140)		68 (47-140)	

data as mean ± SD, or median (range)

Table 2. Longitudinal effect of guar bread in type 1 diabetic patients during high-fibre diet and guar-gum bread.

	baseline	CONTROL BREAD		GUAR BREAD	
		1 month	3 month	1 month	3 month
Fasting blood glucose (mmol/l)	9.9 ± 4.4	10.5 ± 5.31	11.9 ± 5.4	8.9 ± 4.8	11.0 ± 4.8
Postbreakfast blood glucose** (mmol/l)	12.0 ± 4.3	13.6 ± 6.4	13.8 ± 5.3	8.6 ± 3.7 ^a	11.9 ± 5.0
Glycosylated haemoglobin** (%)	12.0 ± 2.0	12.5 ± 2.3	12.1 ± 1.5	12.7 ± 1.9	11.8 ± 1.6
Serum fructosamine (mmol/l)	1.77 ± 0.6	1.85 ± 0.6	1.88 ± 0.7	1.78 ± 0.7	1.76 ± 0.7
Total cholesterol*** (mmol/l)	5.14 ± 1.0	5.40 ± 1.0	5.42 ± 1.1	5.08 ± 0.8	4.95 ± 1.0 ^b
HDL-cholesterol (mmol/l)	0.94 ± 0.4	1.13 ± 0.4	1.15 ± 0.3	1.07 ± 0.3	1.11 ± 0.3
LDL-cholesterol*** (mmol/l)	3.73 ± 1.1	3.84 ± 1.0	3.81 ± 1.1	3.56 ± 0.8	3.29 ± 1.0 ^b
Triglycerides (mmol/l)	1.22 ± 0.7	1.09 ± 0.7	1.15 ± 0.7	1.15 ± 0.7	1.36 ± 1.0
Lipoprotein(a) (mg/l)	92 (8-479)	n.d.	105 (8-1117)	n.d.	126 (8-785)
Glucagon** (pmol/l)	19 (7-30)	19 (7-39)	16 (7-31)	15 (6-29)	16 (6-24)
GIP* (pmol/l)	58 (43-169)	60 (43-139)	54 (25-112)	63 (29-89)	69 (18-94)

performed for 16 patients except for * n=13; ** n=14; *** n=15. data as mean ± SD, or median (range); a: p < 0.001 vs. baseline and high-fibre bread; b: p < 0.01 vs. baseline and high-fibre bread.

Table 3. Longitudinal effect of guar bread in type 2 diabetic patients during high-fibre diet and guar-gum bread.

	baseline	CONTROL BREAD		GUAR BREAD	
		1 month	3 month	1 month	3 month
Fasting blood glucose (mmol/l)	9.8 ± 3.8	10.8 ± 3.5	9.4 ± 3.0	10.7 ± 3.6	9.6 ± 3.4
Postbreakfast blood glucose (mmol/l)	12.9 ± 5.0	14.6 ± 4.7	12.9 ± 4.4	14.5 ± 4.6	13.9 ± 4.0
Glycosylated haemoglobin ** (%)	11.3 ± 2.5	12.5 ± 3.3	11.3 ± 1.9	11.8 ± 2.7	11.5 ± 3.0
Serum fructosamine (mmol/l)	1.39 ± 0.6	1.5 ± 0.6	1.45 ± 0.8	1.45 ± 0.6	1.40 ± 0.6
Total cholesterol *** (mmol/l)	5.18 ± 1.1	5.53 ± 1.1	5.70 ± 1.1	5.23 ± 0.7	5.24 ± 0.6
HDL-cholesterol *** (mmol/l)	0.67 ± 0.2	0.71 ± 0.2	0.78 ± 0.2	0.78 ± 0.2	0.73 ± 0.2
LDL-cholesterol ** (mmol/l)	4.15 ± 0.7	4.24 ± 0.8	4.33 ± 0.9	3.69 ± 0.8 ^a	3.77 ± 0.6 ^a
Triglycerides *** (mmol/l)	1.56 ± 0.5	1.64 ± 0.4	1.74 ± 0.5	1.61 ± 0.5	1.78 ± 0.6
Lipoprotein(a) (mg/l)	67 (13-479)	n.d.	82 (13-819)	n.d.	76 (8-840)
C-peptide (nmol/l)	0.58 (0.27-1.29)	1.01 (0.29-2.22)	1.08 (0.34-1.7)	0.76 (0.42-1.96)	0.79 (0.25-2.03)
Glucagon ** (pmol/l)	32 (6-67)	33 (5-69)	33 (6-75)	27 (6-84)	29 (7-65)
GIP* (pmol/l)	55 (31-97)	69 (34-94)	59 (38-107)	71 (40-114)	66 (36-95)

performed for 12 type 2 diabetic patients except for * n=9; ** n=10; *** n=11; data as mean ± SD, or median (range); a: p < 0.001 vs. baseline and high-fibre bread.

Metabolic effects after 3 months

No period or carry over effects were found.

Type 1 diabetic patients (table 2)

No significant weight changes were observed. Mean weight gain was +0.25 kg (range -4 to +2 kg) during the guar bread period, and +0.53 kg (range -1.3 to +4.5 kg) during the high-fibre bread period. In the guar bread period fasting blood glucose values were identical to the high-fibre bread period. Glucose values 90 minutes after breakfast were significantly lower after guar bread consumption compared to high-fibre bread ($p < 0.001$) after the first month, but gradually returned to the pretest level in the third month. No changes in HbA_{1c} and serum fructosamine concentrations were observed. Total and LDL-choles-

terol levels were lower after 3 months in the guar bread period compared to the high-fibre period (4.95 ± 1.0 vs. 5.42 ± 1.1 mmol/l, and 3.29 ± 1.0 vs. 3.81 ± 1.1 mmol/l, both $p < 0.01$). The concentrations of HDL-cholesterol, triglycerides and lipoprotein(a) remained unchanged, as did glucagon and GIP levels.

Type 2 diabetic patients (table 3)

As in type 1 patients no significant weight changes were observed. Mean weight change was $+0.21$ kg (range -3.9 to $+1.4$) during guar bread, and $+0.49$ kg (range -3.6 to $+6.2$) during high-fibre bread. No changes in fasting and postprandial blood glucose, HbA₁ and serum fructosamine levels were observed, when guar and high-fibre bread were compared. Total and HDL-cholesterol, triglyceride and lipoprotein(a) levels did not differ significantly, only LDL-cholesterol level was lower during guar-gum ($p < 0.001$). Plasma C-peptide, glucagon and GIP levels remained unchanged during both experimental periods.

DISCUSSION

In the present study, no effect of the viscous fibre guar was seen on fasting and postbreakfast blood glucose levels of the patients with type 2 diabetes, neither during the first breakfast, nor after 3 months. HbA₁ and serum fructosamine levels remained unchanged as well. The results in the type 1 patients are comparable, although a transient decrease of postbreakfast blood glucose levels was found. Several Diabetes Associations recommend diets with a high-carbohydrate and a high-fibre content (10,11). These recommendations are based on the fibre hypothesis of Trowell and Burkitt (1) and the practical implementations as described in the literature. Reductions of postprandial blood glucose and plasma insulin responses have been reported after test meals with viscous fibre in diabetic patients and normal volunteers (12,13). However, long-term studies could not always confirm these positive results (14,15), or even reported deleterious effects (16). Our previous study (5) showed only temporary decreases of blood glucose levels 90 minutes after breakfast in type 2 diabetic patients, while no changes occurred in HbA₁. The reasons for these discrepant results are not obvious. The dose of guar may be of importance. Some authors have found beneficial effects only with high doses of guar (6), whereas some obtained beneficial results with low doses (up to 10 g/day) as well (17). In our present study daily guar intake was 11 g. Another explanation may be the use of different guar preparations with various viscosity. As the quality of guar is

not always mentioned in published reports, comparison of results is not possible. In addition, although a bi-weekly control of all patients was done, some compliance problems during the study may have interfered. Finally, the supplement of dietary fibre consumed as guar may be rather limited compared to the habitual fibre intake, which was rather high (mean 26.5 ± 8.4 g/day; type 2 diabetic patients 22.5 ± 7.3 , type 1 29.5 ± 8 g/day).

The literature concerning the influence of dietary fibre on lipid metabolism is controversial, although most studies showed a reduction of total cholesterol almost exclusively provoked by a decrease in LDL-cholesterol levels (6,18). In this study LDL-cholesterol levels were significantly reduced in both groups of patients with diabetes. In our type 2 diabetic patients total cholesterol concentration was lower in the guar bread period compared to the high-fibre bread period but this difference did not reach statistical significance. As our results can not be explained by weight reduction, these and other reports (18) in the literature indicate that guar offers a possible way of treating hyperlipidemia in diabetic patients. No significant effects of guar on lipoprotein(a) levels were found. This fraction is considered to be an independent risk factor for the development of macrovascular disease (19,20). Its accumulation in the aortic wall of patients undergoing bypass-surgery has been demonstrated (21). The true pathologic role of lipoprotein(a) in the development of atherosclerosis remains, however, far from clear. Diet nor inhibitors of cholesterol synthesis seem to influence the plasma level of lipoprotein(a) (22).

As a possible mechanism of action of guar, an influence on GIP (12,23) and glucagon (3) secretion is proposed. In our study GIP values were decreased after the first guar bread meal breakfast in type 1, but not in type 2 diabetic patients. After 3 months, no effect was seen on GIP nor on the glucagon levels. This can be explained by the role of the other constituents of the meals such as proteins and fat, which influence glucagon and GIP values and therefore may have annihilated the effect of the quantity of guar ingested during the meal.

In conclusion, our study implies that addition of guar to a high-fibre bread has no important effect on glucose control in both type 1 and type 2 diabetic patients. On the other hand, guar is effective in lowering serum lipids, in particular total and LDL-cholesterol, which may have consequences for the development and progress of vascular complications.

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Efficacy of guar in complex spaghetti meals on postprandial glucose and C-peptide levels in healthy and non-insulin-dependent diabetes mellitus subjects

JPJE Sels, H de Bruin, MHTA Camps, ThJL Postmes, PPCA Menheere,
BHR Wolffenbuttel, AC Nieuwenhuijzen Kruseman
Horm Metab Res: in press

SUMMARY

The effects of guar incorporated into a complex spaghetti meal on the glycaemic response in 11 healthy volunteers and 6 type 2 diabetic subjects were studied. To this end, subjects consumed spaghetti made of either *Triticum aestivum* or *Triticum durum* wheat with or without 20 g% guar, as part of a complex meal containing 27% fat, 19% protein and 51% carbohydrate. In the healthy volunteers the postprandial incremental blood glucose values were not affected by incorporation of guar into the spaghetti. Only after *T aestivum* guar spaghetti the plasma C-peptide excursions were reduced. This reduction was not found after *T durum* guar spaghetti. In the diabetic subjects the incremental peak values of blood glucose and plasma C-peptide were also not affected by guar, although the time to reach this peak appeared delayed. These limited results may partly be explained by the presence of normal quantities of fat and protein in the meal and suggest that addition of dietary fibre to a complex meal is not useful in the dietary management of diabetes.

INTRODUCTION

There is growing evidence that high fibre foods are important to good health. It has also been shown that dietary fibre has a therapeutic value in the treatment of diabetes mellitus (1). Dietary fibre reduce the absorption of carbohydrates resulting in a decrease of postprandial glucose excursions. Of these fibres guar seems to elicit the greatest effect (1,2). Guar is an unabsorbable, water soluble galactomannan extracted from the leguminous seed *Cyamopsis tetragonoloba* (L.) (3). To increase the palatability of guar it has been incorporated into various foods, for example bread (4,5) and spaghetti (6,7). Several investigators (4,6,7) have shown that this approach results in a significant reduction of the postprandial blood glucose and plasma insulin levels in diabetic and healthy subjects. However, factors other than dietary fibre are known to alter the glycaemic response as well. These include fat, protein, anti-nutrients such as phytates, inhibitors of amylase and other enzymes, and salt (8-14). Food processing also influences the resorption of food and the glycaemic response (15,16). All these factors may have consequences for the effect of guar in more complex meals.

For this reason we have investigated the effects of guar incorporated into spaghetti on the glycaemic response in healthy volunteers and type 2 diabetic subjects when the carbohydrates are ingested as part of a complex meal with a macronutrient composition as recommended by the Dutch Nutrition Council (17). To investigate whether the effects of guar are determined by the species of wheat of which the spaghetti is made, experiments with *Triticum aestivum* as well as *Triticum durum* spaghetti were performed.

SUBJECTS AND METHODS

Subjects

With the approval of the Medical Ethical Committee of the University Hospital Maastricht 11 healthy volunteers (6 women, 5 men, mean age 25 years, range 18-34) and 6 type 2 diabetic subjects (3 women, 3 men, mean age 53 years, range 41-59) participated in this study. Two of the diabetic subjects were treated with diet only, four with oral antidiabetic medication as well. The mean daily dietary fibre consumption of these subjects was 38.9 g (SE 12.7; range 13.0-69.2 g).

Meals

The composition of the meals is given in table 1. The meals were isoenergetic and they differed in spaghetti type only. The amount of normal spaghetti was 80 g (dry weight), whereas that of guar spaghetti was 100 g (dry weight, 20 g% guar). In our experience spaghetti containing up to 200 g guar/kg flour is still palatable. The meals contained 25 g fat (27 %), 40 g protein (19 %) and 106 g carbohydrates (51 %). The calculated amount of dietary fibre, not including guar, was 15 g.

Table 1. Composition and content of the meal.

Composition of the meal		energy	
		kJ	kcal
Vegetable soup	200 ml*	139	33
Spaghetti control	80 g	1174	281
Spaghetti guar (20%)	100 g**	1174	281
Olive oil	7 g (spaghetti)	264	63
Margarine	8 g (sauce)	250	60
Lean minced meat	80 g (sauce)	771	184
Onion	150 g (sauce)	276	66
Mushroom	50 g (sauce)	34	8
Paprica, red	40 g (sauce)	47	11
Salt, pepper, oregano, chili, garlic	(sauce)		
Tomato	250 g (sauce: 200 g; salad: 50 g)	168	40
Lettuce	15 g (salad)	8	2
Cucumber	50 g (salad)	34	8
Salad dressing (176 kJ/100 g)	5 g (salad)	9	2
Apple	100 g (salad: 50 g; dessert: 50 g)	167	40
Cinnamon	(dessert)		
Yoghurt containing skimmed milk	150 g (dessert)	175	42
Mineral water (Spa red)	150 ml		
Total		3516	840

* Soup-packet of Royco (for 1 litre) containing 695 kJ, 4 g fat, 5.6 g protein, 27.6 g carbohydrates and 5 g dietary fibre. ** 100 g guar spaghetti is iso-energetic to 80 g ordinary spaghetti.

Two forms of spaghetti were used. One spaghetti form was made of *Triticum aestivum* flour, which is a mixture of hard and soft wheat. The other spaghetti form was made of the hard wheat *Triticum durum*.

Study protocol

Normal healthy controls. These subjects consumed four meals in the following sequence: 1) *Triticum* (T) *aestivum* spaghetti; 2) T *aestivum* guar spaghetti; 3) T *durum* guar spaghetti; 4) T *durum* spaghetti.

Type 2 diabetic subjects. These subjects consumed two T *aestivum* spaghetti meals only. These meals were taken according to a randomly allocated cross-over design.

Time interval between all test meals was at least 48 hours and the meals were taken according to a double blind fashion. The meals were served at 6 p.m. and the subjects were asked not to eat from 1 p.m. and not to drink from 5 p.m. onwards. As breakfast and lunch they were asked to consume their usual bread meals. At $t=0$ min the subjects began to eat soup. At $t=10$ min they continued with spaghetti, sauce, salad and mineral water, followed by a dessert. All subjects finished their meals within 50 min (mean 47 min, SE 2). After the first meal each subject was allowed to drink 0, 1 or 2 cups of coffee with sweetener and/or imitation milk powder and had to stick to the chosen amount for each meal thereafter.

Blood sampling

A Venflon catheter was inserted into the forearm vein 30 min before the start of the meals. Blood samples were collected prior to the meals ($t=-15$ and 0 min) and at 30, 45, 60, 90 and 120 min thereafter. In the type 2 diabetic subjects an additional sample was taken at 180 min. For C-peptide assay blood was collected into cooled heparinized tubes with Trasylol (500 IU/ml blood). These samples were centrifuged immediately after collection and the plasma was stored at -20°C within 30 min until assay.

Analytical methods

Blood glucose was measured according to the hexokinase method (Glucoquant Boehringer Mannheim, FRG). Plasma C-peptide was determined with an indirect radioimmunoassay after polyethyleenglycol extraction (Byck-Mallinckrodt, Dietzenbach, FRG) using the MRC 76/561 as standard. The intra- and interassay cv for the range of 0.8-1.8 nmol/l were 5.6 and 7.5% respectively.

Statistical analysis

To detect differences in glycaemic or C-peptide response to the different meals incremental blood glucose and C-peptide values at fixed time intervals as well as peak values were compared. The incremental values were calculated by subtracting the basal value (mean $t=-15$ and $t=0$ minutes) from the absolute values. In this way a difference in starting value could not obscure differences between meal responses when expressed as absolute postprandial values. All results are expressed as means $\pm$ SE. In the healthy volunteers one subject was excluded in the calculation of incremental glucose values in the T durum experiment since all values were below the basal blood glucose value. The differences between incremental responses were calculated by the Student's 2-tailed test for paired observations with correction for multiple comparison. In type 2 diabetic patients effect of treatment and period was evaluated according to Hill and Armitage(18).

RESULTS

Blood glucose

Premeal glucose values: in healthy volunteers the mean ($\pm$ SE) premeal blood glucose value on the day that the T durum guar spaghetti was taken, was lower than the fasting blood glucose values on the other days (3.0 ± 0.2 vs 3.9 ± 0.2 , 3.9 ± 0.1 and 3.8 ± 0.9 mmol/l; $p < 0.025$).

In the diabetic subjects the mean premeal blood glucose levels were not different, 6.0 ± 1.05 and 6.43 ± 1.11 mmol/l for T. aestivum and T. aestivum guar spaghetti respectively.

Figure 1. Incremental values (mean $\pm$ SE) of blood glucose and plasma C-peptide after T aestivum spaghetti meal with (continuous line) or without (dashed line) guar in healthy control subjects. * $p < 0.025$

Incremental glucose values: the healthy volunteers showed no differences in incremental peak glucose values and excursions after consumption of spaghetti with or without guar (fig 1 and 2). In the diabetic subjects the incremental blood glucose values were significantly lower in the T aestivum spaghetti with guar compared to T aestivum spaghetti without guar at $t = 60$ min (3.23 ± 0.32 vs

Figure 2. Incremental values (mean $\pm$ SE) of blood glucose and plasma C-peptide after T durum spaghetti meal with (continuous line) or without (dashed line) guar in healthy control subjects.

5.67 ± 0.59 mmol/l; $p < 0.005$) and $t = 90$ min (4.87 ± 0.77 vs 7.03 ± 0.55 mmol/l; $p < 0.02$) (fig 3). The incremental peak values were however not different (7.03 ± 0.55 vs 5.9 ± 1.1 mmol/l, $p = \text{ns}$), although after spaghetti with guar the time to reach this peak was delayed (90 vs 180 min).

Figure 3. Incremental values (mean $\pm$ SE) of blood glucose and plasma C-peptide after T aestivum spaghetti meal with (continuous line) or without (dashed line) guar in NIDDM subjects. * $p < 0.01$; ** $p < 0.05$.

Plasma C-peptide

Premeal C-peptide values: in healthy volunteers the mean ($\pm$ SE) premeal plasma C-peptide values differed significantly between T aestivum spaghetti without and with guar (0.30 ± 0.04 vs 0.51 ± 0.05 nmol/l; $p < 0.005$). No differences were found for the T durum spaghetti meals (0.47 ± 0.08 vs 0.49 ± 0.05 nmol/l). In the diabetic subjects the mean fasting plasma C-peptide values for the T aestivum spaghetti without and with guar were not different (0.54 ± 0.05 vs 0.49 ± 0.03 nmol/l respectively).

Incremental C-peptide values: in the healthy volunteers T aestivum spaghetti with guar compared to T aestivum spaghetti without guar showed a significant lower mean incremental plasma C-peptide value at $t = 90$ min (0.82 ± 0.14 vs 1.35 ± 0.14 nmol/l; $p < 0.025$) and at $t = 120$ min (0.79 ± 0.12 vs 1.27 ± 0.15 nmol/l; $p < 0.025$) (fig 1). The meals with T durum spaghetti showed no differences (fig 2). In the diabetic subjects addition of guar to T aestivum flour showed a significant reduction of the mean incremental C-peptide values at $t = 90$ min (0.54 ± 0.07 vs 0.65 ± 0.1 nmol/l; $p \leq 0.05$), $t = 120$ min (0.72 ± 0.13 vs 0.89 ± 0.09 nmol/l; $p \leq 0.025$) and $t = 150$ min (0.89 ± 0.11 vs 1.05 ± 0.09 nmol/l; $p \leq 0.05$) (fig 3). In healthy volunteers the incremental peak values differed not significantly (1.35 ± 0.14 vs 0.96 ± 0.08 ; $p \geq 0.05$). In diabetic patients the incremental peak values were however not different (1.0 ± 0.1 vs 0.89 ± 0.11 ; $p = \text{ns}$), although as for blood glucose the time to reach this peak was delayed after guar (150 vs 180 min).

DISCUSSION

In patients with diabetes mellitus the insulin response to a meal is inadequate, resulting in excessive postprandial blood glucose excursions. The aim of every treatment is to diminish this glycaemic rise. This can be realised partly by alteration of the composition of the meals, i.e. replacing simple by complex carbohydrate or delaying the absorption of simple carbohydrates by addition of dietary fibre such as guar. As guar in solution is quite rather viscous and unpalatable, it is usually incorporated into a meal constituent such as bread (2,4,5) or spaghetti (6,7). In a previous study we evaluated the effect of a bread meal containing guar in NIDDM patients on postprandial blood glucose values (5). The results of this study were rather unsatisfactory, possibly due to the limited amount of guar (8.1 g/day) that can be ingested in this way. Therefore, we tried to augment the ingested quantity of guar with an acceptable palatability

by incorporating guar into spaghetti. This form permitted also a study with meals of more complex composition compared to a breakfast. This study was performed at supper time as this is in the Netherlands the usual time to consume a cooked meal. To mimick as close as possible the normal daily eating pattern we did not standardize the breakfast and lunches during the study period. If a specified food constituent is effective, it has to be effective in normal daily conditions. Another advantage of the spaghetti is that it permits to change the wheat species (soft vs hard wheat), so one can examine the practical implications of different hardness of the starch kernel in usual food components. We investigated the effect of guar in an amount of 20 g% mixed into a complex spaghetti meal, notwithstanding the presence of other food constituents which influence the glycaemic response. Regarding the incremental blood glucose values, this study demonstrated only a reduction at 60 and 90 min in type 2 diabetic patients but without change in peak values, although the time to reach this peak was delayed. This implies that incorporation of guar into the spaghetti delayed the carbohydrate absorption but insufficient to smoothen the postprandial blood glucose excursion. No changes of incremental glucose values were observed in healthy control subjects after ingestion of T aestivum or T durum spaghetti meals with guar. Our results are in contradiction with the results of Gatti (6) and Tognarelli (7). Several explanations can be proposed.

Firstly, in contrast to other studies in which 50 g carbohydrate portions were used our meals contained 106 g carbohydrates (15,19-21). According to Jenkins *et al.* (8) the rise in blood glucose is smaller when more than 50 g carbohydrate portions are consumed, so possible difference in glycaemic response may than become more difficult to demonstrate.

Secondly, the total quantity of our meals was 1500 g (of which 85% water) while in the studies of Gatti *et al.* (6) and Tognarelli *et al.* (7) meals of about 300 g (50% water), containing nearly the same amount of guar, were consumed. As the volume of a meal influences gastric emptying, the greater volume may have obscured the glucose lowering effect of guar. Similarly, the viscosity of such a meal in the small intestine may be the same, whether there is guar incorporated or not.

Thirdly, complex meals as used in normal life, contain substantial amounts of fat, protein and anti-nutrients (e.g. phytates). Fat ingestion delays gastric emptying and attenuates the postprandial glucose response. Protein stimulates the insulin secretion. The end result of a mixed meal on postprandial blood glucose levels is therefore multifactorial and rather complex. For this reason the glycaemic response to mixed meals probably cannot be predicted by the glycaemic responses to the single food components. This is documented by find-

ings of several investigators that, when individual carbohydrate foods are taken as part of a mixed meal, differences of glycaemic responses between the foods are eliminated (22-26). In contrast, other investigations have shown good predictive ability between the expected glycaemic index of a mixed meal and glycaemic responses to single food (21,27,28). The explanation for these conflicting results is unclear. Our results indicate that in a complex meal containing substantial amounts of fat and protein the effects of these food constituents on the resorption of carbohydrate may be so dominant that the theoretical advantage of adding even great quantities of guar into a meal component is obscured in this situation.

Fourthly, it has been noted by Coulston *et al.* (24) that there exists a large variability in glycaemic responses after meals between individuals. In our study this is indicated by the quite large SE of the incremental glucose values of in particular healthy volunteers. It was, however, not possible to identify certain individuals who consistently failed to show the expected differences in glycaemic responses between the meals containing guar and those without guar.

Finally, it is not known whether the high intake of dietary fibre (39 g/day) of the volunteers compared to the Dutch population (25 g/day) (29) could have reduced the effect of guar.

As blood glucose levels and insulin secretion are linked to each other, one may expect that the results of insulin secretion, measured by C-peptide levels, paralleled the blood glucose levels. We found a significant decrease of incremental C-peptide values at 90 and 120 min in T aestivum spaghetti containing guar in healthy volunteers despite the unaffected blood glucose excursions. This observation can be explained by the possibility that guar has not only an effect on glucose absorption but also on insulin secretion, possibly mediated by gastric inhibitory polypeptide as has been reported by Morgan (30). This additional effect of guar may have hampered the favourable effects of guar on intestinal glucose absorption resulting in unaltered postprandial blood glucose values. An alternative explanation for this may be that guar enhanced the insulin response at receptor or postreceptor level necessitating a lower amount of insulin to regulate the glucose level (31).

In this study, the influence of various species of wheat on the glycaemic and C-peptide responses was also determined. It has been reported that starch granules of hard wheat (*T durum*) form a strong union with the protein (32). The grinding of the wheat leads to damage of the starch. Starch granules of soft wheat, which form a weak union, are only separated and not damaged by grinding (33). Damaged starch is more accessible to amylase and may result in

larger glucose excursions. As is shown in our study with healthy volunteers, this has however no consequences for the glycaemic responses. For this reason no experiments with spaghetti meals prepared with different species of wheat were done in type 2 diabetic patients.

In conclusion, in this experiment with healthy volunteers and type 2 diabetic subjects, we have shown that guar has limited effects on the glycaemic response to mixed complex spaghetti meals. This may partly be explained by the composition and the quantity of the meal. The type of wheat from which the spaghetti is made appeared not to influence the postprandial glucose response. These findings suggest that addition of guar to a complex meal is of limited value in the dietary management of diabetic patients.

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Effects of guar on the enzymatic digestion of starch in 2 spaghetti forms *in vitro*

INTRODUCTION

One of the major factors determining postprandial glucose increase is the quantity of carbohydrates in the food available for enzymatic digestion and absorption in the small intestine. This availability depends on the complexity of the carbohydrates. In particular, complex carbohydrates as native starch are packed into granules which are embedded into a meshwork of polysaccharides and/or fibre to a way that enzymatic digestion is difficult. As low enzymatic digestion of starch reduces generation of oligosaccharides and postprandial blood glucose excursions (1), the postprandial glucose and insulin increases after a meal are not only influenced by the food form, but also by food processing and food composition as well as gastro-intestinal motility (2-5). The significance of these different parameters have been studied with *in vitro* experiments which showed that the susceptibility of food to amylase digestion rather than the viscosity and gastric emptying is the determining factor in postprandial glucose and insulin responses (6-10). Such *in vitro* studies were, however, performed with single nutrient meals like bread, potato, rice or processed starch. It can be questioned therefore whether these results apply to complex meals as well.

Addition of dietary fibre to food may have beneficial effects on the postprandial blood glucose excursions (11). Gatti and co-workers (12) found in a study in patients with type 2 diabetes mellitus that addition of guar to spaghetti reduced postprandial blood glucose values. In contrast, Sels and co-workers (13) were unable to confirm these findings in a study with healthy volunteers and diabetic patients, who ingested a guar spaghetti meal with, in addition to the dietary fibre and carbohydrate, normal quantities of fat and protein. These conflicting results may be due to differences in the composition of the test

meals, the variable effects of dietary fibre on the availability of starch present in different forms of meals and on the diffusion of simple carbohydrates through the intestinal content. To substantiate these possibilities further we performed an *in vitro* study with specimens of guar spaghetti to investigate the effects of guar on the availability of starch for enzymatic digestion and on the diffusion rate of resulting oligosaccharides to reach the intestinal brush border for enzymatic cleavage to monosaccharides and subsequent absorption. Some of the experiments were done after addition of sauce containing fat and protein to determine the effects of these nutrients on the availability of starch.

MATERIAL AND METHODS

Availability of starch for enzymatic digestion

Two forms of spaghetti were investigated. One form was prepared of *Triticum aestivum* flour. The other form was prepared of *Triticum durum* flour. Of both flour forms guar spaghetti was prepared (20% w/w). The diameter of *T. aestivum* spaghetti with or without guar was 1.4 mm. For the *T. durum* spaghetti forms with or without guar these diameters were 1.7 and 1.6 mm respectively. The availability of starch in the spaghetti for enzymatic digestion was determined by the method of van de Kamer (14) with minor modifications. In detail the procedure was performed as follows:

Measurement of total starch

A sample of 20 gr pasta was cut into pieces of 1 cm and cooked in 40 ml distilled water for 2 hours for complete gelatinization in a closed system to exclude evaporation, and then cooled. Subsequently, 10 ml of phosphate buffered (pH 6.8) porcine pancreatic amylase solution (Pancreatine, Merck, Darmstadt, FRG) was added. This mixture was incubated at 38° C for 60 minutes under continuous stirring for digestion to maltose and dextrines. After cooling, the protein content of this suspension was precipitated by addition of 1 ml trichloroacetic acid (20% w/w). Distilled water was added to reach a final volume of 200 ml. An aliquot of 50 ml of the filtered supernatant was hydrolysed with HCL 6 N at 100° C for 2 hours for generation of glucose from the present maltose and dextrines. After neutralisation of this solution, the glucose content was measured by a hexokinase method (Glucoquant, Boehringer Mannheim, FRG). The procedure as outlined above was also performed without addition of the amy-

lase solution for measurement of oligosaccharides already present in the spaghetti. The glucose values of the latter procedure were subtracted from glucose values of the amylase procedure and resulting glucose values were multiplied by 0.9 to obtain total starch values.

Measurement of availability of starch

This was done in cooked and uncooked spaghetti. Spaghetti was cooked al dente which was reached after the cooking times mentioned in table 1. Depending on the water absorption, specimens of the cooked and uncooked spaghetti were subjected to enzymatic digestion with amylase as mentioned above. To investigate the influence of spaghetti diameter on the availability of starch, additional experiments were done with T durum spaghetti with a diameter of 1.4, 1.7 and 1.9 mm. All experiments were done in triplo. The availability of starch was calculated in percentage of the total starch according to the formula:

$$\frac{\text{digested starch}}{\text{total starch}} \times 100$$

Table 1. The different spaghetti forms and optimal cooking times

	diameter (mm)	optimal cooking time (min)
Triticum aestivum	1.4	8
Triticum aestivum + guar	1.4	7
Triticum durum	1.6	9
Triticum durum + guar	1.7	8

Dialysis experiments

Dialysis experiments were performed as a model to investigate the diffusion of oligosaccharides in conditions mimicking the small intestine. Specimens of the 4 spaghetti forms were cooked as specified in table 1. After cooking, samples containing approximately 2.5 gr carbohydrates, including a correction for guar content and water binding capacity, were minced in a mortar and mixed with 10 ml freshly collected saliva. To evaluate the influence of fat and protein on the diffusion of generated maltose and dextrines, the same experiments were done

with samples of T aestivum spaghetti to which 4.1 g of dried spaghetti sauce containing 27% protein, 12% dietary fibre, 29% fat and 32% carbohydrates was added. All samples were adjusted to 30 ml with distilled water and transferred to dialysis bags (Spectrapor 0.11 ml/mm, Spectrum Medical Instruments, Los Angeles, USA). Dialysis was done in 800 ml distilled water at 37° C. Samples of the dialysate were taken at 30, 60, 120 and 180 minutes. After acid hydrolysis and neutralisation of these samples glucose was determined by the hexokinase method.

Statistical analysis

Results are expressed as mean $\pm$ SD. For statistical analysis the unpaired two-tailed Student's t-test was used with correction for multiple comparison by Bonferroni's method. P values < 0.05 were considered statistically significant.

RESULTS

Different quantities of starch were identified in the four spaghetti forms (table 2). Availability of starch for enzymatic digestion was markedly lower in uncooked than in cooked spaghetti. No differences in starch availability were found in the different types of uncooked spaghetti. Cooked T aestivum spaghetti without guar yielded a higher availability of starch compared to T aestivum spaghetti with guar and both T durum spaghetti forms. Availability of starch between the T durum spaghetti with or without guar were not different. The various diameters of T durum spaghetti had no influence on the availability of starch (table 3).

In the dialysis experiments, incorporation of guar in T aestivum spaghetti resulted in a lower quantity of oligosaccharides measured as glucose in the dialysate than found after dialysis of T aestivum spaghetti without guar (2.6 ± 0.4 vs 0.9 ± 0.1 mmol/3 hr; $p < 0.001$; fig 1). The quantity of dialysed oligosaccharides, expressed as proportion of the carbohydrate made up in the dialysis tubing and digested at 3 hours, was reduced by guar from 17.6 to 6.2% ($p < 0.01$). Addition of sauce to T aestivum spaghetti, which increased the quantity of carbohydrate in the dialysis tubing by 52%, resulted in an oligosaccharide appearance in the dialysate not different from the quantity found after dialysis of T aestivum spaghetti without sauce and guar (2.9 ± 0.2 vs 2.6 ± 0.4 mmol/3 hr, $p = \text{ns}$). However, if expressed as proportion of carbohydrate

Table 2. Total starch content and availability of starch in different types of spaghetti.

Spaghetti type	total starch (gr% $\pm$ SD)	availability (%)	
		uncooked	cooked
T aestivum	71.4 $\pm$ 1.5	13.0 $\pm$ 1.7	67.2 $\pm$ 1.4
T aestivum + guar	48.6 $\pm$ 3.1*	9.9 $\pm$ 2.7	52.9 $\pm$ 2.0*
T durum	55.8 $\pm$ 2.9*	16.0 $\pm$ 3.2	55.5 $\pm$ 4.1*
T durum + guar	43.2 $\pm$ 0.7**	16.0 $\pm$ 1.7	59.9 $\pm$ 10.5*

* $p \leq 0.01$ vs T aestivum. ** $p \leq 0.01$ vs T durum.

Table 3. Availability of starch in T durum spaghetti of different diameter.

Diameter (mm)	Available starch (%)
1.4	72.8 $\pm$ 2.4
1.7	62.8 $\pm$ 6.3
1.9	67.2 $\pm$ 8.7

made up in the dialysis tubing, addition of sauce to T aestivum spaghetti had reduced the quantity of dialysed oligosaccharides from 17.6 to 13.1% ($p < 0.05$). In comparison with T aestivum spaghetti without guar, addition of sauce to T aestivum spaghetti with guar resulted in lower quantities of oligosaccharides in the dialysate (2.9 ± 0.2 vs 2.1 ± 0.3 mmol/3hr, $p < 0.01$; fig 2), although in this situation the effect of guar was less marked than found in dialysis experiments without sauce. After dialysis of T aestivum spaghetti with guar and sauce, the proportion of carbohydrate in the dialysis tubing digested at 3 hours was 9.4%, which was lower than that found after dialysis of T aestivum with sauce but no guar (13.1%, $p < 0.05$), but higher than that found with T aestivum spaghetti with guar but no sauce (6.2%, $p < 0.05$). In contrast to the experiments with T aestivum spaghetti, dialysis of T durum spaghetti with or without guar yielded no differences in oligosaccharide concentrations in the dialysate (1.0 vs 1.0 ± 0.1 mmol/3 hr). For this reason no dialysis experiments with T durum spaghetti and sauce were performed.

Figure 1. Concentrations of oligosaccharides (measured as glucose) in dialysate during *in vitro* digestion of T aestivum spaghetti with or without guar. The percentages in bars refer to the proportions of starch digested at 3 hours.

Figure 2. Concentrations of oligosaccharides (measured as glucose) in dialysate during *in vitro* digestion of T aestivum spaghetti with sauce or with guar and sauce. The percentages in bars refer to the proportions of starch digested at 3 hours.

DISCUSSION

In the present study, the recovery of total starch from the various spaghetti forms revealed marked differences, and was in all instances lower than expected. Addition of guar to T aestivum flour resulted in recovery of starch about 10% less than was calculated from the total starch content found in the T aestivum spaghetti without guar. Replacement of 20% of flour by guar in the preparation of the T aestivum spaghetti should have resulted in a total starch content of 57.4 g% guar spaghetti, instead 48.6 g% was found. In comparison with T aestivum flour the identified total starch content in T durum spaghetti was even lower, with also a lower recovery of starch in T durum guar spaghetti than calculated. These low recoveries of starch can partly be explained by the production method, which may have resulted in disruption of starch. In addition, the use of certain emulgating agents and pressure necessary to prepare the spaghetti strings may have resulted in lipid-starch complexes and a structure of the spaghetti that makes the starch less accessible for enzymatic digestion. The

reduced recovery of starch after incorporation of guar suggests that guar is interfering with the method of starch quantification we have applied. Likely, these factors are in particular relevant in the T durum spaghetti.

The availability of starch in uncooked spaghetti was low, as expected, due to the presence of raw starch which is not easily degraded by amylase. In cooked spaghetti, however, the availability of starch for enzymatic digestion was higher in spaghetti prepared from T aestivum flour than that prepared from T durum flour. In addition, incorporation of guar into these two spaghetti forms appeared to effect the availability of starch in T aestivum spaghetti only. In particular, these observations on lower availability of T durum spaghetti compared with that found in T aestivum spaghetti are somewhat surprising. As milling of especially a hard wheat as T durum results in damage of starch granules with enhanced susceptibility for amylase after gelatinization, a higher availability was expected. Obviously, the way we prepared this spaghetti annihilated these proposed advantages of hard wheat on availability of starch. This made also the presence of guar in this type of spaghetti of little significance.

Our dialysis experiments revealed a 65% reduction of oligosaccharide appearance in the dialysate if guar was incorporated into T aestivum spaghetti. Again, no such effect was seen in T durum spaghetti. When a sauce containing fat and protein was added to the T aestivum spaghetti sample made up in the dialysis tubing, the reducing effects of guar on oligosaccharide liberation were still present, but less marked and amounting to 29%. The dialysis experiment done with T aestivum spaghetti with sauce but no guar revealed, however, that the sauce in itself can contribute to a reduction of oligosaccharide liberation.

The liberation of oligosaccharides into the dialysate in the experiments as applied by us is determined by the functional availability of starch and comprises the enzymatic digestion of starch and the rate of diffusion through the food bolus. The reducing effects of guar on this functional availability can be explained by an effect of guar on the enzymatic digestion of the starch and a higher viscosity of the food bolus. The effects of sauce on the reduction of functional availability of starch may partly be explained in the same way. In particular the fat content of the sauce may have altered the viscosity of the food. In addition, it is possible that a change in pH and ionic strength is involved too, as well as the presence of sodium in the sauce. *In vivo* studies have shown that salt can effect the glycaemic response to a meal (15). By comparing the effects of guar and sauce on the liberation of oligosaccharides in the dialysate, our experiments show that if combined the sauce determines in particular the resulting functional availability of the starch. This supports clinical studies

demonstrating that dietary fibre is less effective in reducing postprandial blood glucose excursions if ingested as part of complex meals (13).

Regarding the present and other published *in vitro* studies, one may wonder to what extent obtained results can be transposed to *in vivo* situations. The digestion and absorption of food *in vivo* is far more complex than mimicked in *in vitro* experiments. Prior to enzymatic digestion, diffusion through the food bolus and subsequent intestinal absorption, the glycaemic response can be influenced by a variety of other factors. For instance, the rate of gastric emptying may influence the postprandial blood glucose excursions, and is determined by the volume and temperature of the food, whether the food is in a solid or liquid form, the content of fat and protein in the food and in patients with diabetes mellitus the possible presence of autonomic neuropathy. All these factors can be altered by introduction of a soluble dietary fibre as guar into the food. Different mechanisms of action have been proposed for such dietary fibre incorporated into a meal, such as delay of gastric emptying, interference with pancreatic enzymes, increase of viscosity of the food bolus delaying diffusion of simple carbohydrates through the food bolus, resistance to the convective effects of intestinal contraction, increase of the unstirred water layer and interference with mucosal enzymatic hydrolysis (16). Not all these factors can be studied with *in vitro* experiments. However, several investigators have demonstrated a good correlation between *in vitro* rate of digestion and the glycaemic index, although some discrepancies are reported (5-9). More important, Bornet and co-workers (10) reported recently in a combined *in vitro in vivo* study in normal healthy volunteers that susceptibility of test carbohydrates for enzymatic digestion is the determining factor in postprandial glucose and insulin increments, while viscosity and gastric emptying rate appear to constitute no relevant effects. This suggests that results obtained in *in vitro* studies as used in our investigations can indeed be taken into consideration in predicting glycaemic and insulinaemic responses in at least healthy persons and may even advantageously replace *in vivo* studies. One may wonder, however, whether this also applies to diabetic patients who commonly have disturbed gastric emptying due to autonomic neuropathy.

In conclusion we found that:

1. addition of guar may interfere with the method for starch measurement we have applied in this study,
2. the theoretical higher availability of starch in T durum spaghetti compared to T aestivum spaghetti can be modified during processing,
3. incorporation of guar into the spaghetti forms reduced the availability of starch for enzymatic digestion in T aestivum spaghetti but not in T durum spaghetti,

4. addition of sauce containing fat and protein or incorporation of guar into T aestivum spaghetti reduced the functional availability of starch, of which the sauce appeared when combined with guar the determining factor reducing efficacy of the guar as well,
5. the diameter of the spaghetti had no effect on the availability of the starch.

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General discussion

In this thesis studies in diabetic subjects are described regarding the efficacy and applicability of the soluble dietary fibre guar-gum incorporated into bread and spaghetti.

In summary, these experiments confirm and extend data reported in the literature that diets high in soluble fibre (including supplements) have no relevant long-term effect on carbohydrate metabolism in patients with diabetes mellitus. We found no effect of guar addition to food on glucose control in type 1 and type 2 diabetic subjects if the carbohydrates and guar were consumed as part of complex daily meal containing normal quantities of fat and protein. The *in vivo* and *in vitro* studies with guar spaghetti suggest that fat and protein neutralise in part the effects of guar on carbohydrate digestion and oligo-saccharide diffusion through the food. In addition, it is well known that fat and protein exert in itself an effect on glucose control by affecting the gastro-intestinal motility and entero-insular axis. On the contrary, we found that guar can lower total and low density lipoprotein (LDL) cholesterol. These observations are in agreement with those of other investigators. In this context it can be questioned whether or not these hypolipidaemic effects are due to replacing foods in the diet that contain saturated fat and cholesterol rather than due to a direct action of the soluble fibre. In studies with oatbran and low-fibre wheat supplements in the diet, Swain and co-workers (1) found no differences in cholesterol lowering effects between high-fibre and low-fibre dietary grain supplements, possibly because both replaced dietary fats. It appears that fibre supplementation in diabetes is only beneficial when given with carbohydrate-rich meals, to overcome the excessive increase in postprandial blood glucose as well as the increase of triglycerides and decrease of high density lipoprotein (HDL) cholesterol, which may result from such meals (2).

The dietary management of diabetic patients aims at two objectives. First, dietary adjustment should improve blood glucose control which may contribute to a reduction of acute and chronic morbidity associated with hyperglycaemia. In addition, in particular in patients with type 2 diabetes mellitus improvement of blood glucose control reduces insulin resistance and hyperinsulinaemia, which may be relevant, since insulin is considered an independent and strong risk factor for the development of atherosclerotic disease (3). Second, dietary

adjustment may improve the lipid abnormalities related to the diabetic condition which contribute to the high risk of vascular disease in these patients. These abnormalities are especially present in type 2 diabetic subjects and include an increase in very-low-density lipoprotein (VLDL) triglyceride and a decrease in HDL-cholesterol (4). As demonstrated by the Framingham and the MRFIT studies, an increase of total and VLDL-triglycerides constitutes—at least in the diabetic patient—an independent risk factor for vascular disease (5,6).

In overweight subjects, weight loss is usually effective in improving the metabolic abnormalities outlined before. In addition, high carbohydrate meals are recommended throughout the world, in order to reduce the intake of total fat, saturated fat and cholesterol (table 1)(7,8). However, as high-carbohydrate low-fat meals are considered by many to be unattractive and sometimes unpalatable, one may wonder whether patients with diabetes will follow these advocated dietary advices. It can be questioned also whether alternative and

Table 1. Nutritional recommendations for individuals with diabetes

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1. Calories prescribed to achieve and maintain desirable body weight.
 2. Carbohydrate intake:
 - * liberalised to 55 to 60% of total calories, individualised according to blood glucose and lipid responses and eating pattern.
 - * substitute fibre-containing foods for highly refined foods (25 g/1000 kcal or 40 g/day).
 - * modest amounts of refined sugars (50 g/day) acceptable, depending on metabolic control and body weight.
 3. Protein intake:
 - * 0.8 g/day/kg body weight.
 - * reduced in patients with incipient nephropathy.
 4. Fat intake:
 - * total fat restricted to less than 30% of total calories.
 - * cholesterol less than 300 mg/day.
 - * replacement of saturated (S) with polyunsaturated (PUS) or eicosapentaenoic acid and monounsaturated (MUS) fat is desirable (S: PUS: MUS = 1: 1: 1).
 5. Salt intake:
 - * 1000 mg sodium/1000 kcal or < 3000 mg sodium/day.
 6. The use of various sweeteners is acceptable.
 7. Alcohol should be used with caution.
-

more acceptable food modifications are more effective to improve blood glucose control and to decrease the risk of vascular disease.

Himsworth (9) was the first who introduced high-carbohydrate low-fat meals, based on studies in non-diabetic subjects, in whom an increase of glucose tolerance and insulin sensitivity after intake of meals with a high carbohydrate content was found. Later studies on diabetic subjects confirmed that such high-carbohydrate low-fat meals can lead to an improvement of glucose tolerance, together with a decrease of LDL-cholesterol, and without increasing the triglyceride concentrations (10). However, in these studies the ratio of polyunsaturated to saturated fat of the high-carbohydrate meals was also markedly increased (from approximately 0.3 to at least 1.1), whereas the composition of the meal was essentially a vegetarian one, with about 50% of calories obtained from legumes and about 100 g of fibre. All these factors may in itself have contributed to the fall in plasma levels of both glucose and LDL-cholesterol. When more conventional high-carbohydrate low-fat diets were used, these authors found no improvement in plasma glucose and LDL-cholesterol levels, whereas VLDL-triglyceride levels increased and HDL-cholesterol levels decreased (11). Coulston and co-workers (2) demonstrated in type 2 diabetic subjects that, in comparison with diets containing 40% of total calories as carbohydrate, diets with 60% of total calories as carbohydrate, a reciprocal change of fat content from 40 to 20% and a moderate increase of dietary fibre (from 14 to 18 g/day) may even result in a significant increase of plasma glucose and insulin concentrations throughout the day. In this 6 weeks study, fasting plasma total and VLDL-triglycerides increased by 30% after 1 week and persisted at this level unchanged. Although total cholesterol did not change, VLDL-cholesterol increased, whereas both LDL- and HDL-cholesterol concentrations decreased. Given these results, Coulston concluded that routine recommendations of high-carbohydrate low-fat diets for in particular subjects with type 2 diabetes need to be reconsidered. In contrast, in studies in which type 2 diabetic subjects consumed a high-carbohydrate diet, Abbott and co-workers (12) found reduced LDL-cholesterol concentrations without a change in HDL-cholesterol and body weight. The triglyceride levels were unchanged, but looking at the individual data these responses appear very heterogeneous. This study has also the disadvantage that the ratio of polyunsaturated to saturated fatty acids was increased from 0.3 to 1.2 as well as the fibre content of the meals. In addition, the experiments were carried out in Pima indians and one may wonder to what extent these results are applicable to other racial groups.

Further data supporting the questioning of the efficacy of high-carbohydrate low-fat diets in diabetes are reported by Garg and co-workers (13). These authors compared a high-carbohydrate diet with a high-fat diet (specifically a diet high in monounsaturated fatty acids) in type 2 diabetic subjects receiving insulin therapy. In the high-carbohydrate diet 25% of the energy was in the form of fat and 60% in the form of carbohydrate. In the high-monounsaturated-fat diet 50% of the energy was fat (33% of the total energy in the form of monounsaturated fatty acids) and 35% carbohydrate. The two diets had the same amounts of fibre. As compared with the high-carbohydrate diet, the high-monounsaturated-fat diet resulted in lower plasma glucose levels and reduced insulin requirements, lower levels of plasma triglycerides and VLDL-cholesterol and higher levels of HDL-cholesterol, whereas the levels of total and LDL-cholesterol did not differ significantly in patients on the two diets. Also in non-diabetic individuals high-monounsaturated-fat diets may improve lipid abnormalities. Recent studies (14-16) have shown that the substitution of monounsaturated fats for saturated fats results in reductions in the total and LDL-cholesterol levels that are at least equivalent to the reductions attained by the simple removal of saturated fats. Further indications for a positive effect of monounsaturated fatty acids on lipid metabolism and risk for the development of cardiovascular disease come from the Seven Country Study, which yielded a lower incidence of coronary artery disease in Crete where in the preparation of food in particular olive oil, a known source of monounsaturated fatty acids, is used (17). Obviously, further studies are needed to substantiate the favourable effects of such diets on blood glucose control in diabetes.

As a special form of unsaturated fatty acids fish oil containing omega-3 fatty acids such as eicosapentaenoic acid (EPA) is mentioned as well in the nutritional recommendations for diabetes. This suggestion is based on the observation that Eskimos have a reduced incidence of coronary heart disease, which may be explained by the high content of omega-3 fatty acids in fish, which is the main food of this population (18). In non-diabetic subjects, Kromhout and co-workers (19) demonstrated that consumption of large amounts of fish may indeed reduce the incidence of coronary heart disease. In addition fish oil lowers blood pressure and has powerful anti-thrombogenic effects (20,21). It can be questioned, however, whether this is also applicable to diabetic subjects without affecting glucose control. Friday and co-workers have shown that in type 2 diabetic subjects consumption of omega-3 fatty acids may result in a marked reduction of total and VLDL-cholesterol as well as triglycerides, without significant changes in LDL- and HDL-cholesterol (22). Furthermore, several studies have shown that omega-3 fatty acids may improve platelet

function, blood pressure control and increased microvascular albumine leakage, including microalbuminuria, in diabetes (23). On the other hand, however, in the study of Friday and co-workers (22) the fasting blood glucose levels increased by 22% and the meal stimulated glucose levels by 35%. These adverse effects on glucose control were more apparent in overweight subjects. Other studies have also demonstrated a deterioration of glucose control in diabetes, but with variable changes in total and LDL-cholesterol (24). Thus, in particular for diabetic subjects it can be questioned whether omega-3 fatty acids are to be considered as a gift or a poison from the sea (25,26). At present, the conclusion must still be that the recommendation of high-fish oil diets in diabetic patients should be considered with care.

In the nutritional recommendations for individuals with diabetes inclusion of refined sugars as sucrose are acceptable, depending on the metabolic control and body weight. In short term experiments addition of sucrose to a meal did not increase postprandial glucose excursions (27). Among simple carbohydrates, the smallest increments in glucose concentrations are found after fructose. Based on these observations, Bantle concluded that diabetic people may use moderate amounts of sucrose in their daily meals and fructose as a sweetener (28). However, some precaution has to be emphasized. First, simple carbohydrates as sucrose should be avoided in overweight subjects. Preferably, the simple carbohydrate should be combined with other nutrients as fat, protein and fibre to delay intestinal absorption. There remains also serious doubt whether sucrose does not affect glucose control on long term. Hollenbeck and co-workers (29) demonstrated in a 6 weeks study an increase of plasma triglyceride concentrations in combination with impairment of glucose control. Reviewing other studies, these authors had serious criticism regarding the reported unharmful effects of sucrose on glucose control in diabetes. The majority of these studies appeared uncontrolled, poorly designed and short term with low amounts of sucrose included in the diets and variable fasting blood glucose levels making comparisons impossible.

What will therefore be a reasonable and healthy diet prescription for the diabetic patient? 60% carbohydrate or more? More complex than simple carbohydrate? Unpalatable quantities of legumes to increase carbohydrate content and dietary fibre? Fat restriction or substitution of unsaturated fat for saturated fat? Fish oil supplementation? These questions are still relevant (30,31). It appears that high-carbohydrate diets are not that strictly indicated, as long as the majority of normal quantities of fat are supplied by unsaturated fatty acids. This appears in particular warranted in patients with hypertriglyceridaemia, as high-carbohydrate diets may increase triglyceride concentrations. Moderate amounts

of refined sugars as sucrose appear acceptable, unless there is overweight and, again, hypertriglyceridaemia. Extra dietary fibre is not essential but may have advantages for other reasons than to improve metabolic control in diabetes, unless high-carbohydrate food is prescribed. An important advantage of these reconsiderations is that such diets may be more palatable than the advocated high-carbohydrate low-fat diets, which most European people are not accustomed to eat, which may result in better compliance

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Summary

This thesis describes nutritional investigations using the dietary fibre guar incorporated in bread and spaghetti.

The subjects of this thesis are discussed in general in the introduction.

Chapter 1 deals with dietary fibre as a general nutrition principle. The investigations of Trowell and Burkitt provoked a reappraisal of dietary fibre. Today, it is an essential constituent of healthy nutrition. This chapter gives a review of definition, analysis and mechanisms of action. It concludes with a review of recent literature dealing with the effects of dietary fibre on carbohydrate and fat metabolism. Applicability and safety are considered.

Chapter 2 describes the results of a 6 weeks study with guar bread in type 2 diabetic patients. A mean daily intake of 8.1 g guar resulted in a decreased postbreakfast blood glucose level after 1 month but, afterwards, no changes were found compared to the levels prior to the guar bread period. Fasting blood glucose, HbA₁, HDL-cholesterol and triglycerides values showed no changes. Postbreakfast C-peptide levels diminished significantly during guar bread consumption.

Based on these results, a long-term at random cross-over study of six months was performed with type 1 and type 2 diabetic patients (chapter 3). Mean daily guar intake was 11 g during the guar bread period. Postbreakfast blood glucose level decreased after 1 month of guar bread consumption in type 1 patients only. HbA₁ and fructosamin levels remained unchanged. LDL-cholesterol and, in type 2 diabetic patients only, total cholesterol levels decreased during guar bread consumption. No changes were observed in HDL-cholesterol, triglycerides and Lp(a) levels. Postbreakfast levels of C-peptide increased in type 2 patients on the first day of guar consumption, while GIP levels decreased significantly in type 1 patients. Afterwards, no changes of these 2 parameters were found. Glucagon levels remained unchanged. No severe gastro-intestinal complaints were noted.

In chapter 4 the results of a study with guar spaghetti are described. Spaghetti is a food form which permits to incorporate a larger amount of guar (20 g/kg flour) with an acceptable taste. Healthy volunteers consumed 4 cooked spaghetti meals prepared with 2 different flour types: Triticum (T) aestivum and T durum spaghetti with and without guar. Incorporation of guar in these 2

spaghetti forms did not result in a reduction of blood glucose excursion. Post-prandial C-peptide levels were lower at 90 and 120 min with T aestivum spaghetti but the total increase was not different. Type 2 diabetic patients consumed cooked meals with T aestivum spaghetti only. The incremental peak values of blood glucose and plasma C-peptide levels were not affected by guar, although the time to reach this peak appeared delayed.

Chapter 5 reports an *in vitro* experiment in which the effects of guar in spaghetti on the availability of starch for enzymatic digestion was studied. Relative availability of starch for amylase digestion was lower in T durum spaghetti compared to T aestivum spaghetti. Incorporation of guar reduced this availability in T aestivum but not in T durum. These findings suggest that the processing of T durum flour made the starch less susceptible to amylase digestion. Incorporation of guar into this type of flour is therefore less useful to alter the availability of starch. Dialysis experiments showed that incorporation of guar in T aestivum spaghetti delayed the diffusion of oligosaccharides through the food bolus. This effect was partially annihilated by addition of fat and protein containing sauce. This sauce showed itself a retarding effect on starch digestion. No effect was found when guar was incorporated into T durum spaghetti.

This thesis concludes with a general discussion on nutrition recommendations for diabetic patients. The results described in this thesis permit to conclude that incorporation of guar has no significant effects on glycaemic control in diabetic patients. A reduction of LDL-cholesterol is reaffirmed. It is suggested that the reduced importance of dietary fibre in the regulation of blood glucose levels can be explained by the presence of fat and protein in food products. They annihilate the effects of dietary fibre and have their own effect on digestion, glucose absorption and entero-pancreatic regulation.

Samenvatting

In dit proefschrift worden de resultaten beschreven van voedingsstudies, welke zijn uitgevoerd met guar verwerkt in brood en spaghetti.

In de inleiding wordt het algemeen schema van dit onderzoek uiteengezet.

Hoofdstuk 1 behandelt voedingsvezel in het algemeen. De onderzoeken van Trowell en Burkitt hebben er voor gezorgd dat voedingsvezel op de "maatschappelijke voedingsladder" is gestegen van onverteerbare plantenrest tot een essentieel bestanddeel van een gezonde evenwichtige voeding. Ondanks een zekere consensus blijven er toch controversen bestaan. In dit hoofdstuk wordt een overzicht gegeven van de verschillende definities van voedingsvezel en het probleem van bepalingsmethodieken. Er wordt verder ingegaan op het werkingsmechanisme van voedingsvezel. Een literatuuroverzicht wordt gegeven betreffende de invloed van voedingsvezel op koolhydraat- en vetmetabolisme bij patiënten met diabetes mellitus. Tevens wordt aandacht geschonken aan veiligheid en praktische toepasbaarheid van voedingsvezel.

Hoofdstuk 2 beschrijft de resultaten van een studie waarin type 2 diabetes patiënten gedurende 6 weken guar brood gebruikten. Bij een gemiddelde guar consumptie van 8,1 g per dag werd er een tijdelijke daling van bloedglucose 90 min na ontbijt gezien. Nuchtere bloedglucose en HbA₁ waarden bleven onveranderd. De C-peptide waarden daalden wel significant. Geen effect werd gezien op HDL-cholesterol en triglyceriden waarden.

Aangezien de duur van het onderzoek beschreven in hoofdstuk 2 beperkt was tot 6 weken, werd een lange termijn onderzoek over 6 maanden uitgevoerd, zowel bij type 1 als bij type 2 patiënten in een cross-over schema. De resultaten van deze studie worden besproken in hoofdstuk 3. De gemiddelde guar inname bedroeg 11 g per dag. Er werd alleen bij type 1 patiënten een tijdelijke daling van het bloedglucose gehalte 90 min na ontbijt gevonden na 1 maand guar brood gebruik. Dit effect verdween nadien. Het algeheel effect op de diabetes regulatie zoals weerspiegeld in HbA₁ en fructosamine waarden was nihil. Uitgebreide analyse van plasma lipiden toonde aan dat guar gebruik leidt tot een significante daling van LDL-cholesterol en, alleen in type 2 patiënten, totaal cholesterol waarden. Geen veranderingen werden waargenomen in plasma HDL-cholesterol, triglyceriden en Lp(a) waarden. Postprandiale plasma C-peptide waarden stegen en, in

type 1 patiënten, daalden GIP waarden de eerste dag van guarbrood. Nadien werden echter geen waarden gevonden welke verschilden van de waarden gevonden tijdens de controle periode. Postprandiale plasma glucagon waarden bleven ongewijzigd. Er traden geen ernstige gastrointestinale bijwerkingen op.

In hoofdstuk 4 wordt een guar spaghetti studie besproken. Spaghetti is een voedingsmiddel waarin een grotere hoeveelheid guar verwerkt kan worden (20g/kg bloem) met een aanvaardbare smaak. Gezonde proefpersonen gebruikten volledige warme spaghetti maaltijden bereid met 2 bloemsoorten: Triticum (T) aestivum met en zonder guar en T durum met en zonder guar. Gebruik van guar in spaghetti bereid uit een van deze twee bloemsoorten leidde niet tot een duidelijk verschil in absolute stijging van postprandiale bloed glucose waarden. De plasma C-peptide waarden vertoonden wel een lagere toename na toevoeging van guar aan T aestivum spaghetti na 90 en 120 min in vergelijking met de controle maaltijden, doch de totale stijging was niet verschillend. In patiënten met type 2 diabetes werden alleen studies met T aestivum spaghetti verricht. Guar spaghetti vertoonde een vertraagde postprandiale glucose stijging, maar de glucose piekwaarde verschilde niet van die welke werd gevonden met T aestivum spaghetti zonder guar. De postprandiale C-peptide waarden vertoonden een zelfde patroon.

Hoofdstuk 5 beschrijft een *in vitro* experiment waarbij de invloed van guar in spaghetti op de beschikbaarheid van zetmeel voor enzymatische vertering werd bestudeerd. Hierbij werd een lagere beschikbaarheid van zetmeel voor amylase gevonden bij T durum dan bij T aestivum spaghetti. Na guar incorporatie daalde de beschikbaarheid van zetmeel voor enzymatische vertering in T aestivum spaghetti, maar niet in T durum spaghetti. Kennelijk wordt bij de bereiding van T durum spaghetti het zetmeel zodanig afgeschermd dat enzymatische vertering minder goed mogelijk is. Hierdoor heeft toevoeging van guar aan T durum spaghetti geen toegevoegde waarde. Bij dialyse experimenten met T aestivum spaghetti werd aangetoond dat guar de diffusie van oligosacchariden, die ontstaan door inwerking van amylase, door de voedselmasa vertraagt. Dit vertragend effect werd deels teniet gedaan door toevoeging van vet- en eiwithoudende saus aan de spaghetti. Saus bleek zelf ook een vertragend effect te hebben op de enzymatische vertering van zetmeel en diffusie van gevormde oligosacchariden door de voedselmasa. Bij dialyse experimenten met T durum spaghetti werden geen effecten van guar op de functionele beschikbaarheid van zetmeel voor enzymatische vertering waargenomen.

Dit proefschrift besluit met een algemene discussie over de algemeen geldende voedingsrichtlijnen voor patiënten met diabetes mellitus. Op grond van de onderzoeken die beschreven zijn in dit proefschrift kan geconcludeerd worden dat de betekenis van toevoeging van guar voor de glucose regulatie beperkt is. Guar kan, evenals dat geldt voor andere water oplosbare voedingsvezels, wel een gunstig effect hebben op het vetmetabolisme en in het bijzonder leiden tot een daling van cholesterol en LDL-cholesterol waarden.

Het is aannemelijk dat de beperkte betekenis van voedingsvezel op de glucose regulatie een gevolg is van de effecten van met de voeding genuttigde vet- en eiwithoudende voedingsstoffen die deels de effecten van voedingsvezel neutraliseren en deels een eigen effect hebben op de voedselvertering, glucose absorptie en darm-pancreas regulatie.

Dankwoord

Aan het einde van een proefschrift past een dankwoord.

Prof Dr A.C. Nieuwenhuijzen Kruseman: voor uw essentiële bijdrage in de vorm van continue zorg ten einde binnen het gestelde tijdsschema te blijven. De multiële afleveringen werden op vrijdagavond steeds met een glimlach ontvangen en 's maandags met de nodige kritieken terugbezorgd.

Prof Dr J.A. Flendrig: voor uw onmisbare bijdrage bij het opstarten van dit proefschrift.

Dr Th.J. Postmes: voor uw enthousiasme en dynamisme, waarbij vele hindernissen werden genomen. Voor de vele uren besteed aan de redactie van dit proefschrift.

Dr B. Belderok, Ir P. Sluimer, drs H. van Lonckhuijsen (Instituut voor Graan, Meel en Brood TNO, Wageningen): voor uw kritische adviezen in de voorbereidingsfase, nadien gecompleteerd door de productie van de in dit proefschrift beschreven voedingsmiddelen.

Dr N. Pikaar, Dr W. van Dokkum (CIVO TNO, Zeist): voor uw kritische opmerkingen zowel in de voorbereidingsfase alsook in de afrondende fase van dit proefschrift.

Collegae E. Jaspers, K. van Santen, A. Knols en W. Slits: voor uw hulp bij het uitvoeren van de korte termijn broodstudie.

Mej. M. de Kler, Mej. H. de Bruijn, Mej. M. Camps en Dhr. F. Elbers (studenten Landbouw Universiteit Wageningen): voor uw onmisbare praktische bijdrage bij de *in vivo* en *in vitro* spaghetti studies.

Mevr. J. Budy (diëtiste), mevr. Lemaire, mevr. Pegels en mevr. Oosterbaan (Laboratorium Verpleegkliniek Klevarie), mej. Houben (Klinische Chemie) en dhr. Willems (Nucleaire Geneeskunde): voor uw bijdrage in de korte termijn broodstudie.

Het personeel van de afdeling Klinische Chemie (hoofd: drs C. Degenaar): met oog voor detail en reproduceerbaarheid werden alle bepalingen uitgevoerd door de dames en heren van chemie 3 onder de leiding van mevr. Haesen en de dames en heren van chemie 6 (hoofd: dr P. Menheere) onder de leiding van mevr. Vranken.

Alle proefpersonen die welwillend, met enthousiasme en standvastigheid hebben deelgenomen aan de verschillende studies. Zonder uw medewerking was dit proefschrift onmogelijk te realiseren.

Dhr. F. Nieman: voor uw bereidheid ingewikkelde statistische analyses te verrichten voor iemand die het statistische (s)t(r)ijdperk nauwelijks had betreden.

Mej. M. Durlinger, Dhr. S. Halders, R. Kengen en A. Knols: voor uw praktische bijdrage als lid van de "prikploeg".

Mej. Haemers en Mej. Wishaupt: voor het feilloos bewerken van de verschillende teksten, die in de loop van de jaren het licht zagen.

Drs. A. Knols, beste Dré: alvorens het allemaal begon sprak je de bereidheid uit om mee te werken. Je hulp bij de patiënten recrutering, als lid van de prikploeg en je sportieve steun bij het op peil houden van de algemene konditie waren onmisbaar.

Dr. B. Wolffenbuttel, beste Bruce: aan jouw belangrijke adviezen in de schrijffase van dit proefschrift is het te danken dat dit proefschrift afgerond is. Ook jouw computerkennis is van essentiële betekenis geweest.

Het schrijven van een proefschrift is slechts realiseerbaar indien de nodige randvoorwaarden worden geschapen. Essentieel hierin is het thuisfront. Lies, het zijn lange en niet altijd even vreugdevolle jaren geweest. Je steun en niet aflatende aanmoediging waren belangrijk om het proefschrift niet alleen te beginnen maar ook af te ronden. Jan-Willem, Pieter en Stefan: vooral het laatste jaar is de aanspreekbaarheid minimaal geweest. Toch is jullie interesse in wat ik nu weer aan het schrijven of berekenen was een steun geweest in het gevecht met de tekst.

Curriculum vitae

Geboren te Sint-Truiden (België) op 21 september 1946. Na het behalen van het einddiploma Middelbaar Onderwijs aan het Aangenomen College te Sint-Truiden werd de opleiding tot arts begonnen in 1964 aan de Facultés Notre Dame de la Paix (Namur) en voortgezet aan de Katholieke Universiteit Leuven. De opleiding tot internist volgde vanaf 1971 te Maastricht (Dr J. Coenegracht) en vanaf 1973 te Leuven (prof. Dr J. Vandenbroucke). Registratie tot internist volgde in 1976. Na het vervullen van de militaire dienstplicht is hij vanaf 1977 als internist verbonden aan de afdeling Interne Geneeskunde (hoofd: Dr J. Coenegracht, Prof. Dr J.A. Flendrig), werkgroep Endocrinologie (hoofd: Prof. Dr A.C. Nieuwenhuizen Kruseman) van het Akademisch Ziekenhuis Maastricht.