CHILDHOOD CONSTIPATION: DIAGNOSIS, TREATMENT AND THE ROLE OF DIETARY FIBER

Good fibration?

Cover illustration: Hans Kokke
Book design: Gerrit Vroon
Print: A-D Druk BV, Zeist
ISBN 978-90-816194-2-4

CHILDHOOD CONSTIPATION: DIAGNOSIS, TREATMENT AND THE ROLE OF DIETARY FIBER

Good fibration?

Obstipatie bij kinderen: diagnose, behandeling, en de rol van voedingsvezel

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van rector magnificus prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar
te verdedigen op dinsdag 29 maart 2011 des middags te 4.15 uur

door

Freddy Theodorus Maria Kokke
geboren op 28 mei 1958 te Utrecht

Promotor:

Prof. Dr. J.L.L. Kimpen

Co-promotoren:

Dr. M.A. Benninga

Dr. R.H.J. Houwen

CHILDHOOD CONSTIPATION: DIAGNOSIS, TREATMENT AND THE ROLE OF DIETARY FIBER

Good fibration?

Contents

The research described in this thesis was financially supported by The Scientific Research Foundation (Stichting Wetenschappelijk Onderzoek) project SWO 2001. Kokke received financial support through project no. 9.001, which is a subproject of Business aimed Technological Cooperation project 00176.

The printing of this thesis was financially supported by:
Abbott
Abbott Immunology
G.E.C. K.-P.
J.E. Jurriaanse Stichting
MSD Merck Sharp & Dohme BV
Norgine BV
Nutricia Advanced Medical Nutrition/DANONE Group
Olympus
Orphan Europe
Orthica BV
Zambon Nederland BV

CHAPTER I

General introduction and outline of the thesis

Childhood constipation is a common problem with a prevalence worldwide ranging from 0.7 to 29.6% (median 8.9; inner quartile range 5.3-17.4).[1] The prevalence of laxative use (as a surrogate marker for childhood constipation) in Dutch children ranges from 2-3%.[2] The hallmark symptom is infrequent defecation (less than 3 times per week), which is often painful. Accompanying symptoms may include irritability and/or decreased appetite in infants or toddlers and chronic abdominal pain and/or fecal incontinence in older children. The diagnosis is based on careful history taking in combination with a thorough physical examination.

DEFINING CONSTIPATION

As some of the symptoms associated with constipation can be found in normal children as well, strict diagnostic criteria are necessary to be able to distinguish between constipated and non-constipated children and to compare studies on childhood constipation. In the studies described in this thesis, which were started in 2001, we used the Loening-Baucke criteria (or Iowa criteria),[3] which were adapted by Benninga.[4] In short: children younger than 5 years of age had to have infrequent, painful defecation and should produce hard stools, sometimes in large quantities, with straining, while children aged 5 years or older should fulfill at least 2 out of 4 of the following symptoms: 1. A stool frequency less than 3 times per week; 2. two or more fecal incontinence episodes per week; 3. Periodic passage of large amounts of stool at least once every 7 to 30 days; 4. A palpable abdominal or rectal mass. Recently the diagnostic criteria for constipation in childhood were revised, both for children from 0-4 years of age[5] and for older children.[6] These so-called Rome III criteria (appendix 1) can be considered to be less strict than the criteria used in this thesis. Consequently, in this thesis we have studied a group of children with constipation that is at least as severe as would have been if we had included the patients using the present Rome III criteria.

CAUSE AND CLASSIFICATION

In the majority of children no cause of the constipation can be found. Most authors agree on the fact that it is multi-factorial in origin and involves both physiologic and psychological factors. Common organic causes of childhood constipation include congenital defects of the gut (M. Hirschsprung), neurologic disease (especially cerebral palsy, spinal cord disorders and hypotonia), endocrine and metabolic disorders (hypothyroidism, cystic fibrosis (see below), hypercalcemia, diabetes mellitus, and renal acidosis), and the use of constipation promoting drugs (e.g. antacids, sucralfate, iron, codeine-containing medication, tricyclic antidepressants and phenytoin).[7] However, organic causes account for less than 5% of childhood constipation. The remainder is considered to have functional (idiopathic) constipation. In this group the constipation seems to be multi-factorial in origin, involving both physiologic and psychological factors.[8]

POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS: THE ROLE OF FIBER

Dietary fiber can be defined as *the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete (soluble fiber) or partial fermentation (insoluble fiber) in the large intestine. Dietary fiber includes polysaccharides, oligosaccharides, lignin, and associated plant substances.*[9] (figure 1). An adequate dietary fiber intake is suggested to prevent constipation.[10,11] Indeed, the fermentation of soluble fiber by intestinal microbiota produces short-chain fatty acids (SCFA), which increase the osmotic load of the feces, thereby inducing water transport into the fecal bulk and softening the stools. Gas-production, a by-product of fermentation, adds to this laxative effect.[12] Insoluble fibers are minimally degraded by colonic bacteria but are able to retain some water within their structural matrix, increasing fecal bulk and decreasing intestinal transit time, also giving a laxative effect.[13] Moreover, soluble fiber and lignin bind both bile and fatty acids, making these compounds less accessible for uptake in the small intestine. This will result in the colonic delivery of increased amounts of bile and fatty acids, which are potent laxative agents.[14,15] An overview of these and other beneficial consequences of fiber in pediatric gastroenterology is given in **chapter 2**.

DIETARY FIBER INTAKE AND CONSTIPATION

In recent decades many papers have been published evaluating the effect of dietary fiber intake on childhood constipation. Interestingly, a substantial number of studies did describe an association between low dietary fiber intake and constipation[16-20] but other investigators could not confirm this association.[21-23] Similarly, a low fluid intake has been suggested to be associated with childhood constipation.[24,25] However, others were not able to confirm the role of low fluid intake.[26,27] So far a final verdict for a positive or negative correlation between constipation and dietary fiber or water intake has not been provided. Most papers.[16,17,19,20] supporting the concept that a low fiber and/or fluid intake is associated with constipation generally express intake as gram/day. In contrast, the few papers that were not able to find a correlation, express intake as gram/kilogram body weight/day or gram/Mega-Joule energy consumed/ day.[21-23] Consequently, when we investigated dietary fiber and fluid intake in constipated children and compared this to a group of healthy children from the Dutch National Food Consumption Survey (DNFCS), we expressed intake both as gram/day, gram/kilogram body weight/day and gram/Mega-Joule energy consumed/day. Results are described in **Chapter 3**.

DIAGNOSIS: THE ROLE OF THE ABDOMINAL RADIOGRAPH

The cornerstone for the diagnosis of childhood constipation is a careful medical history in combination with a thorough physical examination and including digital rectal examination. In daily clinical practice it is not unusual to order also a plain abdominal X-ray to support (or reject) the diagnosis of childhood constipation. In this respect several radiological scoring systems have been developed to diagnose constipation: the Barr,[28] Blethyn,[29] and Leech[30] scoring method, while a fourth method has been developed to diagnose constipation in adults.[31] Although the original publications found a good to excellent correlation between the clinical and radiological diagnosis of constipation, in subsequent evaluations each method performed worse.[4,28,32-34] As the fourth method available for judging plain abdominal X-rays in constipation[31] had not been used in children, we evaluated this scoring method to diagnose childhood constipation and compared this method with the often used Barr scoring method.[28] The results of this study are described in **chapter 4**.

CONSTIPATION IN CYSTIC FIBROSIS PATIENTS

Constipation is frequently found in children with cystic fibrosis (CF), an autosomal recessive genetic disorder, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The incidence and prevalence of constipation in CF is not clear however. The only study systematically investigating this problem reported a prevalence of 26% in patients aged 0-20 years[35]. As CF patients might also suffer from other consequences of the inspissated intestinal secretions due to CFTR mutations, such as the distal intestinal obstruction syndrome (DIOS), differentiating between this condition and constipation is not always easy. In this respect the recent ESPGHAN criteria, making a strict distinction between the (sub)acute complete ileocecal obstruction, as seen in DIOS and the gradual fecal impaction of the total colon in CF patients constipation, might be helpful.[36] In **chapter 5** we determined the prevalence of constipation in a large cohort of CF patients, using these criteria.

The main etiological factor for constipation in CF patients seems to be an altered intestinal fluid composition, caused by the defective expression of the CFTR protein in the gut.[37,38] In addition it is generally thought that the current aggressive treatment with pancreas supplements would result in more compact feces, thereby contributing to the development of constipation,[39,40] although no correlation between pancreas supplement dose and constipation was found.[41] As in constipation in the general pediatric population, a low fiber intake is thought to contribute to the development of constipation in CF patients. However the only study investigating fiber intake in CF patients did not find a correlation between a low fiber intake and the existence of constipation in CF.[42] Also, a low fluid intake in patients with CF is considered to be an etiological factor for development of constipation in CF.[35] Once again, no evidence is available to support this assumption. In **chapter 5** we therefore also investigated risk factors for the development of constipation in CF patients, concentrating on fiber and fluid intake, as well as the dose of pancreatic supplements.

Besides a careful medical history and thorough physical examination, often abdominal radiographs are performed to aid in the diagnosis of constipation in CF patients. As pointed out above several scoring systems exist to assess radiological the severity of fecal impaction. The diagnostic value, however, of these scoring systems has only been investigated in patients with functional constipation, but not in CF patients. In **chapter 5** we therefore investigated the diagnostic value of abdominal radiography in CF patients with constipation using the Barr and Leech scoring methods.[28,30]

DIETARY FIBER IN THE TREATMENT OF CONSTIPATION

Medical treatment of constipation generally consists of rectal disimpaction followed by maintenance therapy with oral laxatives such as osmotic laxatives (e.g. lactulose and polyethylene glycol (PEG)) or stimulant laxatives (e.g. bisacodyl and senna).[8] The effect of lactulose, a synthetic disaccharide, is based on its fermentation by bacteria in the colon and the resulting production of SCFA. This leads to an increase in osmolality and water influx, giving rise to a higher water content and larger feces volume. Stools, therefore, become softer and stool frequency increases.[43] A similar effect can be obtained through other oligosaccharides, such as galacto-oligosaccharides (GOS), or larger molecules, such as inulin, a fructose polymer.[12,44-46] Like lactulose, GOS are supposedly fermented in the proximal part of the colon, as the peak in breath hydrogen, indicating fermentation, is already obtained within 3 hours after consumption. With larger molecules, such as inulin, peak hydrogen excretion is only seen after 5-6 hours, so fermentation of inulin seems to occur more distally in the colon. When polymer length increases further, as with soy fiber and resistant starch, it is to be expected that fermentation takes even more time, allowing time for propulsion of the fiber mixture into even more distal parts of the colon. Consequently a combination of short and long dietary fiber, i.e. GOS, inulin, resistant starch and soy fiber, is expected to be fermented not only in the cecum but over more segments of the colon. We therefore hypothesized that a combination of different dietary fibers would be more effective than lactulose in the treatment of functional constipation in children. So, in **chapter 6** we investigated whether a combination of these dietary fibers indeed had a more pronounced laxative effect than lactulose on a weight/weight basis in children with constipation.

CONSEQUENCES OF DIETARY FIBER ON MICROBIOTA

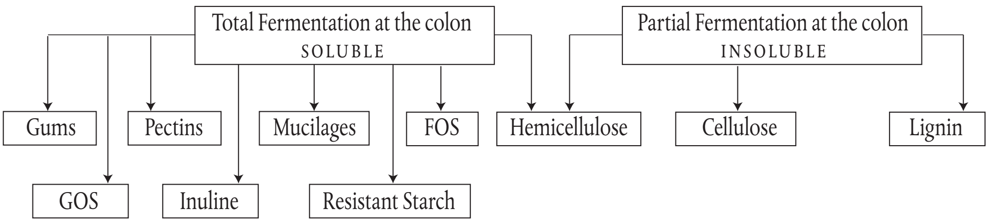
Prebiotics are non-digestible food ingredients that stimulate the growth and/or activity of bacteria in the digestive system and are thought to be beneficial to the general health.[47,48] Inulin and oligofructose, but also lactulose, favor the growth of indigenous Lactobacilli and bifidobacteria[49,50] as is seen with other dietary carbohydrates like resistant starch.[51] Furthermore, *Clostridia* were found in higher numbers in constipated than in non-constipated children, which could be reversed by the administration of prebiotics.[52] *Clostridia* may play a role in the onset of constipation. For example Jonsson *et al.* showed that *Clostridia* produce medium-chain fatty acids that increase colonic water absorption, resulting in constipation.[53] Stimulating the growth of Bifidobacteria at the cost of *Clostridia* through prebiotics could therefore have a potential additional laxative effect. Once again it seems logical that a fiber mixture with a supposedly extended effect, i.e. a combination of GOS, inulin, resistant starch and soy fiber, would be more effective in inducing this shift in microbiota than lactulose. This hypothesis was investigated in **chapter 7**. In this chapter we also describe whether this fiber mixture was superior to lactulose in inducing SCFA production.

Appendix 1

Table 1 The Rome III criteria for children 0-4 years of age[5] and for older children[6]

Diagnostic criteria for functional constipation in **neonate/toddler** are the following: (must include 1 month of *at least* 2 of the following in infants up to 4 years of age.) 1. Two or fewer defecations per week 2. At least 1 episode per week of incontinence after the acquisition of toileting skills 3. History of excessive stool retention 4. History of painful or hard bowel movements 5. Presence of large fecal mass in the rectum 6. History of large-diameter stools that may obstruct the toilet Accompanying symptoms may include irritability, decreased appetite, and/or early satiety. The accompanying symptoms disappear immediately following passage of a large stool.
Diagnostic criteria (criteria fulfilled at least once per week for at least 2 months before diagnosis) for functional constipation in **children** are the following: (must include *2 or more* of the following in a child with a developmental age of *at least* 4 years with insufficient criteria for diagnosis of IBS.) 1. Two or fewer defecations in the toilet per week 2. At least 1 episode of fecal incontinence per week 3. History of retentive posturing or excessive volitional stool retention 4. History of painful or hard bowel movements 5. Presence of a large fecal mass in the rectum 6. History of large diameter stools that may obstruct the toilet

Figure 1 Fiber classification by fermentability degree[54]



References

1. van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol 2006; 101:2401-9.
2. Eleveld SC, Koop HI, de Vries TW, van den Berg PB, de Jong-van den Berg LTW. Laxantiagebruik bij kinderen, reden voor zorg? Wetenschappelijk Platform 2008; 2:175-8.
3. Loening-Baucke V. Constipation in early childhood: patient characteristics, treatment, and longterm follow up. Gut 1993; 34:1400-4.
4. Benninga MA, Buller HA, Staalman CR, et al. Defaecation disorders in children, colonic transit time versus the Barr-score. Eur J Pediatr 1995; 154:277-84.
5. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2006; 130:1519-26.
6. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006; 130:1527-37.
7. Milla PJ. The pathophysiology of constipation. Ann Nestlé [Engl] 2007; 65:55-61.
8. Benninga MA, Voskuijl WP, Taminiau JA. Childhood constipation: is there new light in the tunnel? J Pediatr Gastroenterol Nutr 2004; 39:448-64.
9. AACC. The definition of dietary fiber. Cereal Foods World 2001; 46:112-26.
10. Burkitt DP. Relationship as a clue to causation. Lancet 1970; 2:1237-40.
11. Burkitt DP. Diseases of the alimentary tract and western diets. Pathol Microbiol (Basel) 1973; 39:177-86.
12. Roberfroid M. Dietary fiber, inulin, and oligofructose: a review comparing their physiological effects. Crit Rev Food Sci Nutr 1993; 33:103-48.
13. Jenkins DJ, Jenkins AL, Wolever TM, Rao AV, Thompson LU. Fiber and starchy foods: gut function and implications in disease. Am J Gastroenterol 1986; 81:920-30.
14. Anderson JW, Baird P, Davis RH, Jr., et al. Health benefits of dietary fiber. Nutr Rev 2009; 67:188-205.
15. Graham DY, Moser SE, Estes MK. The effect of bran on bowel function in constipation. Am J Gastroenterol 1982; 77:599-603.
16. de Araújo Sant'Ana AMG, Calcado AC. Constipation in school-aged children at public schools in Rio de Janeiro, Brazil. J Pediatr Gastroenterol Nutr 1999; 29:190-3.
17. Morais MB, Vitolo MR, Aguirre AN, Fagundes-Neto U. Measurement of low dietary fiber intake as a risk factor for chronic constipation in children. J Pediatr Gastroenterol Nutr 1999; 29:132-5.
18. Roma E, Adamidis D, Nikolara R, Constantopoulos A, Messaritakis J. Diet and chronic constipation in children: the role of fiber. J Pediatr Gastroenterol Nutr 1999; 28:169-74.
19. Gomes RC, Maranhao HS, Pedrosa Lde F, Morais MB. [Fiber and nutrients intake in children with chronic constipation]. Arq Gastroenterol 2003; 40:181-7.
20. Ip KS, Lee WT, Chan JS, Young BW. A community-based study of the prevalence of constipation in young children and the role of dietary fibre. Hong Kong Med J 2005; 11:431-6.
21. Mooren GC, van der Plas RN, Bossuyt PM, Taminiau JA, Buller HA. [The relationship between intake of dietary fiber and chronic constipation in children]. Ned Tijdschr Geneeskd 1996; 140:2036-9.

22. Guimaraes EV, Goulart EM, Penna FJ. Dietary fiber intake, stool frequency and colonic transit time in chronic functional constipation in children. Braz J Med Biol Res 2001; 34:1147-53.
23. de Carvalho EB, Vitolo MR, Gama CM, Lopez FA, Taddei JA, de Morais MB. Fiber intake, constipation, and overweight among adolescents living in Sao Paulo City. Nutrition 2006; 22:744-9.
24. Anti M, Pignataro G, Armuzzi A, et al. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. Hepatogastroenterology 1998; 45:727-32.
25. Arnaud MJ. Mild dehydration: a risk factor of constipation? Eur J Clin Nutr 2003; 57 Suppl 2:S88-95.
26. Young RJ, Beerman LE, Vanderhoof JA. Increasing oral fluids in chronic constipation in children. Gastroenterol Nurs 1998; 21:156-61.
27. Chung BD, Parekh U, Sellin JH. Effect of increased fluid intake on stool output in normal healthy volunteers. J Clin Gastroenterol 1999; 28:29-32.
28. Barr RG, Levine MD, Wilkinson RH, Mulvihill D. Chronic and occult stool retention: a clinical tool for its evaluation in school-aged children. Clin Pediatr (Phila) 1979; 18:674, 676, 677-9, passim.
29. Blethyn AJ, Verrier Jones K, Newcombe R, Roberts GM, Jenkins HR. Radiological assessment of constipation. Arch Dis Child 1995; 73:532-3.
30. Leech SC, McHugh K, Sullivan PB. Evaluation of a method of assessing faecal loading on plain abdominal radiographs in children. Pediatr Radiol 1999; 29:255-8.
31. Starreveld JS, Pols MA, Van Wijk HJ, Bogaard JW, Poen H, Smout AJ. The plain abdominal radiograph in the assessment of constipation. Z Gastroenterol 1990; 28:335-8.
32. van den Bosch M, Graafmans D, Nievelstein R, Beek E. Systematic assessment of constipation on plain abdominal radiographs in children. Pediatr Radiol 2006; 36:224-6.
33. de Lorijn F, van Rijn RR, Heijmans J, et al. The Leech method for diagnosing constipation: intra- and interobserver variability and accuracy. Pediatr Radiol 2006; 36:43-9.
34. Jackson CR, Lee RE, Wylie AB, Adams C, Jaffray B. Diagnostic accuracy of the Barr and Blethyn radiological scoring systems for childhood constipation assessed using colonic transit time as the gold standard. Pediatr Radiol 2009; 39:664-7.
35. Rubinstein S, Moss R, Lewiston N. Constipation and meconium ileus equivalent in patients with cystic fibrosis. Pediatrics 1986; 78:473-9.
36. Houwen RH, van der Doef HP, Sermet I, et al. Defining DIOS and Constipation in Cystic Fibrosis With a Multicentre Study on the Incidence, Characteristics, and Treatment of DIOS. J Pediatr Gastroenterol Nutr 2010; 50:38-42.
37. Sinaasappel M. Relationship between intestinal function and chloride secretion in patients with cystic fibrosis. Neth J Med 1992; 41:110-4.
38. Mall M, Kreda SM, Mengos A, et al. The DeltaF508 mutation results in loss of CFTR function and mature protein in native human colon. Gastroenterology 2004; 126: 32-41.
39. Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. Pediatr Pulmonol 2006; 41:35-49.

40. Sinaasappel M, Stern M, Littlewood J, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros 2002; 1:51-75.
41. Baker SS, Borowitz D, Duffy L, Fitzpatrick L, Gyamfi J, Baker RD. Pancreatic enzyme therapy and clinical outcomes in patients with cystic fibrosis. J Pediatr 2005; 146: 189-93.
42. Proesmans M, De Boeck K. Evaluation of dietary fiber intake in Belgian children with cystic fibrosis: is there a link with gastrointestinal complaints? J Pediatr Gastroenterol Nutr 2002; 35:610-4.
43. Schumann C. Medical, nutritional and technological properties of lactulose. An update. Eur J Nutr 2002; 41 Suppl 1:I17-25.
44. Rumessen JJ, Gudmand-Hoyer E. Fructans of chicory: intestinal transport and fermentation of different chain lengths and relation to fructose and sorbitol malabsorption. Am J Clin Nutr 1998; 68:357-64.
45. Cummings JH, Macfarlane GT, Englyst HN. Prebiotic digestion and fermentation. Am J Clin Nutr 2001; 73:415S-420S.
46. Olesen M, Rumessen JJ, Gudmand-Hoyer E. Intestinal transport and fermentation of resistant starch evaluated by the hydrogen breath test. Eur J Clin Nutr 1994; 48:692-701.
47. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 1995; 125:1401-12.
48. Roberfroid M. Prebiotics: the concept revisited. J Nutr 2007; 137:830S-7S.
49. Ballongue J, Schumann C, Quignon P. Effects of lactulose and lactitol on colonic microflora and enzymatic activity. Scand J Gastroenterol Suppl 1997; 222:41-4.
50. Guarner F. Inulin and oligofructose: impact on intestinal diseases and disorders. Br J Nutr 2005; 93 Suppl 1:S61-5.
51. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol 2006; 40:235-43.
52. Zoppi G, Cinquetti M, Luciano A, Benini A, Muner A, Bertazzoni Minelli E. The intestinal ecosystem in chronic functional constipation. Acta Paediatr 1998; 87:836-41.
53. Jonsson G, Midtvedt AC, Norman A, Midtvedt T. Intestinal microbial bile acid transformation in healthy infants. J Pediatr Gastroenterol Nutr 1995; 20:394-402.
54. Escudero Alvarez E, Gonzalez Sanchez P. Dietary fibre. Nutr Hosp 2006; 21 Suppl 2:60-71, 61-72.

CHAPTER 2

The Role of Dietary Fiber in Childhood and Its Applications in Pediatric Gastroenterology

Freddy T.M. Kokke[1], Jan A.J.M. Taminiau[2], and Marc A. Benninga[2]

1. Department of Pediatrics, Rijnstate Hospital Arnhem, and
2. Department of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Centre, Amsterdam, The Netherlands

Nestlé Nutr Workshop Ser Pediatr Program 2005; 56:111-26.

Introduction

Since the 1970s the importance of dietary fiber for human health has been acknowledged and investigated. In the 1970s a relation was found for the first time between constipation, hemorrhoids and fiber-depleted food. The term dietary fiber is familiar to most people, although many do not fully understand the nature of dietary fiber and its role in the diet. Dietary fiber is a normal constituent of healthy food. Both in enteral and oral feeding the presence of fiber is necessary; not only in the face of problems like constipation and encopresis but also for a wide range of other disorders in adults and children such as diabetes mellitus, hypercholesterolemia, high blood pressure and colon cancer. In this chapter we will review the nomenclature, physiological properties and fate of fiber in man and its applications in pediatric gastroenterology.[1] The role of fiber in colorectal neoplasia will not be discussed here.

DEFINITION

Since Hipsley[2] introduced the term dietary fiber in 1953, the exact definition has been controversial as scientists have studied various aspects of the impact of food supply and dietary fibers upon health. Two important questions arise when a definition for dietary fiber is sought: first which polymers should be categorized as dietary fiber? And secondly, can the term 'fiber' be correctly assigned to substances that are not metabolized, and are also not fibrous in chemical structure. Here we will adopt the definition for dietary fiber as put forward by the Dietary Fiber Definition Committee of the American Association of Cereal Chemists:[3] 'Dietary fiber is the edible part of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fiber includes polysaccharides, oligosaccharides, lignin, and associated plant substances.
Dietary fibers promote beneficial physiological effects including laxation, and/or blood cholesterol attenuation and/or blood glucose attenuation.' However, this focus on digestibility has been contested in Europe.[4] There is no proof that digestibility is beneficial. Having a definition on the percentage of non-starch polysaccharide content of natural foods in food tables better serves the potential benefits of these plant cell walls (table 1).

According to the American definition, food components having the above properties can also be taken as dietary fibers such as resistant starch and non-digestible oligosaccharides. Resistant starch is the sum of starch and starch-degradation products not absorbed in the stomach and small intestine. Three types can be separated: RS1, physical non-approachable starch (lentils, beans);

Table 1. Dietary fiber content of foods (g/serving)

Food groups	Food	Serving size	Total dietary fiber
Fruits	Apple, large with skin	1 apple	3.7
	Banana	1 banana	2.8
	Figs, dried	2 figs	4.6
	Orange	1 orange	3.1
	Peach, canned	1/2	1.3
	Pear	1 pear	4.0
	Prunes, dried	5	3.0
	Raisins	1 miniature box (14 g)	0.6
	Strawberries, raw	1 cup, sliced	3.8
Vegetables	Beans, kidney, canned	1/2 cup	4.5
	Broccoli, raw	1/2 cup	1.3
	Brussels sprouts, cooked	1/2 cup	2.0
	Carrots, raw	1/2 cup	1.8
	Celery, raw	1/2 cup	1.0
	Lentils, cooked	1/2cup	7.8
	Lettuce, iceberg	1 cup, shredded	0.8
	Peas, green, canned	1/2 cup	3.5
	Peas, split, cooked	1/2 cup	8.1
	Potatoes, boiled	1/2 cup	1.6
	Spinach, cooked	1/2 cup	2.2
Grains	Bread, white, wheat	1 slice	0.6
	Bread, whole wheat	1 slice	1.9
	Cheerios	1 cup	2.6
	Crackers, graham	2 squares	0.4
	Cream of wheat	1 cup	2.9
	Oat bran muffin	1 muffin	2.6
	Oatmeal, cooked	3/4 cup	3.0
	Raisin bran	1 cup	7.5
	Rice, brown, cooked	1 cup	3.5
	Rye crisp bread	1 wafer	1.7
	Shredded wheat	2 biscuits	5.0
	Wheat bran flakes	3/4 cup	4.6
Other	Apple pie	1 piece	1.9
	Chocolate cake	1 slice	1.8
	Nuts, mixed, dry roast	28 g	2.6
	Yellow cake	1 slice	0.2

Source: USDA Nutrient Database for Standard Reference.

RS2, ungelatinized starch (bananas and potatoes), and RS3, retrograded starch (mainly amylose). These RS fibers are fermented at different rates in the colon and the amount in food is dependable on food production (heating and cooling down).[5,6] Legumes appear to be the single most important source of resistant starch, with as much as 35% of legume starch escaping digestion.[7]

Non-digestible oligosaccharides are naturally present in food, mostly in fruits, vegetables or grains, or produced by biosynthesis from natural sugars or polysaccharides and added to food products because of their nutritional properties.[8] They consist mainly of fructo-oligosaccharides (FOS; one glucose molecule connected to as many as 60 fructose molecules or fructose molecules alone; the bond is of the (2–1) type). In nature these are mainly found in inulin, a mixture of FOS that can be turned into a mixture of FOS of 8 units by hydrolysis. If the fructose molecule is exchanged by a galactose molecule then galacto-oligosaccharides (GOS) occur. The latter are found in soybeans. GOS can also be synthesized from lactulose. FOS and GOS can be obtained quite pure and can be added to food as functional ingredients.

Today both FOS and GOS are also recognized as prebiotics. Prebiotics beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon. Recent data indicated that a prebiotic mixture of FOS and GOS was able to stimulate the development of a microbial flora similar to that of breastfed infants.[9] The authors suggested that prebiotics might play a role as modulators of the postnatal development of the immune system. Furthermore the GOS/FOS mixture significantly increased the number of bifidobacteria and reduced the number of pathogens in term as well as in preterm infants when compared with a group of infants fed a formula without supplement.[10] Stool consistency and fecal pH were also positively affected. These data were confirmed in a double-blind randomized controlled study in infants comparing a FOS-supplemented cereal (0.75 g FOS/cereal) with placebo.[11] The FOS-supplemented cereal was well tolerated and improved stool regularity and consistency.

Table 2. Function of non-fermentable dietary fibers

Non-fermentable dietary fibers are hardly digested in the colon but still have important functions such as:

- Shortening the transit time
- Fluid uptake, feces content increase and softer stools
- Positive effect on gut integrity by trophic effects on colonic mucosa (increase in cell turnover and secretion of gut hormones)

It has to be addressed that the effect of prebiotics is only temporary and strictly related to intake. More research is needed to delineate optimal fiber intake for infants and children <2 years of age, the quantity and types of fiber that would be most appropriate, and if prebiotic supplementation leads to measurable long- and short-term benefits for infants.

THE EFFECT OF DIETARY FIBER ON GASTROINTESTINAL FUNCTION

The effect of dietary fiber on the gastrointestinal tract is explained by its osmotic properties, its stimulating effect on intestinal motility and the water-retaining capacity in the intestine (table 2). The water-retaining capacity of crude fibers is greater than that of fine fibers, and raw fibers have better laxative effects than cooked ones. Insoluble fibers such as cellulose and lignin are minimally degraded by colonic bacteria and thereby retain water, increase fecal bulk and decrease the intestinal transit time.[12] Soluble fibers such as hemicellulose and pectin are largely broken down by the colonic microflora. They have little effect on fecal weight, but they increase fecal volume and soften the stool by increasing the bacterial mass.[13]

Dietary fibers are also able to bind bile salts and fatty acids in the small intestine. They are liberated in the colon after fermentation of fiber and thereby have a laxative effect. Moreover, during fermentation of polysaccharides, gas and short-chain fatty acids (SCFAS) are produced. The predominant acids include acetate, propionate and butyrate. The production of SCFAS through fermentation of oligosaccharides by colonic flora is important because the SCFAS have well-described effects in the intestinal tract. For example, it is largely accepted that butyrate has an essential role in maintaining the metabolism, proliferation and differentiation of the different epithelial cell types.[14] Although, it has to be admitted that, despite its prominent role, the taxonomy, population structure, and dynamics of predominant butyrate-producing bacteria in the human intestinal tract are poorly understood.[15] Current research is focussed on developing new probes such as the 16S rRNA-targeted oligonucleotide probe to investigate the quantitative and qualitative distribution of bacteria in the gastrointestinal tract.[15] However, even experience with this new probe could not detect bacteria in all fecal samples further emphasizing the diversity of the colonic microbiota at the strain level. Future research probably will find inter- individual differences possibly due to diet, genetic constitution or geographic location.

FIBER INTAKE RECOMMENDATIONS

The amount of fiber needed by children varies by the age and weight of the child. The first recommendations about fiber intake were given by the American Academy of Pediatrics published in 1981. The revised recommendations were published in 1994 and 1995 and were based on the age of the child, health benefits such as controlling or preventing obesity, hyperlipidemia, diabetes and colon carcinoma and safety concerns.[16] In both European and American studies children consume amounts of fiber that are inadequate for health promotion and disease prevention.[17-19] Therefore, the American Health Foundation and the American Academy of Pediatrics recommends a minimal intake for children and adolescents 3–20 years of age to be equivalent to the age of the child plus 5 g of dietary fiber/day (age +5). The age +5 g level of fiber intake for children is similar to the American Academy of Pediatrics recommendation (0.5 g/kg/day) up to the age of 10 years, but lower for older adolescents. Furthermore, this recommendation is consistent with current guidelines for adult dietary fiber intake (25–35 g/ day).

The current concern about recommending a high-fiber diet is that it has the potential for reduced energy density, reduced calorie intake, and poor growth, especially in very young infants. Secondary to these factors is the concern that such diets reduce the bioavailability of iron, calcium, magnesium and zinc. However, most investigators nowadays state that when dietary fiber intake is according to the recommendations given above and the dietary fiber is consumed within a proper balanced diet, mineral deficiencies will be of no real concern.[16]

Despite the availability of fiber supplements it is sometimes difficult to achieve the recommended fiber intake. Especially constipated children are often trapped in a vicious circle of poor appetite resulting in poor intake. Moreover, side effects such as intolerance, ineffectiveness and tastelessness of the fiber product may lead to poor compliance of ingesting adequate fiber.

Despite the good intentions of the parents and advice by their primary care physicians, only half of the children receive the recommended amounts of dietary fiber.[17] Further public education with regard to fiber intake is warranted.

CONSTIPATION

When healthy volunteers add fiber to their diet, such as cereal brans, psyllium seed husk, methylcellulose or a mixed high-fiber cereal, stool weight increased and gastrointestinal transit time decreased. The increase in stool weight is caused by the presence of the fiber, by the water content of the fiber and by partial fermentation of the fiber which increases the amount of bacteria in stool. Already in 1927 a publication in the American Journal of Physiology suggested the laxative action of wheat bran.[20] Since then many papers have emerged in which a possible association is suggested between fiber intake and motility disorders. However, the association between fiber intake and constipation is still controversial.[21] To date, there are no large randomized clinical trials that have addressed the role of fiber in the treatment of constipation in otherwise healthy children.

Two case-control studies in children showed a lower fiber intake in constipated children compared to healthy controls.[22,23] Discriminant analysis showed that only fiber intake was independently correlated with constipation.[22] On the other hand, it has been demonstrated that constipated children do generally not consume less fiber than healthy persons and treatment with increased fiber intake did not result in large clinical effects.[18,24-27] Side effects such as intolerance and tastelessness of the fiber product may lead to poor compliance. Moreover, in the studies by Guimaraes et al.[26] and Mooren et al.,[18] no correlation was found between dietary fiber intake and transit time in each of the colonic segments studied. Those children with prolonged colonic transit time did not differ in fiber intake compared with the group of children with normal colonic transit time. Surprisingly, patients with a fiber intake below the recommended levels had a shorter right, left and total colonic transit time (although not reaching statistically significant levels) than those with adequate fiber intakes.

Recently, two small double-blind placebo-controlled trials in 20 neuro- logically impaired constipated children and in 31 otherwise healthy constipated children showed the beneficial effects of glucomannan (a fiber gel polysaccharide from the tubers of the Japanese Konjac plant that has no unpleasant taste or smell) 100 mg/kg body weight (maximum 5 g/day) on defecation frequency, stool consistency, soiling episodes, suppository use and side effects.[25,27] Although the defecation frequency significantly increased after glucomannan intake no correlation between fiber intake and transit time was shown. Tse et al.[28] documented a very low fiber intake of 2 g/day in children (3–17 years) with severe developmental disabilities living in residential institutions. By increasing fiber intake to 17 g/day relief of constipation and a significant reduction in the use of laxatives was achieved. A further increase in fiber intake to 21 g/day showed a further reduction in the use of laxatives. Although the authors suggest continuing to recommend increasing the fiber intake in children with constipation, larger clinical trials are needed to confirm the outcome of these studies. In contrast to the studies by Staiano et al.[27] and Loening Baucke et al.,[25] in a small randomized double-blind clinical trial (n = 30) Motta et al.[29] in Brazil showed no positive effect on treatment outcome and gastrointestinal transit time of soya polysaccharide fiber (10–20 g/day) in children with chronic constipation.

DIARRHEA

Diarrheal disease is one of the two main causes of death in children in developing countries, claiming the lives of more than 3 million children every year.[30] Although standard glucose-based oral rehydration therapy corrects the dehydration caused by cholera, it does not reduce the diarrhea. SCFAs, which are produced in the colon from non-absorbed carbohydrates, enhance sodium absorption. In a beautiful randomized controlled trial Ramakrishna et al.[31] showed that 50 g of high-amylose maize starch, an amylase-resistant starch, per liter of oral rehydration solution significantly lowered diarrheal output compared to the standard oral rehydration therapy in 48 adolescents and adults with cholera. Furthermore, the mean duration of diarrhea was significantly shorter in the amylase-resistant starch group than in the conventional treatment group.

Recently, a significant clinical improvement in diarrhea was described in an 11-year-old patient affected by congenital chloride diarrhea after oral butyrate intake at a dose of 100 mg/kg/day.[32] As already discussed above, SCFAs have a great capacity for stimulating ion and water absorption; they provide energy and induce a trophic effect on both colonic and small bowel mucosa. Moreover, it has been shown that SCFAs, particularly butyrate, are avidly absorbed by the intestinal mucosa and that this process is responsible for the transport of Na^+ and Cl^- through different mechanisms, primarily by the stimulation of an electro-neutral NaCl absorptive mechanism activated by parallel Cl^-/butyrate and Na^+/H^+ exchanger and secondarily by upregulation of the Na^+/H^+ and Cl^-/HCO_3^- exchangers.[33] Finally, butyrate is able to limit Cl^- secretion, inhibiting the Na^+-K^+-$2Cl^-$ co-transporter activity.

CYSTIC FIBROSIS

Patients with cystic fibrosis (CF) often have gastrointestinal complaints. Atypical abdominal pain, constipation, and obstruction from inspissated intestinal contents in the terminal ileum (distal intestinal obstruction syndrome, DIOS) are frequent complications. Slowing of intestinal transit secondary to persistent steatorrhea is believed to play a role. Gavin et al.[34] compared the mean daily intake of fibers in 28 children with CF and compared their data with 28 age-matched controls. The mean daily fiber intake in CF children was significantly lower compared to healthy controls. Furthermore, they found that the mean fiber intake in children with moderate or severe abdominal pain was significantly lower than children with occasional but mild symptoms. The authors suggested that abdominal complaints and DIOS might be secondary to the low dietary fiber content in the diet of patients with CF. In contrast, in Belgian children with CF no relation was found between fiber intake and gastrointestinal complaints or DIOS.[35] The overall intake of fiber was adequate in this group of CF children. Further studies are needed to evaluate the need of dietary fiber in this specific group of patients.

APPENDICITIS IN CHILDREN

It has been postulated that acute appendicitis is a serious disease to emerge with the adoption of fiber-depleted diets. In order to investigate the possible role of fiber in the etiology of acute appendicitis, Adamidis et al.[36] studied 203 consecutive appendectomized children with histologically proved appendicitis and 1,922 controls using the diet history method. This Greek group of researchers found that appendectomized children had a statistically significant lower mean daily intake of fiber (17.4 vs. 20.4 g, $p < 0.001$) including all fiber fractions: cellulose, pentose, exose and lignin. No statistical significant difference was found for energy, protein, carbohydrate and fat intake. Discriminant analysis proved that only cellulose and exose were independently correlated to appendicitis and lower fiber intake was thought to be the cause in 70% of the cases. Their results suggest that low fiber intake might play an important role in the pathogenesis of appendicitis. In contrast, Naaeder and Archampong[37] in their (much smaller) study of 173 children and adults did not find a correlation between dietary fiber intake and appendicitis. It is clear that more studies are needed to clarify the exact role of fibers and its relation with acute appendicitis, but it exemplifies the importance of sufficient fiber intake in children.

IRRITABLE BOWEL SYNDROME

The main aim of dietary intervention in irritable bowel syndrome (IBS) is to manipulate colonic fermentation. High-fiber diets have long been used in adults with IBS but no studies exist in children with IBS. As fibers decrease the whole gut transit time, fiber-enriched diets may be more useful in the subgroup of children with IBS and constipation. Hammonds and Whorwell[38] examined the outcome of 13 trials in which fiber was used to supplement the diet of IBS patients. Only 1 of 6 studies using bran reported an improvement in symptoms. The outcome of their survey was that the role of fibers is limited to those patients whose problem is predominantly constipation.

In patients with IBS and symptoms such as bloating, diarrhea and flatulence, low fiber or exclusion diets are the treatment of choice. Response rates of between 50 and 70% have been reported.[39]

CONCLUSION

Fiber likely plays a valuable role both in the prevention and treatment of several gastrointestinal disorders. However, there is an obvious need for large clinical trials to test the efficacy and safety of fiber as a therapeutic agent in the clinical treatment of children with constipation, diarrhea, IBS and acute appendicitis.

References

1. Saperstein S, Spiller GA: Dietary fiber. Am J Dis Child 1978;132:657–60.
2. Hipsley EH: Dietary 'fibre' and pregnancy toxaemia. Br Med J 1953;16:420–22.
3. Report of the Dietary Fiber Definition Committee: The definition of dietary fiber. Cereal Foods World 2001;46:112–6.
4. Goodlad RA, Englyst HN: Redefining dietary fibre: Potentially a recipe for disaster. Lancet 2001;358:1833–4.
5. Trowell H: Dietary fiber definitions. Am J Clin Nutr 1988;48:1079–80.
6. Schrezenmeir J, de Vrese M: Probiotics, prebiotics, and synbiotics – Approaching a definition. Am J Clin Nutr. 2001;73(suppl):361S–4S.
7. Marlett JA: Comparisons of dietary fiber and selected nutrient compositions of oat and other grain fractions; in Wood PJ (ed): Oat Bran. American Association of Cereal Chemists, St Paul, Minn, 1989, pp 49–82.
8. Delzenne NM: Oligosaccharides: State of the art. Proc Nutr Soc 2003;62:177–82.
9. Boehm G, Jelinek J, Stahl B, et al: Prebiotics in infant formulas. J Clin Gastroenterol. 2004;38(suppl):S76–9.
10. Moro GE, Mosca F, Miniello V, et al: Effects of a new mixture of prebiotics on faecal flora and stools in term infants. Acta Paediatr 2003;91(suppl):77–9.
11. Moore N, Chao C, Yang LP, et al: Effects of fructo-oligosaccharide-supplemented infant cereal: a double-blind, randomized trial. Br J Nutr 2003;90:581–7.
12. Jenkins DJ, Jenkins AL, Wolever TM, et al: Fiber and starchy foods: Gut function and implica- tions in disease. Am J Gastroenterol 1986;81:920–30.
13. Roberfroid M: Dietary fiber, inulin, and oligofructose: A review comparing their physiological effects. Crit Rev Food Sci Nutr 1993;33:103–48.
14. Blottière HM, Champ M, Hoebler C, et al: Production and digestive effects of short-chain fatty acids: From production towards gastrointestinal physiological effects. Sci Aliments 1999;19:269–90.
15. Hold GL, Schwiertz A, Aminov RI, et al: Oligonucleotide probes that detect quantitatively sig- nificant groups of butyrate-producing bacteria in human feces. Appl Environ Microbiol 2003;69:4320–4.
16. Williams CL, Bollella M, Wynder EL: A new recommendation for dietary fiber in childhood Pediatrics 1995;96:985–8.
17. Saldanha LG: Fiber in the diet of US children: Results of national surveys. Pediatrics 1995;96:994–7.
18. Mooren GC, van der Plas RN, Bossuyt PM, et al: The relationship between intake of dietary fiber and chronic constipation in children. Ned Tijdschr Geneeskd 1996;140:2036–9.
19. McClung HJ, Boyne L, Heitlinger L: Constipation and dietary fiber intake in children Pediatrics 1995;96:999–1000.
20. Williams GA: A study of the laxative action of wheat bran. Am J Physiol 1927;83:1–14.
21. Olness K, Tobin J Sr: Chronic constipation in children: can it be managed by diet alone? Postgrad Med 1982;72:149–54.
22. Morais MB, Vitolo MR, Aguirre AN, Fagundes-Neto U: Measurement of low dietary fiber intake as a risk factor for chronic constipation in children. J Pediatr Gastroenterol Nutr 1999;29:132–5.

23. Roma E, Adamidis D, Nikolara R, et al: Diet and chronic constipation in children: The role of fiber. J Pediatr Gastroenterol Nutr 1999;28:169–74.
24. Myo K, Thein WN, Kyaw-Hla S, et al: A prospective study on defecation frequency, stool weight, and consistency. Arch Dis Child 1994;71:311–3.
25. Loening-Baucke V, Miele E, Staiano A: Fiber (glucomannan) is beneficial in the treatment of childhood constipation. Pediatrics 2004;113:e259–64.
26. Guimaraes EV, Goulart EM, Penna FJ: Dietary fiber intake, stool frequency and colonic transit time in chronic functional constipation in children. Braz J Med Biol Res 2001;34:1147–53.
27. Staiano A, Simeone D, Del GE, et al: Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. J Pediatr 2000;136:41–5.
28. Tse PW, Leung SS, Chan T, et al: Dietary fibre intake and constipation in children with severe developmental disabilities. J Paediatr Child Health 2000;36:236–9.
29. Motta MFA, Tahan S, Fagundes-Neto U, Morais MB: Randomized double-blind clinical trial of efficacy of soy polysaccharide fiber in chronic functional constipation in children. J Pediatr Gastroenterol Nutr 2004;39(suppl 1):A026.
30. Bern C, Martines J, de Zoysa I, Glass RI: The magnitude of the global problem of diarrhoeal disease: A ten-year update. Bull World Health Organ 1992;70:705–14.
31. Ramakrishna BS, Venkataraman S, Srinivasan P, et al: Amylase-resistant starch plus oral rehydration solution for cholera. N Engl J Med 2000;342:308–13.
32. Canani RB, Terrin G, Cirillo P, et al: Butyrate as an effective treatment of congenital chloride diarrhea. Gastroenterology 2004;127:630–4.
33. Kunzelmann K, Mall M: Electrolyte transport in the mammalian colon. Mechanism and implications for disease. Physiol Rev 2002;82:245–89.
34. Gavin J, Ellis J, Dewar AL, et al: Dietary fibre and the occurrence of gut symptoms in cystic fibrosis. Arch Dis Child 1997;76:35–7.
35. Proesmans M, De Boeck K: Evaluation of dietary fiber intake in Belgian children with cystic fibrosis: Is there a link with gastrointestinal complaints? J Pediatr Gastroenterol Nutr 2002;35:610–4.
36. Adamidis D, Roma-Giannikou E, Karamolegou K, et al: Fiber intake and childhood appendicitis. Int J Food Sci Nutr 2000;51:153–7.
37. Naaeder SB, Archampong EQ: Acute appendicitis and dietary fibre intake. West Afr J Med 1998;17:264–7.
38. Hammonds R, Whorwell PJ: The role of fibre in IBS. Int J Gastroenterol 1997;00:9–12.
39. Jones VA, McLaughlan P, Shorthouse M, et al: Food intolerance: A major factor in the patho- genesis of irritable bowel syndrome. Lancet 1982;ii:1115–7.

Discussion

DR. AGGETT: Can I ask you to comment because I think one of the biggest problems concerning fibers is that no one knows what they are. You gave us a definition, but when it comes to labeling food, planning diets, giving recommendations, anticipating what the outcomes may be of manipulating so-called fiber intakes, etc., there is very little awareness of the sensitivity of what the components of fiber are actually doing or how one can actually measure them. As far as I know there are something like 3 or 4 different accepted ways to measure fiber for the sake of labeling foods. There is now a standardized approach within the European Union even though it is not necessarily accepted with enthusiasm amongst the constituent members. You gave reference to the ESPGHAN Committee on Nutrition commentary on fibers, and one of the main points behind getting that report drafted was the comments and concerns that I have just expressed. So I was wondering if you would like to comment on the difficulty of defining it and whether or not we should stop using the term fiber and start to be much more discriminatory about the components of fiber and what we think their specific effects might be. That would be better for our development of products and also our practice.

DR. BENNINGA: If, as you, the experts in the field find it very difficult to give a clear answer to this question at this time, I do have not a better suggestion.

DR. AGGETT: I didn't want you to worry about the definition. What I am implying is that perhaps we should forget about the definition; perhaps we should start thinking about the various independent components of this thing we call fiber, the same way we are starting to mature our thoughts about fat. Now fat is totally meaningless to me in many ways, and similarly I think fiber is as well, because as you said one would be far more concerned about resistant starch or a-amylase-resistant starch. In that case is it a native resistant starch or is it a natural state starch that has been cooled and has gone into a glass state and is therefore a-amylase-resistant? Are we talking about some of the sources of gums, all of which have different effects, and really I think understanding these effects and how they arise is going to take us forward far more effectively than just being concerned about fiber. I don't think it helps us characterize the benefits and the problems.

DR. BENNINGA: I am not aware at this moment if there is a diagnosis test or a labo- ratory procedure which gives you insights into which fiber you deal with. I am not aware of this, I don't know if the audience has some suggestions about this.

DR. TAMINIAU: But if you wish to separate it, then the goal might be to say I want this fiber separate because there is evidence, or we as pediatricians should study it in a certain context. Is that what you mean?

DR. AGGETT: Yes, we already have one simple demarcation between soluble and insoluble fibers, and we envisage that insoluble fibers work by water retention per- haps. Let's face it, there is some degradation and fermentation in the colon on some of the insoluble fibers, and then one comes to the soluble fibers which might have different effects. Of course it is in the soluble fibers that many people are looking for due product development, and one of the big discussions recently has been in the area of probiotics. Whether or not one could actually accept, not fiber but inulin for example, as a fiber, that was the first grade discussion. The decision is whether or not one would like to accept inulin as a non-digestible carbohydrate fructo-oligosaccharide in the diet for a specific effect, and it is this functionality that I am really asking about, I am not really looking for a description of the state of the art. There is strategy for organizing our current knowledge to take it forward so we can then think in terms of the intraluminal fate of these various components and then in turn their impact on gas- trointestinal and systemic function.

DR. H. HOEKSTRA: Perhaps I can help a little bit in the discussion. We have defined fermentable and non-fermentable fibers. In a previous discussion we talked about the water-holding properties of the feces.[1] It seems that water-holding properties in non-diarrheal stools are very constant, and normal and hard stools may not differ so much in this respect. If the non-fermentable fibers are responsible for the water- holding properties the net difference in the situation of constipation might be the aspects of the fermentable fibers. So if there is good fermentation that leads to good colonic function, we can explain the studies you presented. In a situation with adequate amounts of non-fermentable fibers more of these sorts of fibers will not be beneficial, but more fermentable fibers such as glucomannan could be helpful. So I would suggest having studies addressing both components, the fermentable and the non-fermentable, in constipation.

DR. BENNINGA: I agree with this opinion. However, if you look at the diet of children then all kinds of fibers will be included. It will therefore be very difficult to strictly separate the soluble and the insoluble, or the fermented or the non-fermented fibers, and truly know which effect of fibers is beneficial in children with constipation.

DR. HERNELL: Isn't that one of the problems, because most of the studies that you showed discussed only dietary fibers. With respect to functional outcomes you don't really know exactly what people have been comparing because, as Dr. Aggett says, dietary fiber is not well defined. I think we need to agree on some kind of definition. If we want to compare functional outcomes we must really know what type of fiber we are comparing.

DR. BENNINGA: I agree. But the same is true if you look at the studies in adults with a lower risk of developing colonic carcinoma. It is not known if this is caused by the effect of fibers or that other supplements are important in decreasing the risk of colorectal cancer.

DR. LEATHWOOD: Once you have defined fiber to your own satisfaction and identified the effects, the next problem is to communicate this information to consumers. We must not forget that many consumers attribute all sorts of benefits to fiber, and these do not necessarily bear much relation to expert opinions about the benefits of fiber.

DR. BENNINGA: Yes, but it gives rise to the same discussion. As we really don't know how to define fibers and how to divide them, it makes it difficult to explain.

DR. HERNELL: When you give a recommendation as you did, age plus 5 g, one may wonder if the same type of fibers is applicable to all ages, or if different types of dietary fibers should be recommended for different age groups?

DR. BENNINGA: I haven't really thought about it. If you look at children's diets, 75% of the fiber intake is non-soluble whereas only 25% is soluble, so perhaps we have to make this recommendation.

DR. HERNELL: I was thinking about breast milk. 20 or 15 years ago, we used to say that infants should not have too much fiber in their diets because they were not used to it, there is no dietary fiber in breast milk. Then we changed the definition of dietary fiber to non-digestible carbohydrates and all of a sudden there are a substantial amount of dietary fiber (oligosaccharides) in breast milk. So I mean it is perhaps time to question what type of dietary fiber should be recommended for what age group? May be we shouldn't recommend dietary fiber, we should recommend how much fruits and vegetables children in various age groups should eat.

DR. TAMINIAU: Is there any concern about micronutrients, with regard to age or risk?

DR. AGGETT: I don't think there is. As Dr. Benninga pointed out, the opinion is that if one eats fiber at a reasonable level then there will not be a negative impact on nutrition in general and particularly on the minerals. Now clearly some of the issues arising from mineral availability relates to perceptions that there may be ionic binding between cations and fibers that would limit their availability. But interestingly I don't think there are really any good studies over an extended period to substantiate if there is a negative impact of so-called high-fiber intakes. This has mainly been done in vegetarians, there is clearly a lot of adaptive capacity to acquire the calcium, magnesium, iron and zinc that is necessary. Perhaps when there is so much non-digestible carbohydrate that it displaces other items from the diet then there may be a negative impact, but that would apply to all nutrients and not just minerals.

DR. SCHMITZ: Is it a question of definition to explain the contrast between two of the results you presented, the first one being the nice slide in which the increase in the amount of ingested fiber increased stool weight, and the following slide in which you showed that in the pediatric age there is nearly no difference between the ingestion of fibers in constipated and non-constipated children? Otherwise this contrast is difficult to understand.

DR. BENNINGA: Adding more fibers to the diet is the first-line treatment in adults with constipation. More importantly it works in these patients. However in children with constipation, we don't find beneficial effects of fibers on defecation frequency and stool consistency. Children don't often take the fiber supplements because of the nasty taste. A solution might be the use of glucomannan.

DR. TAMINIAU: You presented 14 g in Brazil, 11 g in Greece, and Holland 7 g. Is there a difference in fiber intake in the world?

DR. BENNINGA: Although there are not many papers describing the amount of fiber ingestion, I think that there will not be a large difference between the Western world and South America. Even in higher socioeconomic class families, the same intake of fiber was found.

DR. TAMINIAU: So is there any epidemiology in fiber content in the world you didn't mention?

DR. BENNINGA: There are not very many papers talking about fiber ingestion. But if you estimate there is not a big difference between the Western world and South America; in all countries there is a decreased intake of fibers, even when looking at higher socioeconomic class families, and it didn't make any difference when they looked at fiber intake. So I think Holland is not very different from the rest of the world.

DR. H. HOEKSTRA: I would like to confront you with one of your statements with respect to the effect of fibers on constipation. You said that there is a need for larger studies, but in my opinion a large study is not always better than a small study. So I would like to ask you whether the negative studies were underpowered? My second question is: if you try to make a conclusion from several studies, you almost always end up with inconsistencies. The solution to that is that the studies are compared with respect to the patients, whether they are the patients that are being treated as well, or looking at the methodology. Are the pro studies better than the con studies?

DR. BENNINGA: You pointed out the difficulties in studying constipation. I think that you have to ask Dr. Staiano if she thinks that her study was underpowered. Of course you are correct that we don't always need higher power studies, but in the majority of studies we did we always needed to have only a small beneficial effect, at least 150 patients, so I think 20 is perhaps not enough, but we will hear it from Dr. Staiano in a few moments. Another very difficult point in studying children with constipation is that there is not one definition for constipation. As I showed you in the Brazilian and Greek studies, I really think that the definition of constipation was not good. Therefore I think it is important that in a few weeks new criteria will be made and if we all stick to these criteria we might get the same population and more insight into the pathophysiology and how to treat these patients. I think that is the main weakness of our studies.

DR. KLEINMAN: Do you think that there is some value in separating prevention from treatment when talking about constipation, given that for the most part when we treat constipation now most recommend increased dietary fibers? The compliance is so poor, however, that most of us now turn to a synthetic polyethylene glycol mixture that can be used very effectively often without additional stimulant laxatives. In discussing this, clearly if you are talking about a population-based approached, changing the diet makes a lot of sense, and yet if you are talking about treatment so many other things impact on successful resolution of constipation, particularly when it has been in place for months or years, that increased dietary fiber alone is likely to have less benefit there.

DR. BENNINGA: I think it is a good point to talk about prevention in these children. Future studies will hopefully answer your question if early adjustments of prebiotics, such as FOS and GOS, will cause less constipation.

DR. SINAASAPPEL: To continue this point: is it possible to identify risk groups that are prone to constipation? When prophylactic measures are needed, I think it is wiser to concentrate on these risk groups and not on the whole population.

DR. BENNINGA: That is a very good question too. It will be difficult however to identify risk groups. We know now that 30% of the children with constipation have a first- or second-degree relative who has constipation too. It might be useful to follow the children of parents who had childhood constipation themselves.

DR. VERLOOVE: Can I come back to this prevention issue? Most of you from the Netherlands are aware that a nutritional analysis of Dutch children was done. From that, as I remember it, it was clear that the consumption of fiber-containing foods by children in the Netherlands is tremendously low. So if you could change the dietary habits, as you showed last week during the pediatric conference in the Netherlands, by letting them eat full-fiber pasta, if you get children to eat that kind of pasta and brown bread and fruits and vegetables, I think 50% of the problem would be solved, and you don't need to identify risk groups and give them additional fibers whatsoever. But that should be our first concern in my opinion.

DR. BENNINGA: I think this is wishful thinking. As I stated before, in 1995 a conference was held in the US on adding fibers to supplements for children in the US. Disappointingly the outcome of this conference was that the fiber and vitamin intake didn't change despite an enormous advertising campaign and information to the public.

DR. VERLOOVE: You are probably right. Tomorrow morning we are going to talk about junk food, so I won't say anything more but I will come back to it tomorrow.

DR. H. HOEKSTRA: Not looking at your slide, it must not be too difficult for industry to make a fiber-enriched product that tastes good to children.

DR. BENNINGA: You mean that it won't be difficult because there are of course already fiber-enriched supplements, but are you talking about healthy or are you talking about constipated patients?

DR. H. HOEKSTRA: We can talk about all categories, but if you talk about constipated patients then it must be possible. I mean children don't always like fruits, they want other things that taste better in their opinion, and it has to be possible to make something that tastes sweet and contains fibers. Why can't we make that? It is not that difficult.

DR. BENNINGA: I will ask the people from Nestlé.

MRS. GAILING: We are following the recommendation of age plus 5 for the toddlers after 1 year of age, but between 6 months and 1 year it is more difficult to make a precise recommendation. I was just doing the calculation in our infant cereal. For stage 1 globally we have two portions, so between 4–6 and 6–8 months, we have about 2.5 g fiber from infant cereal. So if some fruits in jars are added in which there are also fibers and vegetables, particularly carrots, the intake of fibers could be fulfilled. But we don't know if age plus 5 must also be followed between 6 and 12 months.

DR. BENNINGA: Was it is not difficult to make the product?

MRS. GAILING: No, it is not difficult to make the product, but a difference must be made between cellulose and other dietary fibers because it is probably less palatable when cellulose is increased.

DR. H. HOEKSTRA: But I think you have to make something like a candy bar, some- thing that taste like Bounty or Mars and contains fibers. You really have to adjust it to the tastes of the children.

DR. VERLOOVE: Let's wait until tomorrow with that discussion.

DR. CAROLI: It seems to me that we are going to medicalize our children too much, because if we are going to make a candy bar with vegetables I know many more tastier foods that can be useful in this respect. In your slides I did not see the length of the observation in the treatment of constipation with vegetables and fruits, nor the age of the subjects. So I would like to know your opinion on the minimal time of using normal and tasty food before going on to using a laxative, because children comply differently to adults. In my opinion miracles do not appear all the time, so we probably need time to get good results using correct food.

DR. BENNINGA: I can't answer, I don't know what the best time to start with laxatives is. As you know lactulose is also a non-digestible carbohydrate and we start it immediately if we think that the child needs it, and that can be already after 10 days or even earlier. I never wait in starting laxative if the child really has problems. It is also very difficult to define what constipation is because I think that is what you mean, how long can you wait until the defecation problems resolve, and I can't answer this question. If the child has pain during defecation, if he cries around the defecation and the defecation frequency is less than 3 times/week, then I think you have a good reason to start laxatives. We know now from studies by Dr. Staiano and our group that if you start treating these constipated infants early, then they tend to do better in life than children who started treatment later.

DR. TAMINIAU: Dr. Staiano can you comment and then can you comment on what Dr. Benninga published on glucomannan. There is a limit of 5, why didn't you give more? Perhaps Dr. Kneepkens can also comment because he worked with glucomannan in the stomach to delay emptying.

DR. STAIANO: I want to say that we should make a difference between the efficacy of fibers in normal subjects and in constipated children. In adults, fibers have a very good efficacy on stool habit, even in constipated adults because one of the effects of the fibers is to increase stool size which determines the distention of the lumen and this evokes peristalsis. We know that in most constipated adults the problem is delayed transit in the proximal colonic segments. In contrast, in children constipation is mainly due to delayed transit in the rectum.[1] The effect of fibers in rectal constipation is different than in patients with a delay in the more proximal segments of the colon. In fact, it has been reported that an increased amount of fibers in adults with rectal dyschexia, i.e. a rectal delay in the transit time just at the level of the rectum, may worsen the constipation due to the difficulty in the elimination of stools with an increased size. So far, in children with functional constipation, if we increase the amount of fibers too much we could create a further problem in the elimination of this larger stool. In the past, we evaluated the efficacy of glucomannan, a soluble fiber, as a treatment for chronic constipation in children with severe brain damage.[2] The study demonstrated that glucomannan has a beneficial effect only on bowel habits but not on gastrointestinal transit time. The increased bowel frequency despite the prolonged transit time, could be explained by the frequent passage of small amounts of less consistent feces, without improvement in the progression of the intestinal contents. So, in these patients, severe damage to central structures could be responsible for the disregulation of normal content progression through the large bowel. Differently, in the last study done by Loening-Baucke et al.,[3] the effect of glucomannan and placebo was evaluated in 31 children with chronic functional constipation with and without encopresis, recruited from the Pediatric Clinics of the University of Iowa and the University of Naples. We used glucomannan at a dose of 100 mg/kg body weight daily, maximal 5 g/day, just to be sure not to give too much fiber so as to have an opposite effect. Also in these children we found fiber to be beneficial in the treatment of con- stipation with and without encopresis, with an improvement in bowel habits. Symptomatic children already on laxatives still benefit from the addition of fibers. In conclusion an adequate amount of fiber in the diet is certainly very important for the treatment of constipated children, however I believe that we have to be careful in advising large amounts of fibers because in children there is a delay in the rectum and sometimes fibers could worsen the condition.

DR. KNEEPKENS: I don't have much to add to that, but we have to realize that gluco- mannan is not very much different from galactomannan, present in carob gum, that we use in the treatment of regurgitation in infants, and we know that it also influences the stools of the children. Both galactomannan and glucomannan are fermented completely in the proximal colon, but at a rate which is a lot lower than, for instance, lactulose. It may act as something in between lactulose and non-fermentable fiber and have an influence especially on bacterial growth, bacterial mass, and fecal mass. So there may be a possibility for galactomannan and glucomannan to be used in constipation, but I don't think they are better than what we use at the moment, microgal, which also increases fecal weight.

DR. BENNINGA: I totally agree.

DR. TAMINIAU: I would like to reemphasize what Dr. Benninga showed about the digestible fibers and that digestion is not solid and water absorption but also the energy absorption. Adults can absorb about 80–100 g, it is 400 kcal in the colon and also medium-chain triglycerides, if they arrive in the colon, they are digested and about 100 g of medium-chain triglycerides can be put into short chains and absorbed, so there is about 400–800 cal. Then there are the beautiful studies by Diamond on maximal absorption in animals. He used a python as a model and let him eat a sheep to study the upregulation of absorption, what the maximum is. He showed that our nutrient-absorbed carriers such as the glucose sodium carrier are not upregulated in the human because we probably have so much reserve capacity in the colon, also in the newborn and the premature, up to 800 cal. So it is really the digestive organ that is very important because we don't upregulate in the small bowel. I would like to thank you all for participating. I would like to thank Dr. Staiano for talking about motility, Dr. Bueno for going from motility to transport and pathophysiology, Dr. Benninga for addressing fiber with all its problems, and Dr. Aggett for defining the problems we have with the definition.

References

1. Corazziari E, Cucchiara S, Staiano A, et al: Gastrointestinal transit time, frequency of defecation, and anorectal manometry in healthy and constipated children. J Pediatr 1985;106:379–82.
2. Staiano A, Simeone D, Del Giudice E, et al: Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. J Pediatr 2000;136:41–5.
3. Loening-Baucke V, Miele E, Staiano A: Fiber (glucomannan) is beneficial in the treatment of childhood constipation. Pediatrics 2004;113:e259–64.

CHAPTER 3

Dietary fiber and fluid intake in constipated and healthy children

Freddy TM Kokke MD[1], Jan LL Kimpen MD, PhD[1],
Marc A Benninga MD, PhD[2] and Roderick HJ Houwen MD, PhD[1]

1. Departments of Pediatric Gastroenterology and Pediatrics - Wilhelmina Children's Hospital - University Medical Center Utrecht, the Netherlands
2. Department of Pediatric Gastroenterology – Emma Children's Hospital / Academic Medical Center - Amsterdam, the Netherlands

(not published)

Abstract

BACKGROUND/OBJECTIVES

Low dietary fiber and fluid intake are often considered as important causative factors in the development of childhood constipation. However, studies investigating this relation have been contradictory so far. We therefore investigated dietary fiber and fluid intake in constipated and healthy children.

SUBJECTS/METHODS

In a cohort of patients with childhood constipation referred to a non-academic hospital in the Netherlands, food intake was recorded using a standardized 3-day food diary. Dietary fiber, fluid and energy intake were calculated and compared with the intake of a large healthy cohort of children. In addition dietary fiber intake was compared with the Dutch Guideline.

RESULTS

Ninety-one constipated children completed the food diary. Dietary fiber intake expressed in gram per day was significantly lower in the constipated children. However, when expressed in gram per megajoule energy intake per day, the amount was similar in constipated and healthy controls. Water intake expressed in gram per day was significantly lower in constipated children. However, when expressed in gram per kilogram body weight per day or gram per megajoule energy intake per day, fluid consumption was similar. Neither the constipated nor the healthy controls did meet Dutch recommendations for dietary fiber intake.

CONCLUSIONS

Absolute intake of dietary fiber and fluid are significantly lower in constipated children. However when related to the amount of energy consumed no difference is found. These different outcomes, depending on the unit used, could be an explanation for the contradictory results found in literature.

Keywords: Childhood Constipation, Dietary Fiber, Fluid Intake.

Introduction

Childhood constipation is a common problem with a prevalence in the general population ranging from 0.7 to 29.6%.[1] It seems to be a multi-factorial disease with low dietary fiber and inadequate fluid intake considered to be major contributing factors.[2,3] However, results of studies done so far are not consistent with respect to the association between low daily fiber intake and constipation in childhood. Some authors found an association between low fiber intake and the existence of constipation in otherwise healthy children and adolescents[4-7] whereas others could not confirm this.[8-10]

Studies that looked at the daily intake of water or fluid in constipated children are scarce. In a recent study in children aged 7-10 years old, children consuming less fluid were more likely to be constipated.[7]

The rationale for considering dietary fiber and fluid intake as important factors in the etiology of (childhood) constipation relates to its properties: dietary fiber has water-retaining capacity (although this capacity may be relatively low),[11] and stimulates gastrointestinal motility by increasing feces volume, bacterial growth, and bacterial degradation products and should thus facilitate defecation.[2,12,13] However, others question the importance of low dietary fiber intake in the development of constipation.[14,15]

The purpose of the this study was therefore to assess differences in dietary fiber and fluid intake between a group of Dutch constipated children aged 1 to 12 years and a cohort of healthy Dutch children of the same age studied by the Dutch National Food Consumption Survey (DNFCS).

Subjects and Methods

PATIENTS

Between September 2001 and April 2004 all constipated children (aged 1 to 12 years), referred by general practitioners and public health physicians to the outpatient pediatric clinic of a local hospital in Arnhem, The Netherlands, were eligible for inclusion in this study. Children aged less than 5 years had to have infrequent, painful defecation with often hard stools, sometimes in large quantities, with straining. Children aged 5 years or more had to fulfill at least 2 out of 4 criteria of childhood constipation: stool frequency less than 3 times per week, fecal incontinence 2 or more times per week, periodic passage of very large amounts of stool at least once every 7-30 days, or a palpable abdominal or rectal mass.[16]

Children with organic causes of defecation disorders, including Hirschsprung's disease, spina bifida occulta, hypothyroidism or other metabolic or renal abnormalities, mental retardation, and children using drugs influencing gastrointestinal function other than laxatives as well as children having used lactulose or other laxatives, pre- or probiotics, or antibiotics in the 4 weeks before the first visit were excluded from the study. Written informed consent was obtained before the start of the study. The study protocol was approved by the medical ethics committee of the hospital.

STUDY DESIGN AND STUDY OUTLINE

After informed consent a standardized history was taken and a standardized physical examination done at the outpatient clinic. Food intake was recorded in the first week after the first outpatient clinic visit using a standardized 3-day food diary.

DUTCH NATIONAL FOOD CONSUMPTION SURVEY (DNFCS)

As part of the Dutch dietary monitoring system, a food consumption survey in a large representative sample of Dutch inhabitants is performed on a regular basis (*http://www.zuivelengezondheid.nl/tno/Index/Deel-2/Start_tekst.htm*). The results from this survey were used in the current study. Participants (cohort 1997-1998) in the DNFCS consisted of a representative panel of families (with female/male housekeeper younger than 75 years) from the Netherlands. Persons living in institutions, persons not fluently speaking Dutch and children younger than 1 year old were excluded. A two-day food diary (two consecutive days) was used for collection of dietary data. Anthropometric data (weight and height) were recorded as well as consumption of groups of food, the intake of energy and nutrients and, finally, the contribution of food groups (percentage) to the intake of nutrients. The data obtained from children aged 1 to 12 years were used in this study.

PRIMARY OUTCOME PARAMETERS

The primary outcome parameters were daily mean energy intake, dietary fiber intake, water intake and weight. In both groups these parameters were calculated in the same manner, with water intake including water from all beverages as well as the moisture in food. In addition dietary fiber intake of constipated and healthy children was compared with the Dutch Guideline for Dietary Fiber Intake (Health Council of the Netherlands, 2006).

STATISTICS

Dietary intake in the 1-12 year old children in the DNFCS was initially represented in 4 age groups (1-4, 4-7, 7-10, 10-12 yrs), but data were converted to one reference group for boys aged 1-12 years and one for girls 1-12 years according to Portney and Watkins.[17]

The one-sample T test was performed to compare the mean daily dietary fiber intake and mean water intake of constipated children with children from the DNFCS, and to compare daily dietary fiber intake in the constipated children with recommendations from the Dutch Guideline for Dietary Fiber Intake. Statistical analyses were performed using SPSS-PC v.17.0 (SPSS Inc, Chicago, Ill) software. A p-value of <0.05 was considered statistically significant.

Results

GROUP CHARACTERISTICS

A total of 147 patients were eligible for this study. Twelve patients and their caregivers received information but chose not to participate. Of these 135 patients, 91 (67%) had correctly completed the 3-day food consumption diary. More females than males (51 vs. 40) with constipation entered the study, but this finding was not statistically significant. Median age was 5 years.

ENERGY, DIETARY FIBER, AND FLUID INTAKE OF CONSTIPATED CHILDREN COMPARED TO CHILDREN FROM THE DNFCS

Intake of energy, dietary fiber, and water in the children from the DNFCS and the constipated children are given in the table. Interestingly the intake of energy (MJ/day) was significantly lower in constipated children ($p<0.01$ in both boys and girls) compared to the healthy controls.

Table 1 Comparison of dietary fiber and water intake between children from the DNFCS and constipated children. Data are given as mean ± SD.

Boys (1-12 years)	DNFCS	Constipated children	
number of boys	*489*	*40*	P
Energy (MJ/d)	7.6 ± 2.2	6.0 ± 1.4	<0.01
Fiber (g/d)	15.2 ± 5.6	12.3 ± 4.1	<0.01
Fiber (g/kg/d)	0.68 ± 0.26	0.58 ± 0.26	0.02
Fiber (g/MJ/d)	2.02 ± 0.60	2.07 ± 0.57	0.48
Water (g/d)	1312 ± 388	1093 ± 251	<0.01
Water (g/kg/d)	59 ± 23	56 ± 23	0.35
Water (g/MJ/d)	2.0 ± 0.02	1.9 ± 0.05	0.15
Weight (kg)	24.4 ± 9.3	23.4 ± 9.5	0.69
Girls (1-12 Years)	DNFCS	Constipated children	
number of girls	*515*	*51*	P
Energy (MJ/d)	7.0 ± 2.0	6.0 ± 1.1	<0.01
Fiber (g/d)	14.0 ± 5.2	12.8 ± 3.8	0.03
Fiber (g/kg/d)	0.61 ± 0.26	0.59 ± 0.17	0.53
Fiber (g/MJ/d)	2.00 ± 0.67	2.1 ± 0.53	0.11
Water (g/d)	1242 ± 332	1126 ± 283	<0.01
Water (g/kg/d)	55 ± 22	55 ± 18	0.99
Water (g/MJ/d)	2.0 ± 0.02	1.9 ± 0.04	0.27
Weight (kg)	25.3 ± 9.8	23.0 ± 8.1	0.10

g/d=gram/day, g/kg/d=grams per kilogram of bodyweight per day,
(g)/MJ/d=(gram) per mega-joule energy intake per day

Also dietary fiber intake expressed in grams per day was significantly lower in constipated children (p<0.01 in boys and p=0.03 in girls). When expressed as grams per kilogram bodyweight per day, fiber intake was still significantly lower in boys (p=0.02), but almost identical in girls (p=0.53). However, when corrected for energy intake (dietary fiber density expressed in grams per megajoule per day), the dietary fiber intake was comparable between the constipated and the healthy control group (p=0.48 in boys and p=0.11 in girls).

The absolute water intake was lower in constipated children (p<0.01 for both boys and girls). However, when corrected for body weight (grams per kilogram body weight per day), water intake was comparable between both groups (p=0.35 in boys and p=0.99 in girls). A similar result was obtained when expressed as g/MJ/day (p=0.15 in boys and p= 0.27 in girls).

DIETARY FIBER INTAKE OF CONSTIPATED AND NON-CONSTIPATED CHILDREN COMPARED TO THE DUTCH GUIDELINE

Recommended dietary fiber intake according to the Dutch Guidelines (Health Council of the Netherlands, 2006) is 15 gram per day for children under 4 years of age, 20 gram per day for girls and 25 gram for boys aged 4-8 years and, finally, 25 gram per day for girls and 30 gram for boys aged 9-12 years. None of the constipated children had a dietary fiber intake that came even close, while group average was roughly two thirds of the recommended intake in all girls as well as the youngest boys and just half in the older boys.

Similarly children in the DNFCS remained far from recommendations for fiber intake (data not shown).

Discussion

Low dietary fiber and low fluid intake are considered to be important causative factors in childhood constipation. This study shows that fiber and fluid intake are indeed significantly lower in constipated children. Also children with chronic constipation, both boys and girls, have a lower energy intake than control subjects, as was described earlier.[8,19] It is unclear, however, whether a lower energy intake is the result of constipation, through a reduction of appetite, or whether this difference was already present before the children became symptomatic. Nevertheless, this difference in energy intake resulted in a fiber and fluid intake comparable between constipated children and non-constipated children when expressed as gram/MJ of energy intake.

Our study confirms the lower absolute fiber intake in children with constipation, as was described in numerous studies.[4,5,7,19-21] However it is questionable whether expressing absolute fiber intake is the correct approach. Fiber exerts its effects, mainly increasing feces volume and softening stools, by water retention. Obviously in this respect the volume of the chyme, and thus the amount of ingested food, is important. Therefore it was suggested that fiber intake should be studied in relation to the median energy intake.[22] Consequently, we correlated fiber intake with the dietary energy intake (dietary fiber density) and indeed were not able to show a difference between constipated children and controls with respect to fiber intake. These results are in accordance with studies in constipated adolescents[23] and constipated children.[8] Only in one population based survey a significant difference ($p<0.001$) between constipated and non-constipated children with respect to dietary fiber density was found.[19]

Low fluid intake is also often mentioned as an etiologic factor in childhood constipation.[24] Indeed absolute fluid intake was lower in our group of constipated children. However when expressed as g/kg/day or g/MJ/day no difference was found, as was also described by Murakami.[23] In addition in a study by Young in constipated children aged 2 to 12 years an increase in water intake to 150% of their individual baseline (measured during the first week) did not result in changes in stool frequency, consistency, and difficulty to pass stools.[25] Similar results were found in adults.[26] This suggests that an increase in water intake plays no important role in the treatment of childhood constipation.

In accordance with earlier findings, the daily intake of fibers in both constipated and non-constipated children was lower than suggested by international experts.[5,10,27-32] At this moment guidelines, both for adults and children, advice an intake of fiber of 3.4g/MJ (=14g/1000kcal).[22] In some countries, such as The Netherlands, for the younger age groups the recommendations are adjusted downwards because children rarely or never consume 3.4 grams of dietary fiber per megajoule. In fact such a recommendation could jeopardize the energy intake especially in the youngest children.[18] Consequently, although the rationale for recommending a high dietary fiber intake is understandable, this guideline seems not realistic, at least in children.

Conclusion

The absolute daily intake of dietary fiber and fluid is lower in constipated children than in controls. However, when corrected for energy intake, fiber and fluid consumption were identical in constipated and non-constipated children. These different outcomes, depending on the unit used (g/day or g/MJ/day), could be an explanation for the contradictory results found in literature.

Acknowledgement

We would like to thank Petra Scholtens and Martine Alles of Danone Research for help in study design and execution.

References:

1. van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol 2006; 101:2401-9.
2. Hillemeier C. An overview of the effects of dietary fiber on gastrointestinal transit. Pediatrics 1995; 96:997-9.
3. Arnaud MJ. Mild dehydration: a risk factor of constipation? Eur J Clin Nutr 2003; 57 Suppl 2:S88-95.
4. Morais MB, Vitolo MR, Aguirre AN, Fagundes-Neto U. Measurement of low dietary fiber intake as a risk factor for chronic constipation in children. J Pediatr Gastroenterol Nutr 1999; 29:132-5.
5. Gonlachanvit S, Patcharatrakul T. Causes of idiopathic constipation in Thai patients: associations between the causes and constipation symptoms as defined in the Rome II criteria. J Med Assoc Thai 2004; 87 Suppl 2:S22-8.
6. Inan M, Aydiner CY, Tokuc B, et al. Factors associated with childhood constipation. J Paediatr Child Health 2007; 43:700-6.
7. Jennings A, Davies GJ, Costarelli V, Dettmar PW. Dietary fibre, fluids and physical activity in relation to constipation symptoms in pre-adolescent children. J Child Health Care 2009; 13:116-27.
8. Mooren GC, van der Plas RN, Bossuyt PM, Taminiau JA, Buller HA. [The relationship between intake of dietary fiber and chronic constipation in children]. Ned Tijdschr Geneeskd 1996; 140:2036-9.
9. Guimaraes EV, Goulart EM, Penna FJ. Dietary fiber intake, stool frequency and colonic transit time in chronic functional constipation in children. Braz J Med Biol Res 2001; 34:1147-53.
10. de Carvalho EB, Vitolo MR, Gama CM, Lopez FA, Taddei JA, de Morais MB. Fiber intake, constipation, and overweight among adolescents living in Sao Paulo City. Nutrition 2006; 22:744-9.
11. Monro JA. Faecal bulking efficacy of Australasian breakfast cereals. Asia Pac J Clin Nutr 2002; 11:176-85.
12. Mate-Jimenez J, Gomez-Cedenilla A. Dietary fiber and the gut: action in gastrointestinal disorders. Methods Find Exp Clin Pharmacol 1996; 18 Suppl B:3-6.
13. Maffei HV. Chronic functional constipation. Which supplementary fiber to choose? J Pediatr (Rio J) 2004; 80:167-8.
14. Muller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. Am J Gastroenterol 2005; 100:232-42.
15. Macfarlane S, Macfarlane GT, Cummings JH. Review article: prebiotics in the gastrointestinal tract. Aliment Pharmacol Ther 2006; 24:701-14.
16. Loening-Baucke V. Modulation of abnormal defecation dynamics by biofeedback treatment in chronically constipated children with encopresis. J Pediatr 1990; 116:214-22.
17. Portney LG, Watkins MP. Foundations of Clinical Research: Applications to Practice. Saddle River: Prentice Hall., 2000:373, 379.
18. HCN. Guideline for dietary fibre intake. The Hague: Health Council of the Netherlands, 2006.

19. Roma E, Adamidis D, Nikolara R, Constantopoulos A, Messaritakis J. Diet and chronic constipation in children: the role of fiber. J Pediatr Gastroenterol Nutr 1999; 28:169-74.
20. Gomes RC, Maranhao HS, Pedrosa Lde F, Morais MB. [Fiber and nutrients intake in children with chronic constipation]. Arq Gastroenterol 2003; 40:181-7.
21. Paulo AZ, Amancio OM, de Morais MB, Tabacow KM. Low-dietary fiber intake as a risk factor for recurrent abdominal pain in children. Eur J Clin Nutr 2006.
22. Medicine Io. Chapter 7. Dietary, Functional, and Total Fiber. In: Medicine Io, ed. DRI Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: The National Academies Press, 2005.
23. Murakami K, Sasaki S, Okubo H, Takahashi Y, Hosoi Y, Itabashi M. Association between dietary fiber, water and magnesium intake and functional constipation among young Japanese women. Eur J Clin Nutr 2007; 61:616-22.
24. Leung AK, Chan PY, Cho HY. Constipation in children. Am Fam Physician 1996; 54:611-8, 627.
25. Young RJ, Beerman LE, Vanderhoof JA. Increasing oral fluids in chronic constipation in children. Gastroenterol Nurs 1998; 21:156-61.
26. Chung BD, Parekh U, Sellin JH. Effect of increased fluid intake on stool output in normal healthy volunteers. J Clin Gastroenterol 1999; 28:29-32.
27. McClung HJ, Boyne L, Heitlinger L. Constipation and dietary fiber intake in children. Pediatrics 1995; 96:999-1000.
28. Saldanha LG. Fiber in the diet of US children: results of national surveys. Pediatrics 1995; 96:994-7.
29. Ganji V, Hampl,J.S., Betts, N. Macronutrients, cholesterol, sodium and fiber intakes of 1-10 year old children by age, gender and race. Nutr Res 1998; 18:465-73.
30. Hampl JS, Betts NM, Benes BA. The 'age+5' rule: comparisons of dietary fiber intake among 4- to 10-year-old children. J Am Diet Assoc 1998; 98:1418-23.
31. Kersting M, Sichert-Hellert W, Alexy U, Manz F, Schoch G. Macronutrient intake of 1 to 18 year old German children and adolescents. Z Ernahrungswiss 1998; 37:252-9.
32. Kranz S. Meeting the dietary reference intakes for fiber: sociodemographic characteristics of preschoolers with high fiber intakes. Am J Public Health 2006; 96:1538-41.

CHAPTER 4

Starreveld scoring method in diagnosing pediatric constipation

Freddy TM Kokke[1], Judith Sittig[1], Annemiek de Bruijn[2], Tjeerd Wiersma[2], Rick R van Rijn[3], Jan LL Kimpen[1], Roderick HJ Houwen[1], Kathelijn Fischer[4], Marc A Benninga[5].
JS, AdB, TW and RvR were equally involved.

1. Departments of Pediatric Gastroenterology and Pediatrics, Wilhelmina Children's Hospital, University Medical Center, Utrecht, the Netherlands
2. Department of Radiology, Rijnstate Hospital, Arnhem, the Netherlands
3. Department of Radiology, Emma Children's Hospital / Academic Medical Center, Amsterdam, the Netherlands
4. Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands
5. Department of Pediatric Gastroenterology, Emma Children's Hospital / Academic Medical Center, Amsterdam, the Netherlands

Pediatr Radiol 2010, 40:89-93.

Abstract

BACKGROUND

Four scoring methods exist to assess severity of fecal loading on plain abdominal radiographs in constipated patients (Barr-, Starreveld-, Blethyn- and Leech). So far, the Starreveld score was used only in adult patients.

OBJECTIVE

To determine accuracy and intra- and inter-observer agreement of the Starreveld scoring method in the diagnosis of functional constipation among pediatric patients. In addition, we compared the Starreveld with the Barr scoring method.

MATERIALS AND METHODS

Thirty-four constipated and 34 non-constipated children were included. Abdominal radiographs, obtained before treatment, were rated (Starreveld- and Barr) by 4 observers. A second observation after 4 weeks was done by 3 observers. Cut-off level for the Starreveld score, accuracy as measured by the area under the receiver operator characteristics curve, and inter- and intra-observer agreement were calculated.

RESULTS

Cut-off value for the Starreveld score was 10. AUC for Starreveld score was 0.54 and for Barr score 0.38, indicating poor discriminating power. Inter-observer agreement was 0.49-0.52 (Starreveld) and 0.44 (Barr), which is considered moderate. Intra-observer agreement was 0.52-0.71 (Starreveld) and 0.62- 0.76 (Barr).

CONCLUSION

The Starreveld scoring method to assess fecal loading on a plain abdominal radiograph is of limited value in the diagnosis of childhood constipation.

Keywords: Constipation, Scoring, Abdominal, Radiograph, Child

Introduction

Constipation is a common gastrointestinal complaint in children with a prevalence ranging from 0.7% to 29.6% both in Western and non-Western countries.[1] The symptoms may vary from mild, short-lived to severe chronic constipation with fecal impaction and the involuntary loss of feces. Medical history together with a thorough physical examination is generally sufficient for diagnosis and treatment of most children with constipation. However, many clinicians additionally order a plain abdominal radiograph to assess the presence of retained stool or enlargement of the distal gastrointestinal tract to confirm the diagnosis. Others use this test to evaluate severity of constipation, to evaluate treatment or to convince parents that constipation is the cause of their child's complaints.

To date three scoring systems have been described to assess the severity of fecal loading using an abdominal radiograph in constipated children.[2-4] These papers described a good diagnostic accuracy, with more than 80% of the constipated and non-constipated patients identified correctly. When evaluated by others however, accuracy was lower with an area under the curve (AUC) in the receiver operator characteristics of 0.68 for the Leech method[5] and 0.84 respectively 0.74 for the Barr and Blethyn scoring methods.[6] Another important parameter for the usefulness of these methods, intra-observer and inter-observer agreement, was good to excellent in the original description of these methods.[2-4] Although some investigators could reproduce this for the Leech[7] and Barr score,[8] others could not, finding a much lower intra- and inter observer agreement.[5-6,9]

Three scoring systems were specifically designed for and evaluated in children.[2-4] So far a fourth was only used in adults.[10] As this Starreveld scoring system might be applicable in children as well, we assessed the accuracy of this method in the diagnosis of functional constipation in pediatric patients, as well as its intra- and inter-observer agreement. Furthermore, we compared the performance of the Starreveld score with the Barr score, the oldest and most widely used method for evaluating constipation through a plain abdominal radiograph.

Materials and methods

STUDY POPULATION

Between September 2001 and April 2004 all children with functional constipation, aged 7 to 12 years, referred by general practitioners and public health physicians to the outpatient clinic of a large teaching hospital (Hospital Rijnstate, Arnhem, the Netherlands), were eligible for this study. All children had to fulfill at least 2 out of 4 criteria of constipation: stool frequency < 3 per week, ≥ 2 episodes of fecal incontinence per week, periodic passage of very large amounts of stool at least once every 7-30 days, or a palpable abdominal or rectal mass at physical examination.[11] Medical history, defecation frequency, fecal incontinence frequency, fecal consistency using the Bristol stool form scale[12] and passage of a large amount of feces were recorded in a standardized bowel diary. Children with organic causes of constipation, including Hirschsprung's disease, spina bifida, hypothyroidism, metabolic or renal abnormalities, mental retardation, and children using drugs influencing gastrointestinal function (laxatives or other medications), pre- or probiotics, or antibiotics in the previous 4 weeks before the first visit were excluded from the study.

Controls consisted of a group of children fulfilling the Rome II criteria for functional non-retentive fecal incontinence (FNRFI) and functional abdominal pain (FAP).[13]

Participation in the study was voluntary, and written informed consent was obtained before the start of the study. The medical ethics committee of the hospital approved the protocol.

ABDOMINAL RADIOGRAPHY AND SCORING METHODS

Starreveld-score

The Starreveld-score quantifies the amount of feces in four different bowel segments (ascending colon, transverse colon, descending colon and recto-sigmoid). For each bowel segment fecal stasis is scored as follows: no feces,[1] small amount of feces,[2] moderate fecal stasis,[3] or severe fecal stasis.[4] Therefore, the minimum score is 4 and maximum score is 16. A cut-off point at which the score is considered positive for constipation was not provided by Starreveld in his original paper.[10]

Barr-score

The Barr-score quantifies the amount of feces in four different bowel segments (ascending colon, transverse colon, descending colon and rectum) and also the quality of feces, i.e. granular and rock-like feces. Minimum score is 0 and maximum score is 22. A radiograph is considered positive for constipation, according to the Barr score, when the score is 10 points or more.[2]

Observers

Four observers, a medical student (JS), a resident radiologist in an academic medical center (AdB), a senior radiologist in a large teaching hospital (TW), and a senior pediatric radiologist in an academic center (RvR) independently scored the same abdominal radiographs in random order. The student was trained to apply the two scoring systems by a senior radiologist on two occasions. All observers were blinded to the patient characteristics. To assess intra-observer agreement, all abdominal radiographs were rated a second time by 3 of the 4 observers (JS, AdB, TW) after an interval of 4 weeks.

Statistical analysis

Nonparametric tests were used to compare general characteristics between patients diagnosed with functional constipation and the control group with FNRFI and FAP.

Absence or presence of constipation was compared for different scores in both methods. For the Starreveld score the optimum cut-off value was determined by the lowest Youden index: i.e. sum of false-positives and false-negatives.[14] A cut-off of 10 was used for the Barr scoring method.[2]

A receiver operator characteristic (ROC) plot was constructed for both the Starreveld and Barr scoring method. The area under the ROC curve (AUC) was used as a single indicator of diagnostic accuracy. The AUC can be interpreted as the probability that a randomly chosen case with functional constipation has a higher Starreveld or Barr score than a randomly chosen control (FNRFI or FAP). The perfect test has an AUC of 1.

Inter-observer agreement was assessed by two-way intra-class correlation coefficient (ICC) for ordinal data on the first observation session for total Starreveld- and Barr- scores comparing the data from the 4 observers. Kappa and ICC were classified according to arbitrary cut-off values as poor (<0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80) or very good (0.81-1.00) agreement.

Intra-observer agreement was calculated using Cohen's K statistics for ordinal data comparing the data of the first and second observation from 3 observers.

Two statistical software packages were used: R statistics [R Development Core Team (2006). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org] and specifically the separately downloaded *irr* Package (Version 0.62), and SPSS-PC v.17.0 (SPSS Inc, Chicago, IL, USA).

Results

BASELINE CHARACTERISTICS

A total of 34 patients fulfilling the criteria of childhood constipation were included and compared to 34 non-constipated children. Baseline characteristics of the two groups are summarized in table 1. Significant differences between constipated children and controls were found with respect to defecation frequency, incontinence and abdominal and rectal scybala.

Table 1 Clinical characteristics of the study and control group.

	Controls (n=34)	Constipation (n=34)	Significance
Characteristics			
Boys/girls	21/13	18/16	0.47
Median Age in years (range)	9.0 (7-12)	9.0 (7-12)	0.08
Median duration of complaints in months (range)	18 (1-84)	12 (1-104)	0.27
Median defecation frequency / week (range)	7 (2-14)	3 (1-7)	<0.01
Median score stools (BSFS# 1 or 2)	5 (15)	4 (12)	0.66
Painful defecation (%)	8/34 (24)	6/34 (18)	0.44
Abdominal pain (%)	20/34 (59)	27/34 (79)	0.13
Loening-Baucke Criteria			
Stool frequency < 3 / week	5/34 (15)	25/34 (74)	<0.01
Incontinence ≥2 time / week (%)	19/34 (56)	9/34 (26)	0.02
Large amounts of stool (%)	3/34 (9)	8/34 (24)	0.28
Abdominal and / or rectal scybala (%)	0/34 (0)	26/34 (76)	<0.01

Values are mean (range) or numbers (%). (# BSFS = Bristol stool form scale).[12]

PERFORMANCE OF STARREVELD AND BARR SCORES

When applying the Youden index, an optimal cut-off level of ≥10 for the Starreveld score was found, using the mean score of the first observation of 4 observers. Youden index, positive and negative predictive value (PPV, NPV) according to different Starreveld cut-off levels and at the recommended Barr cut-off level of ≥10 are shown in table 2. Using the optimal cut-off level for the Starreveld score 23/34 constipated patients were correctly labeled while 14/34 non-constipated patients were mislabeled. Using the cut-off level for the Barr score only 14/34 constipated patients were correctly labeled while 20 out of 34 non-constipated patients were mislabeled as constipated.

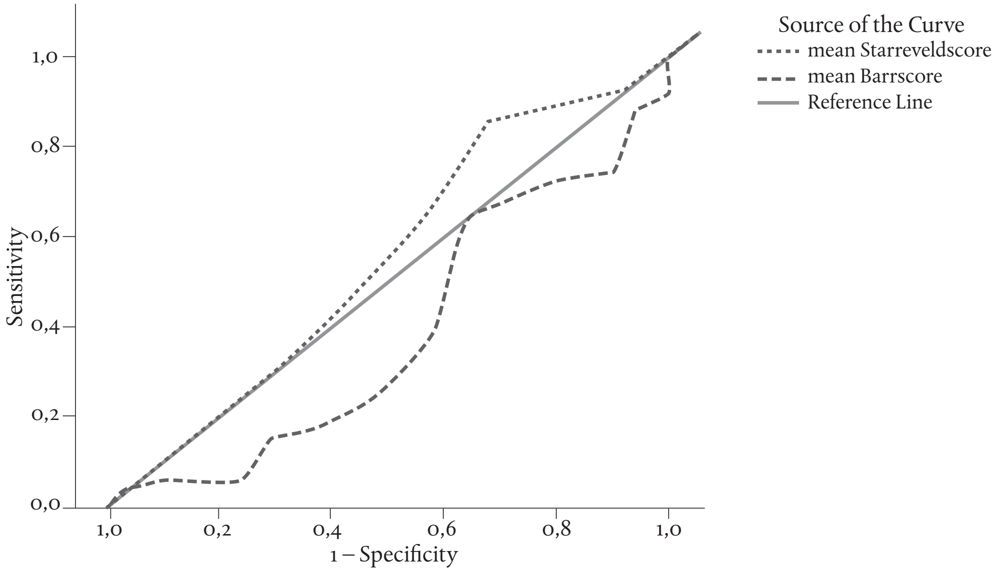
Similar results were found when computing a ROC curve. The AUC (using the mean of the scores from the first observation of all 4 observers) for Starreveld scoring method was 0.54 (95% CI: 0.40–0.68), only slightly above the result expected by chance, while the AUC for the Barr score was even worse (0.38, 95% CI: 0.25–0.52)(figure). Interestingly, the AUC obtained was significantly different between the four observers, with a highest AUC obtained of 0.72 and a lowest of 0.28 for the Starreveld score and a highest vs. lowest AUC for the Barr score of 0.63 vs. 0.09. There was no correlation between experience in evaluating abdominal x-rays and AUC obtained.

Table 2. Sensitivity, specificity, Youden index, PPV, and NPV according to different cut-off values of the Starreveld score and the standard cut-off for the Barr score.

Method (n=68)	Positive if ≥	Constipated Radiological/ Clinical	Youden index	Positive predictive value	Negative predictive value
Starreveld	7	65/32	35	0.49	0.33
Starreveld	8	61/31	33	0.51	0.57
Starreveld	9	52/29	28	0.56	0.69
Starreveld	**10**	37/23	**25**	0.62	0.65
Starreveld	11	31/16	33	0.52	0.51
Starreveld	12	20/10	34	0.50	0.50
Barr	10	34/14	40	0.41	0.41

Youden index[14] is the sum of false positives in the control group and false negatives in the constipated group, the optimum being the lowest index. The positive predictive value is the proportion of patients with positive test results who are correctly diagnosed with constipation whereas the negative predictive value is the proportion of patients with negative test results who are correctly diagnosed as not being constipated.

Figure ROC-curve for both mean Starreveld and mean Barr scores generated by 4 observers.



Finally, the inter-observer agreement using the intra class correlation coefficient was only moderate (table 3) for all observers. Intra-observer agreement was moderate to good for the Starreveld score (Kappa's ranging from 0.52 to 0.71) and good for Barr scores (Kappa's ranging from 0.62-0.76).

Table 3 Inter-observer-agreement according to observer and scoring method after a four-week interval using intra-class correlation coefficient (ICC) in a two-way model.

	Observers	ICC	95% CI
Starreveld 1st	4	0.52	0.40 – 0.62
Starreveld 2nd	3	0.49	0.36 – 0.60
Barr 1st	4	0.44	0.24 – 0.59
Barr 2nd	3	0.44	0.31 – 0.56

95% CI = 95% confidence interval; Interpretation of agreement: poor (<0.20), fair (0.20-0.39), moderate (0.40-0.59), good (0.60-0.79) or very good (0.80-1.0).

Discussion

In this study we show that both the Starreveld and the Barr scoring method for assessing fecal loading on a plain abdominal radiograph are of limited value in the diagnosis of pediatric constipation. Although the Starreveld score performed better than the Barr score, diagnostic discrimination of both methods was poor.

This study was conducted using strict criteria for constipation as described by Loening-Baucke.[11] For functional abdominal pain (FAP) and functional non-retentive fecal incontinence (FNRFI) the Rome II criteria were applied.[13] Similar control groups have been used by others.[5] However it cannot be excluded that in patients with functional abdominal pain and non-retentive fecal incontinence an overfilled colon is found more frequently than in the general population. A control group as used by Jackson,[6] consisting of patients with trauma, ureteric colic, insertion of a ventriculo-peritoneal drain or nonspecific abdominal pain might have given a better representation of the "normal" population.

Our results in children differed from those obtained by Starreveld in adults. While in the original study[10] the scores given by the 4 individual observers were highly significantly correlated, we obtained only a moderate inter-observer agreement. In addition Starreveld described a significant correlation between the actual image as seen on the abdominal X-ray and defecation frequency. However, no controls were included, so the actual performance, using a ROC curve, could not be assessed. Our analysis actually showed a diagnostic accuracy which, with an AUC of 0.54, was only marginally above results that can be obtained by chance.

The other three scoring systems for evaluating constipation by using an abdominal radiograph[2-4] also had a good sensitivity and specificity in the original publications. However, when in a subsequent evaluation a ROC curve was obtained, the AUC of the Leech score did not exceed 0.68.[5] For the Barr and Blethyn scores the AUC obtained was 0.84 and 0.74 respectively,[6] when scoring was done by an experienced radiologist, but lower when performed by a student or trainee. Interestingly in our study more experience did not result in an improved AUC. The best AUC, 0.72 for the Starreveld and 0.63 for the Barr score, was obtained by the student. This AUC, which is still far from ideal, is similar to values obtained by others for the Leech, Blethyn and Barr scores.[5,6]

In our study inter-observer variability for both the Starreveld and Barr score was not good. Similar results were obtained by others for both Barr and Blethyn scores,[5-7] although the Leech score performed unexpectedly well in another evaluation.[7] However, we and others found a good agreement between the two evaluations of the same observer at different time points.[5-7] Obviously each observer develops his or her own interpretation of the original guidelines, resulting in a considerable inter-observer variability. However, each observer remains consistent in time given the acceptable intra-observer agreement.

Conclusion

The four scores developed for evaluating constipation by using an abdominal radiograph did well on initial evaluation.[2-4,10] However on subsequent independent evaluation, both in the current study and in others, these good initial results could not be repeated.[5-6] Given both the suboptimal AUC and the large inter-observer variability the abdominal radiograph should not be part of the routine work up of pediatric constipation.

References

1. van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol 2006; 101:2401-9.
2. Barr RG, Levine MD, Wilkinson RH et al. Chronic and occult stool retention: a clinical tool for its evaluation in school-aged children. Clin Pediatr (Phila) 1929; 18:674-9.
3. Blethyn AJ, Verrier Jones K, Newcombe R et al. Radiological assessment of constipation. Arch Dis Child 1995; 73:532-3.
4. Leech SC, McHugh K, Sullivan PB. Evaluation of a method of assessing faecal loading on plain abdominal radiographs in children. Pediatr Radiol 1999; 29:255-8.
5. de Lorijn F, van Rijn RR, Heijmans J et al. The Leech method for diagnosing constipation: intra- and interobserver variability and accuracy. Pediatr Radiol 2006; 36:43-9.
6. Jackson CR, Lee RE, Wylie AB et al. Diagnostic accuracy of the Barr and Blethyn radiological scoring systems for childhood constipation assessed using colonic transit time as the gold standard. Pediatr Radiol 2009; 39:664-7.
7. van den Bosch M, Graafmans D, Nievelstein R et al. Systematic assessment of constipation on plain abdominal radiographs in children. Pediatr Radiol 2006; 36:224-6.
8. Rockney RM, McQuade WH, Days AL. The plain abdominal roentgenogram in the management of encopresis. Arch Pediatr Adolesc Med 1995; 149:623-7.
9. Benninga MA, Buller HA, Staalman CR et al. Defaecation disorders in children, colonic transit time versus the Barr-score. Eur J Pediatr 1995; 154:277-84.
10. Starreveld JS, Pols MA, Van Wijk HJ et al. The plain abdominal radiograph in the assessment of constipation. Z Gastroenterol 1990; 28:335-8.
11. Loening-Baucke V. Modulation of abnormal defecation dynamics by biofeedback treatment in chronically constipated children with encopresis. J Pediatr 1990; 116:214-22.
12. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997; 32:920-4.
13. Rasquin-Weber A, Hyman PE, Cucchiara S et al. Childhood functional gastrointestinal disorders. Gut 1999; 45 Suppl 2:II60-8.
14. Youden WJ. Index for rating diagnostic tests. Cancer 1950; 3:32-5.

CHAPTER 5

Constipation in pediatric Cystic Fibrosis patients: An underestimated medical condition

H.P.J. van der Doef [1*], F.T.M. Kokke[1], F.J.A. Beek[1],
J.W. Woestenenk[2], S.P. Froeling [1], R.H.J. Houwen[1]

1. Wilhelmina Children's Hospital, University Medical Center Utrecht,
Lundlaan 6, 3584 EA, Utrecht, The Netherlands
2. Julius Centre for Health, Sciences and Primary Care, Department of
Dietetics and Nutritional Science, University Medical Center Utrecht,
Universiteitsweg 100, 3584 CG Utrecht, The Netherlands

Received 18 August 2009; received in revised form 4 November 2009;
accepted 5 November 2009
Available online 8 December 2009

J Cyst Fibrosis 2010; 9:59-63.

Abstract

BACKGROUND

The aims of this study were to determine prevalence, risk factors and treatment of constipation in patients with Cystic Fibrosis (CF), as well as the diagnostic value of abdominal radiography.

METHODS

A cohort of 214 pediatric CF patients was investigated. Furthermore, 106 abdominal radiographs of CF patients with or without constipation were independently assessed by three observers on two separate occasions using the Barr and Leech scores.

RESULTS

The prevalence of constipation was 47%. Low total fat absorption and meconium ileus were independent risk factors for constipation in CF, while fiber and fluid intake were not associated. In CF patients the inter and intraobserver variabilities of the Barr and Leech scores were poor to moderate.

CONCLUSION

Constipation is a significant medical issue in CF and was associated with low total fat absorption and a history of meconium ileus.

Finally, abdominal radiography seems of little value in the regular follow-up of CF patients.

Keywords: Abdominal radiography; Interobserver variability; Intraobserver variability; Fat malabsorption; Meconium ileus; Steatorrhea; Total fat absorption

1. Introduction

Constipation is one of the gastrointestinal manifestations of Cystic Fibrosis (CF). It is characterized by a reduced stool frequency and increased consistency, usually in combination with abdominal pain and distension and generally responds well to conservative medical treatment.[1,2] The frequency of this condition in CF is unclear. The only study addressing this problem so far reported a prevalence of 26% in patients aged 0–20 years.[2]

The main etiological factor for constipation in CF patients seems to be an altered intestinal fluid composition, caused by a defective expression of the Cystic Fibrosis transmembrane regulator (CFTR) protein in the gut.[3,4] In addition it is generally thought that a more aggressive treatment with pancreas supplements would result in more compact feces leading to fecal impaction,[5,6] although no correlation between pancreas supplement dose and constipation was found.[7]
Key elements in the diagnosis of constipation are a careful medical history and physical examination. In addition abdominal radiography is frequently performed when constipation is suspected. In this respect several scoring systems, like the Barr[8] and the Leech[9] scores, are available to assess the severity of fecal impaction. However the diagnostic value of these scores has only been investigated in patients with functional constipation, but not in CF.

Recently the ESPGHAN CF Working Group made a strict distinction between the (sub)acute complete ileocecal obstruction, as seen in the distal intestinal obstruction syndrome (DIOS) and the gradual fecal impaction of the total colon in constipation.[1]

DIOS patients are treated generally successfully with intensive laxative treatment (meglumine diatrizoate enema, polyethylene glycol lavage, oral laxatives or an enema).[1] It seems logical that in constipated CF patients generally a milder laxative regime will be used, but no such data are available at present.

The aims of this study were therefore to determine the prevalence of constipation, its risk factors and diagnostic value of abdominal radiography in patients with CF. In addition we listed laxative treatment used.

2. Methods

2.1. PREVALENCE AND RISK FACTORS

A retrospective cohort study of all pediatric CF patients (age ≤ 18 years) under treatment at the University Medical Center Utrecht, The Netherlands on January 1st, 2006 was performed according to the guidelines of the medical ethics board of the University Medical Center Utrecht, The Netherlands.

For constipation and DIOS the recently published definitions of the ESPGHAN CF Working Group were used.[1] Constipation was defined as [1] abdominal pain and/or distension or [2a] a reduced frequency of bowel movements in the last few weeks and/ or [2b] increased consistency of stools in the last few weeks, while [3] the symptoms are relieved by the use of laxatives. DIOS was defined as the combination of [1] complete intestinal obstruction, as evidenced by vomiting of bilious material and/or fluid levels in small intestine on an abdominal radiograph with [2] a fecal mass in ileocecum and [3] abdominal pain and/or distension. Incomplete or impending DIOS was defined as [1] a short history (days) of abdominal pain or distension or both and [2] a fecal mass in ileocecum, but without signs of complete obstruction.

Three-day dietary records (3 consecutive days including 1 weekend day) were completed by patient and/or family every year and analyzed by a registered dietitian (J.W.). The dietary data used for analysis were obtained 0 to 6 months before patients presented for the first time with constipation and were compared with the last available dietary data obtained in the patients without constipation or DIOS (complete or incomplete). Nutrient intake was expressed as percentage of the gender- and age-specific Reference Daily Intake (RDI).[10] Total fat absorption was calculated from the mean daily fat intake of three-day dietary records and the daily fecal fat output and was expressed as percentage of the mean daily fat intake.

For the determination of CFTR genotypes only alleles with known mutations were analyzed. Then the CFTR genotypes of the CF patients were subdivided into two groups: the first group consisted of patients with a severe genotype, defined as 2 severe CFTR mutations (class I–III) and the second group consisted of patients with a mild genotype, defined as at least 1 mild mutation (class IV–V).[11] The distribution of DF508 homozygous patients was also examined.

2.2. ABDOMINAL RADIOGRAPHY

Between April and December 2006 all pediatric CF patients (age ≤ 18 years) who visited the outpatient clinic for the annual check-up in the University Medical Center Utrecht underwent abdominal radiography regardless of the presence or absence of abdominal symptoms or constipation. A retrospective analysis of this group was subsequently performed according to the guidelines of the medical ethics board of the University Medical Center Utrecht, The Nether- lands. Three observers; a medical student (S.F.), an experienced pediatric radiologist (F.B.) and an experienced pediatric gastroenterologist (F.K.) independently assessed the abdominal radiographs taken. The three observers were blinded to the study objective and each abdominal radiograph was evaluated on two separate occasions, 3 weeks apart. Each abdominal radiograph was scored according to two different scoring systems and before the first scoring, the different systems were not discussed by the observers. The first method, described by Barr et al.,[8] quantifies the amount of feces in four different bowel segments (ascending colon, transverse colon, descending colon and rectum) and is scored respectively from 0 to 2, 0 to 5, 0 to 5 and 0 to 5. Also the consistency of the feces, i.e. granular or rocky stools is scored respectively from 0 to 3 and 0 to 5. Constipation is defined as a score ≥ 10. The second method was described more recently by Leech et al.[9] In this system the colon is divided into three colonic segments (the right colon, the left colon and the rectosigmoid segment) and the amount of feces in each segment is scored from 0 to 5. Constipation is defined as a score ≥ 9.

The presence of radiological constipation in the first evaluation of all three observers according to the Barr and Leech scores were compared with the presence of constipation according to the ESPGHAN criteria[1] as gold standard and the sensitivity, specificity, positive and negative predictive values (PPV and NPV) were calculated. Furthermore, the interobserver variability of the Barr and Leech scores was calculated using the first evaluation of the three observers and the intraobserver variability was calculated using both evaluations of the observers.

2.3. STATISTICAL ANALYSIS

Data were described as mean and standard deviation for ordinal values, and absolute and relative frequencies for nominal values. Logistic regression was used to test the effect of potential risk factors and variables contributing significantly ($p < 0.05$) were included in the multivariate analysis. Unweighted kappa coefficients were calculated as indicators of inter and intraobserver variabilities for nominal variables (presence or absence of radiological constipation) and weighted kappa coefficients were calculated for ordinal variables (amount of points scored by the observers).

Kappa coefficients <0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.00 were considered to indicate poor, fair, moderate, good and very good agreement, respectively.[12] Values were considered significant if $p \leq 0.05$. The weighted kappa coefficient was calculated using R software (Free Software Foundation Inc., Boston, MA, USA), while all other statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. PREVALENCE AND RISK FACTORS

The study group consisted of 230 pediatric CF patients (age ≤ 18 years) under treatment at the University Medical Center Utrecht, The Netherlands on January 1st, 2006. Within this study group, 107 patients (47%) had a history of constipation, while 46 patients (20%) were constipated at January 1st, 2006.

Sixteen patients with a history of DIOS (complete or incomplete) were excluded in the analysis of risk factors. The characteristics of the 107 constipation patients were compared with 107 CF patients without a history of constipation or DIOS (complete or incomplete) and are reported in Table 1.

Meconium ileus was significantly more frequent in patients with a history of constipation than in patients without constipation (13% vs. 5%, p = 0.038). In the subgroup of the 19 meconium ileus patients surgical treatment for meconium ileus was more common in constipation patients than in patients without constipation (71% vs. 60%), although no statistical significance was reached (p = 1.00). Also pancreatic insufficiency was more common in the constipated group than

Table 1 Clinical characteristics associated with constipation in Cystic Fibrosis.

Characteristics	All patients	Constipation	Controls	*p*-value	OR (95%CI)
Patient number	214	107	107		
Gender (male)	119 (56%)	61 (57%)	58 (54%)	0.68	1.10 (0.65–1.92)
Age diagnosis CF[a]	1.31 (2.08)	1.12 (1.64)	1.49 (2.43)	0.20	0.92 (0.80–1.05)
Current age[a]	9.96 (4.64)	10.31 (4.37)	9.60 (4.90)	0.26	1.03 (0.98–1.10)
CFTR genotype					
Severe	174 (81%)	93 (87%)	81 (76%)	0.34[b]	1.64 (0.60–4.51)[b]
DF508/DF508	130 (61%)	73 (68%)	57 (53%)	0.25[b]	1.83 (0.66–5.11)[b]
Mild	17 (8%)	7 (7%)	10 (9%)		
Clinical manifestations					
Pancreas insufficiency	207 (97%)	106 (99%)	101 (94%)	0.091	0.16 (0.019–1.34)
Meconium ileus	19 (9%)	14 (13%)	5 (5%)	0.038	3.07 (1.07–8.86)
Dietary intake					
Fiber (% RDI)[a]	0.58 (0.19)	0.58 (0.23)	0.58 (0.17)	0.93	0.92 (0.14–6.27)
Fluid (% RDI)[a]	0.87 (0.21)	0.89 (0.21)	0.86 (0.21)	0.46	1.88 (0.35–10.00)
Total fat absorption[a]	0.89 (0.08)	0.86 (0.09)	0.90 (0.07)	0.012	0.003 (0.00–0.28)

a Mean (SD).
b Severe genotype or DF508 homozygous vs. mild genotype.

in control CF patients (99% vs. 94%), although this difference was not significant ($p = 0.091$). However total fat absorption was significantly lower in patients with constipation than in patients without constipation (0.86 ± 0.09 vs. 0.90 ± 0.07, $p = 0.012$). All other variables (current age, age at diagnosis of CF, gender, CFTR genotype, mean fiber intake and mean fluid intake) were not significantly different between patients with or without constipation.

Logistic regression analysis showed that meconium ileus at birth ($p = 0.024$; OR 4.69, 95% CI 1.22–18.0) and low total fat absorption ($p = 0.010$; OR 0.002, 95% CI 0.000–0.24) were indeed both independently associated with constipation.

3.2. ABDOMINAL RADIOGRAPHY

Abdominal radiography was performed in the 106 CF patients who visited the outpatient clinic for the annual check-up in the University Medical Center Utrecht, The Netherlands between April and December 2006. Of the 106 patients 36 (34%) were constipated and 70 (66%) were not constipated according to the ESPGHAN criteria.[1] With this criterion as a gold standard sensitivity, specificity, PPV and NPV of radiological constipation according to the different scoring systems generally was low (Table 2). For the Barr score the observers reported sensitivities ranging from 0.14 to 0.61, specificities ranging from 0.43 to 0.96, PPV ranging from 0.35 to 0.63 and NPV ranging from 0.68 to 0.71. For the Leech score the observers report sensitivities ranging from 0.11 to 0.72, specificities ranging from 0.34 to 0.93, PPV ranging from 0.36 to 0.44 and NPV ranging from 0.67 to 0.71.

Table 2 Sensitivity, specificity and positive and negative predictive values of the presence of radiological constipation according to the Barr and Leech scores in children with Cystic Fibrosis.

	Radiologist	Gastroenterologist	Medical student
Barr score			
Sensitivity	0.61	0.14	0.53
Specificity	0.43	0.96	0.59
Positive predictive value	0.35	0.63	0.40
Negative predictive value	0.68	0.68	0.71
Leech score			
Sensitivity	0.72	0.11	0.50
Specificity	0.34	0.93	0.63
Positive predictive value	0.36	0.44	0.41
Negative predictive value	0.71	0.67	0.71

Furthermore, the inter and intraobserver variabilities of the three observers according to the two different scoring systems generally were low too. The inter and intraobserver variabilities of the Barr and Leech scores for the presence of radiological constipation (Barr score <10 vs. ≥10 and Leech score <9 vs. ≥9) ranged from an unweighted kappa coefficient of 0.08 (poor) to 0.44 (moderate) and the inter and intraobserver variabilities of the Barr and Leech scores for the amount of points scored ranged from a weighted kappa coefficient of 0.09 (poor) to 0.55 (moderate).

3.3. TREATMENT OF CONSTIPATION PATIENTS

In our patient group 58% had had at least 1 oral laxative (OL), 26% 2 OL, 8% 3 OL, 6% 4 OL and 2% 5 OL. Generally patients started with lactulose or polyethylene glycol. If the effect was insufficient one or two additional OLs were added. In 53 patients (50%) at least once an enema was necessary and in 14 patients (13%) intestinal lavage. Eight patients received a stimulant laxative for a short period.

4. Discussion

In this study we determined the prevalence, risk factors and treatment of constipation in a cohort of CF patients, as well as the diagnostic value of abdominal radiography in this condition.

One hundred and seven out of 230 patients (47%) had a history of constipation, while 46 out of 230 patients (20%) were constipated at January 1st, 2006. Prevalence numbers of constipation in CF are scarce; only one study published in 1986 has reported prevalence numbers of constipation in CF.[2] This study observed that constipation had been present in 26% of all CF patients aged 0–20 years,[2] which is significantly lower than prevalence in the present study ($p < 0.001$). While it is possible that the prevalence of constipation has increased over time, it is as likely that laxatives are prescribed more easily nowadays in CF patients suspected of constipation, especially as current laxatives are almost devoid of side effects. As both in our definition for constipation and in the definition of Rubinstein et al.[2] the use of laxatives is a key component, such a change in practice might result in the increasing prevalence numbers we here describe.

In the current study we found that meconium ileus was independently associated with constipation. An association between meconium ileus and DIOS has been reported previously.[13] It seems indeed logical that both meconium ileus, DIOS and constipation in CF are an interrelated group of manifestations, ranging from severe to mild intestinal obstruction and sharing a common pathophysiology.

The relationship between pancreatic insufficiency or poorly controlled steatorrhea and constipation is unclear and conflicting results have been published. In general, it is thought that constipation is correlated with highly dosed pancreatic supplements.[5,6] However this is not supported by Baker et al.,[7] who report no correlation between constipation and the dosage of pancreatic supplements. We now found that constipation patients have a lower total fat absorption than control patients, although both patient groups (with and without constipation) had an adequate control of steatorrhea with a mean total fat absorption of 86% and 90% respectively.[14] Slow intestinal transit and malabsorption may allow undigested food to enter the colon over a prolonged period.[15,16] This could lead, in combination with impaired intestinal secretion,[3,4] to sticky intestinal mucus and constipation.

Finally, in concordance with a report describing Belgian CF patients,[17] fiber intake was not correlated with constipation in CF. Furthermore, no differences in the fluid intake between patients with or without constipation were found, despite the general opinion that inadequate fluid intake is an etiological factor of constipation in CF.[2]

In children with CF the Barr and Leech scores have poor sensitivity, specificity, PPV and NPV for diagnosing constipation, with a considerable overlap in Barr and Leech scores between constipated and nonconstipated patients. In addition, poor inter and intraobserver variabilities were found when scoring abdominal radiographs in CF patients. Similar results have been published in patients with functional constipation; a systematic review showed a low diagnostic value of abdominal radiography (sensitivity 60–80% and specificity 35–90%),[18] while the inter and intraobserver variabilities of the different scoring systems are poor too.[19,20] Consequently, abdominal radiography is not recommended as a standard diagnostic tool in the regular gastrointestinal follow-up of CF patients. However, abdominal radiography is useful to differentiate between constipation and the distal intestinal obstruction syndrome in CF patients with acute abdominal pain.[1]

Currently, polyethylene glycol seems to be the preferred initial treatment for both constipation and DIOS (complete and incomplete), because it is as effective and does not have the side effects that are inherent to lactulose (flatulence and abdominal cramps).[21]

In conclusion, constipation is a significant medical issue in CF patients, with a prevalence of 47%. Furthermore, we found that low total fat absorption and meconium ileus were independent risk factors for constipation in CF, while fiber and fluid intake were not associated with constipation in CF. In addition, the diagnostic value of abdominal radiography in CF is limited. Abdominal radiography is therefore not recommended in the regular follow-up of CF patients.

Acknowledgments

The authors wish to thank S. van Zuilen, secretary of the Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands for her contribution to the database construction and wish to thank J. van der Laag of the Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands for his contribution to the discussion.

The study was funded by the Wilhelmina Research Fund, grant number OZF 2005/04. This organization had no involvement in the study design, in the collection and interpretation of data, in the writing of the manuscript and in the decision to submit the manuscript for publication.

References

1. Houwen RH, van der Doef HP, Sermet I, Munck A, Hauser B, Walkowiak J, et al. The ESPGHAN Cystic Fibrosis Working Group: Defining DIOS and Constipation in Cystic Fibrosis with a multicenter study on the incidence, characteristics and treatment of DIOS. J Pediatr Gastroenterol Nutr. 2010;50:38–42.
2. Rubinstein S, Moss R, Lewiston N. Constipation and meconium ileus equivalent in patients with cystic fibrosis. Pediatrics 1986;78:473–9.
3. Sinaasappel M. Relationship between intestinal function and chloride secretion in patients with cystic fibrosis. Neth J Med 1992;41:110–4.
4. Mall M, Kreda SM, Mengos A, Jensen TJ, Hirtz S, Seydewitz HH, et al. The DeltaF508 mutation results in loss of CFTR function and mature protein in native human colon. Gastroenterology 2004;126:32–41.
5. Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. Pediatr Pulmonol 2006;41:35–49.
6. Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HG, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros 2002;1:51–75.
7. Baker SS, Borowitz D, Duffy L, Fitzpatrick L, Gyamfi J, Baker RD, et al. Pancreatic enzyme therapy and clinical outcomes in patients with cystic fibrosis. J Pediatr 2005;146:189–93.
8. Barr RG, Levine MD, Wilkinson RH, Mulvihill D. Chronic and occult stool retention: a clinical tool for its evaluation in school-aged children. Clin Pediatr (Phila) 1979;18(674):676–9.
9. Leech SC, McHugh K, Sullivan PB. Evaluation of a method of assessing faecal loading on plain abdominal radiographs in children. Pediatr Radiol 1999;29:255–8.
10. Health Council of The Netherlands. Dietary Reference Intakes: energy, proteins, fats and digestible carbohydrates. The Hague: Health Council of The Netherlands, 2001; publication no. 2001/19.
11. Welsh MJ, Smith AE. Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. Cell 1993;2(73):1251–4.
12. Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1991. p. 403–9.
13. Blackman SM, Deering-Brose R, McWilliams R, Naughton K, Coleman B, Lai T, et al. Relative contribution of genetic and nongenetic modifiers to intestinal obstruction in cystic fibrosis. Gastroenterology 2006;131:1030–9.
14. Walkowiak J, Nousia-Arvanitakis S, Henker J, Stern M, Sinaasappel M, Dodge JA. Indirect pancreatic function tests in children. J Pediatr Gastroenterol Nutr 2005;40:107–14.
15. Bali A, Stableforth DE, Asquith P. Prolonged small-intestinal transit time in cystic fibrosis. Br Med J 1983;287:1011–3.
16. Escobar H, Perdomo M, Vasconez F, Camarero C, del Olmo MT, Suárez L. Intestinal permeability to 51Cr-EDTA and orocecal transit time in cystic fibrosis. J Pediatr Gastroenterol Nutr 1992;14:204–7.
17. Proesmans M, De Boeck K. Evaluation of dietary fiber intake in Belgian children with cystic fibrosis: is there a link with gastrointestinal complaints? J Pediatr Gastroenterol Nutr 2002;35:610–4.

18. Reuchlin-Vroklage LM, Bierma-Zeinstra S, Benninga MA, Berger MY. Diagnostic value of abdominal radiography in constipated children: a systematic review. Arch Pediatr Adolesc Med 2005;159:671–8.
19. de Lorijn F, van Rijn RR, Heijmans J, Reitsma JB, Voskuijl WP, Henneman OD, et al. The Leech method for diagnosing constipation: intra- and interobserver variability and accuracy. Pediatr Radiol 2006;36:43–9.
20. Benninga MA, Büller HA, Staalman CR, Gubler FM, Bossuyt PM, van der Plas RN, et al. Defaecation disorders in children, colonic transit time versus the Barr-score. Eur J Pediatr 1995;154:277–84.
21. Dupont C, Leluyer B, Maamri N, Morali A, Joye JP, Fiorini JM, et al. Double-blind randomized evaluation of clinical and biological tolerance of polyethylene glycol 4000 versus lactulose in constipated children. J Pediatric Gastroenterol Nutr 2005;41:625–33.

CHAPTER 6

A Dietary Fiber Mixture versus Lactulose in the Treatment of Childhood Constipation: A Double-blind Randomized Controlled Trial

Freddy T.M. Kokke[1], Petra A.M.J. Scholtens[2], Martine S. Alles[2], Tom S. Decates[3], Theo J.W. Fiselier[4], Jules J.M. Tolboom[4], Jan L.L. Kimpen[1], and Marc A. Benninga[3]

1. Departments of Paediatric Gastroenterology and Paediatrics, Wilhelmina Children's Hospital, Utrecht
2. Numico Research, Wageningen
3. Department of Paediatrics and Paediatric Gastroenterology, Radboud University Hospital, Nijmegen
4. Department of Paediatric Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands

J Pediatr Gastroenterol Nutr 2008; 47:592-7.

Abstract

BACKGROUND

Constipation is a common problem in children. As first-line treatment, increased dietary fiber is often advocated. To our knowledge, however, no large studies evaluating the effect of dietary fibers in childhood constipation have been published.

PATIENTS AND METHODS

A randomized, double-blind, prospective controlled study was performed. Patients received either a fiber mixture or lactulose in a yogurt drink. After a baseline period of 1 week, patients were treated for 8 weeks followed by 4 weeks of weaning. Polyethylene glycol 3350 was added if no clinical improvement was observed after 3 weeks. Using a standardized bowel diary, parents recorded defecation frequency during the treatment period. In addition, incontinence frequency, stool consistency, presence of abdominal pain and flatulence, necessity for step-up medication, and dry weight of feces were recorded, as were adverse effects.

RESULTS

A total of 147 children were eligible; 12 children wished not to participate. Of the remaining children, 65 were randomized to treatment with fiber mixture and 70 to treatment with lactulose. In all, 97 children completed the study. No difference was found between the groups after the treatment period concerning defecation frequency ($p=0.481$) and fecal incontinence frequency ($p=0.084$). However, consistency of stools was softer in the lactulose group ($p=0.01$). Abdominal pain and flatulence scores were comparable ($p=0.395$ and $p=0.739$, respectively). The necessity of step-up medication during the treatment period was comparable ($p=0.996$), as were taste scores ($p=0.657$). No serious adverse effects were registered.

CONCLUSIONS

A fluid fiber mixture and lactulose give comparable results in the treatment of childhood constipation.

Key Words: Dietary fiber – Lactulose – Childhood constipation – Randomized controlled trial.

Constipation, defined as infrequent, painful bowel movements sometimes in combination with the involuntary loss of feces in the underwear is a common problem in children.[1] The current treatment advice in cases of simple constipation consists of toilet training and a high- fiber diet, whereas chronic childhood constipation is treated with oral and sometimes rectal laxatives for an extended time.[1] Two large randomized controlled trials in pediatric patients have been published, evaluating the effect of laxative treatment (lactulose, polyethylene glycol solution).[2,3] These studies showed that polyethylene glycol was superior to lactulose in the treatment of constipation.

Despite intense debate on its efficacy, no large controlled trials studying the effect of dietary fiber in children with constipation have been performed to our knowledge.[4-6] Two small randomized controlled trials showed a beneficial effect of glucomannan, a non-absorbable fiber gel polysaccharide, on defecation frequency and stool consistency in children with constipation.[7,8]

Dietary fibers have water-retaining capacity and stimu- late gastrointestinal motility by increasing feces volume, bacterial growth, and bacterial degradation products.[9,10] This promotes colonic propulsion, reduces transit time, and facilitates defecation.[7,8,12-14]

In previous studies, only single types of fiber were used. A more effective approach might be the use of a combination of different types of fiber: short- and long-chain fibers. In this way degradation products can be expected to be produced throughout the colon, in contrast to lactulose, which has its effect mainly in the proximal colon.[15-18] The aim of the present study was to assess the clinical efficacy and safety of a dietary fiber mixture and compare it with lactulose in the treatment of childhood constipation.

Patients And Methods

Constipated children, referred by general practitioners and public health physicians to the outpatient pediatric clinic of the Hospital Rijnstate, Arnhem, the Netherlands, were eligible for this study. All of the children had to fulfill at least 2 of 4 criteria for constipation: stool frequency less than 3 times per week, fecal incontinence 2 or more times per week, periodic passage of large amounts of stool at least once every 7 to 30 days, or a palpable abdominal or rectal mass.[19] Children ages 1 to 13 years were included. Children with organic causes of defecation disorders, including Hirschsprung disease, spina bifida, hypothyroidism or other metabolic or renal abnormalities, and mental retardation; children using drugs influencing gastrointestinal function other than laxatives; and children having used lactulose or other laxatives, prebiotics or probiotics, or antibiotics in the previous 4 weeks before the first visit were excluded from the study. Written informed consent was obtained before the start of the study. The study protocol was approved by the medical ethics committee of the hospital.

STUDY PRODUCTS

Patients received either a yogurt drink with mixed dietary fibers (10g/125 mL) or a yogurt drink containing lactulose (10 g/125 mL) (Duphalac Lactulose, Solvay, the Netherlands). The fiber mixture yogurt contained 3.0 g transgalacto-oligosaccharides (Vivinal GOS Elixor Sirup, Friesland Foods Domo, Zwolle, the Netherlands), 3.0g inulin (Frutafit TEX, Cosun, Roosendaal, the Netherlands), 1.6g soy fiber (Fibrim 2000, J. Rettenmaier & Sohne, Ellwangen, Germany), and 0.33g resistant starch 3 (Novelose 330, National Starch & Chemical GmbH, Neustadt, Germany) per 100 mL.

Bottles with yogurt were prepared and packed by Numico Research (Wageningen, the Netherlands), transported to the hospital, and stored at room temperature. Storage and delivery were supervised by the local hospital pharmacist. The treatment products could not be distinguished from each other with respect to color, taste, or consistency.

The amount of fiber and fluid intake depended on body weight. Patients with a weight <15 kg received 1 bottle (125 mL, 10g fibers) daily, those with a weight between 15 kg and 20 kg received 2 bottles (250 mL, 20g) daily, and those with a weight above 20 kg received 3 bottles (375 mL, 30g) daily. The study product was taken at breakfast and, in the case of 2 or more bottles, also at lunch.

STUDY DESIGN AND STUDY OUTLINE

The study had a randomized double-blind parallel-group design. Randomization was performed by use of sequential numbers allocated to the patients at study entry and coordinated by the logistics manager of Numico Research using a block design. The study period consisted of 3 phases: a 1-week baseline period, an 8-week intervention period, and a 4-week weaning period (Table 1).

Table 1 Weaning dose regimen (in bottles/day) during weeks 9 - 12

Weight, kg	Treatment period	Week 9 - 10	Week 11 - 12	Week 13
>15	3	2	1	0
15–20	2	1	1 every other day	0
<15	1	0.5	0.5 every other day	0

Patients were screened during their first visit to the hospital. A detailed medical history using a standard questionnaire was taken, and a complete physical examination, including abdominal and rectal examination, was performed. In case of rectal impaction, an enema was given during the first visit.

During the baseline period, defecation frequency, frequency of fecal incontinence, consistency of stool, abdominal pain, and flatulence were recorded. During the treatment period, patients were seen at the outpatient clinic 3 and 8 weeks after inclusion. In addition, data were recorded daily in the bowel diary by the parents or patient. Finally, parents of patients were contacted by a research nurse by telephone 1 and 4 weeks after inclusion. If clinical parameters compared with baseline did not improve 3 weeks after the start of the intervention period, then step-up medication (macrogol 3350) was given per protocol. During the weaning period, the patients' study medication was lowered. If persistent diarrhea was reported, the original dose was reduced by 50%. After 4 and 8 weeks of treatment, patients who were able to write and read filled in a questionnaire themselves to evaluate the drink with a figure between 0 and 10. During the baseline period and after 3 weeks, fecal samples were collected for determination of dry weight.

Finally, all adverse events encountered during the study were recorded. An adverse event was defined as any adverse change from baseline (pre-treatment) condition, which occurred during the course of the study after treatment had started, whether it was considered to be related to treatment.

OUTCOME PARAMETERS

The primary outcome parameter was defecation frequency per week; defecation was noted on a daily basis during the treatment period. Secondary outcome parameters were fecal incontinence each day (yes or no), stool consistency according to the Bristol Stool Form Scale[20] (stools are rated based on water content of the feces, with 1 meaning hard stools to 7 meaning liquid stools), abdominal pain (0 = not at all, 1 = sometimes, 2 = often, and 3 = continuous), flatulence (0 = not at all, 1 = sometimes, 2 = often, and 3 = continuous), use of step-up medication (yes or no), taste (1-10), dry weight of feces at week 0 and 3, and adverse effects.

Table 2 Baseline characteristics of the 2 study groups

Characteristics	Fiber mix group (n = 42)	Lactulose group (n = 55)
Boys/girls	20/22	23/32
Age, y (median and range)	5.5 (1 - 12)	5.0 (1 - 12)
Duration of complaints, mo (median)	12.0 (1 - 72)	12.0 (1 - 104)
Defecation frequency/wk (median and range)	3,0 (1 - 28)	2,5 (1 - 9)
Hard stools (BSFS 1 or 2)	26 (62%)	32 (58%)
Fecal incontinence, age >4y	13 (32%)	18 (33%)
Production of large amounts of stool	14 (33%)	13 (23%)
Painful defecation	11 (26%)	11 (20%)
Abdominal pain	31 (74%)	39 (71%)
Abdominal scybala	22 (52,4%)	27 (49,1%)
Rectal scybala	16 (38%)	27 (49%)
Exclusion afterward	0	2*

* One patient with celiac disease and 1 patient with spina bifida occulta.

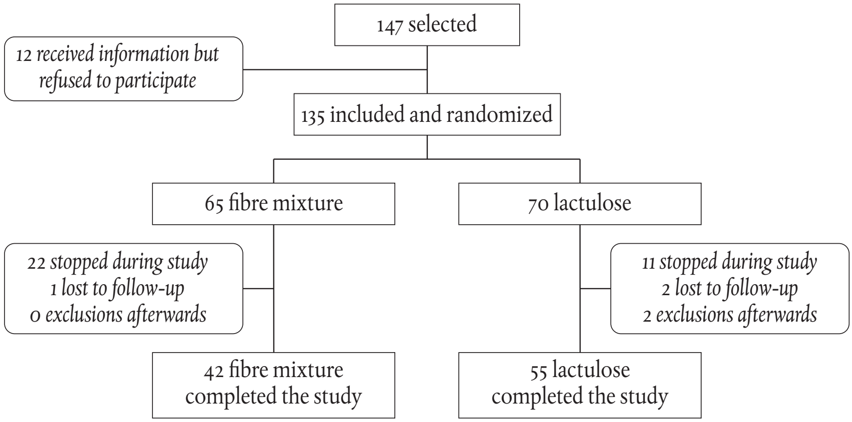
STATISTICS

The sample size for the study was based on the primary outcome variable defecation frequency. It was calculated that a random allocation of 150 children would allow for the detection of a mean difference in defecation of 1.0/week between the 2 treatment groups with a power of 80% and a = 0.05.[21] Comparisons between the 2 treatment groups at specific different time points were performed by use of the Student t test or the nonparametric Mann-Whitney U test depending on the distribution of values. Frequencies in Table 2 are given as minimum and maximum; distribution was skewed, so median is given instead of mean. Statistical analysis was performed by use of SPSS-PC version 13.0 (SPSS Inc, Chicago, IL, USA) software. $p<0.05$ was considered statistically significant.

Results

Between September 2001 and April 2004, 147 patients were eligible (Fig. 1). Twelve patients and their parents received information but chose not to participate. During the treatment period, 33 patients dropped out: 22 in the fiber group after 1 to 56 days (median 7) and 11 in the lactulose group after 1 to 51 days (median 8) ($p=0.020$). Those patients refused to continue to drink the yogurt. Therefore, the final data set consisted of a total of 97 patients (42 in the fiber mix group and 55 in the lactulose group). No significant differences were found in baseline characteristics between the 2 groups (Table 2). Defecation frequency per week

Figuur 1 Study participants flowchart



showed no difference between groups after 8 weeks of treatment (7 times per week in the fiber group vs 6 in the lactulose group; p=0.481).

No significant difference between the fiber mix and lactulose group was found with respect to the number of patients with 1 or more fecal incontinence episodes per week (9/42 vs 5/55 patients; p=0.084), nor were statistically significant reductions found between baseline and the end of the intervention period within each group: in the fiber mix group 8 versus 9 patients (p=0.664) and in the lactulose group 7 versus 5 patients (p=0.423).

Improvement in consistency of stools was observed within both groups. In the fiber mix group, a trend toward statistically significant softer stools was observed after 3 weeks of treatment, and significantly softer stools were observed at the end of the intervention period (p=0.07 and p=0.036, respectively). The consistency of stools in the lactulose group significantly changed to softer stools after 3 and 8 weeks of therapy (p<0.001 and p<0.001, respectively). The presence of abdominal pain and flatulence scores did not differ between groups (Table 3).

Table 3 Secondary outcome parameters after 3 and 8 weeks of treatment comparing fiber mix with the lactulose group

	F/L after week 0	p	F/L after week 3	p	F/L after week 8	p
Stool consistency, mean	3.2/3.2	0.88	3.5/4.5	<0.01	3.6/4.0	0.01
Abdominal pain, mean	1.59/1.58	0.81	1.58/1.43	0.33	1.49/1.39	0.50
Flatulence, mean	1.7/1.6	0.51	1.9/2.0	0.70	2.0/1.9	0.94

F = fiber group; L = lactulose group.

Step-up medication was given to a significantly greater number of fiber-treated patients after 3 weeks (p=0.028). However, this difference disappeared after 8 weeks (p=0.356) and 12 weeks (p=0.793) (Table 4). Taste score at 4 weeks in the fiber-treated group was 8 (median), with a range from 1 to 10, and in the lactulose group 7 (range 1 – 10) (p=0.516) and at 8 weeks 8 (1 – 10) and 7 (1 – 10) (p=0.712). The percentage dry weight of feces decreased significantly from week 0 to week 3 in the lactulose group (30.4% vs 25.3%; p=0.006) but not in the fiber-treated group (28.1% vs 26.7%; p=0.124).

During the 8-week study period, no serious or significant adverse effects were recorded in the 2 study groups.

In 3 cases (1 in the fiber mixture group and 2 in the lactulose group), the study yogurt intake was decreased because of persistent diarrhea.

Discussion

This trial shows that both a fluid fiber mixture and lactulose are effective in the treatment of childhood constipation. In our study population, a defecation frequency of 2 or fewer times per week was observed in 44% of the patients, lower than that observed in previous studies showing percentages of 60%.[2,22,23] Moreover, only 32% of the patients in this study had fecal incontinence. This is in contrast with others, who have reported 60% to 80% of constipated patients with fecal incontinence.[2,8] Most likely these differences occurred because our group of patients consisted of children referred by general practitioners and public health physicians. In the above-mentioned studies, patients were referred to tertiary centers, suggesting more severe constipation. Inasmuch as the results of this study probably apply to children with more mild to moderate complaints of constipation, it may have been more difficult to observe clinically relevant improvements in stool characteristics in an 8-week intervention period.

Table 4 Number of patients receiving step-up medication (macrogol 3350) if no improvement compared with baseline was found at 3, 8, and 12 weeks (cumulative data)

Time	Fiber group	Lactulose group	P
After 3 wk	13	7	0.028
After 8 wk	20	21	0.356
After 12 wk	21	26	0.793

Subjective measurement of consistency of stools according to the 7-point Bristol stool form scale showed an improvement within both groups, with (trends toward) significantly softer stools after 3 and 8 weeks of intervention in both groups. A statistically significant softer consistency of stools was observed in the lactulose group in comparison with the fiber group after 3 and 8 weeks of treatment. In the fiber group, improvement in consistency was steady and slow compared with that in the lactulose group. Notably, stools in the lactulose group at 8 weeks became harder again. Lactulose can be considered as a semi-synthetic undigestible carbohydrate, reaching the cecum intact and broken down by bacteria into short-chain fatty acids. Subsequently, the intra-luminal pH value decreases causing an increase of peristaltic movements. The short-chain fatty acids are absorbed together with water and electrolytes, tending to reduction of fecal water content. Fermentation, however, stimulates bacterial growth, which contributes to increased stool weight and volume, and bowel wall dilatation, which then triggers the reflex action of the bowel peristalsis. The fate of the dietary fibers in our mixture is comparable to that of lactulose except for the difference in fermentation site and rate. Different strains of bacteria and their inducible enzymes are involved and probably may take more time to efficiently degrade fibers consisting of multiple units, in comparison with lactulose consisting of only 2 units.[24-26] This could explain the more prolonged softening of stool seen in the fiber group. Stool softness caused by lactulose may reach a maximum earlier in the treatment, but the effect may be short-lived.

The higher need for step-up medication in the fiber mix group after 3 weeks of treatment, which disappeared at week 8, underlines this hypothesis.

To avoid taste problems, we developed a palatable yogurt drink containing a high dose of dietary fiber or containing an equal dose in grams of lactulose. However, 33 patients were not able to continue to drink this yogurt for a period of 12 weeks. Patients complained about taste, the large volume to drink every day, and/or the lack of choice in taste. None of the children stopped because of worsening of complaints connected to constipation. The larger number of dropouts in the fiber group, although overall taste was rated as 8 in this group versus 7 in the lactulose group, cannot be explained by increased side effects, which were comparable in both groups. In comparison with other studies in childhood constipation,[2,3] however, the number of dropouts was considerable. In 1 study that compared polyethylene glycols without electrolytes (28 patients) and milk of magnesia (21 patients), none of the patients taking polyethylene glycols refused the medication, in contrast to 33% of the patients refusing milk of magnesia.[27] Our taste questionnaire showed large disagreement among the patients about the taste of the yogurt drinks (scores ranging from 1 to 10), and this did not correlate with age.

Decrease in the percentage of dry weight of feces between weeks 0 and 3 was larger in the lactulose group than in the fiber mixture group. Lactulose can be expected to be fermented almost completely, in contrast to the fiber mixture. Therefore, the percentage dry weight of children in the lactulose group can be expected to be lower because of the lower amount of undigested fibers. The percentage dry weight of feces still containing a certain amount of fiber can be expected to be relatively higher. By contrast, other factors, like the osmotic effect of lactulose (resulting in a higher water content) and the effect of the growth of bacterial mass (resulting in a higher water content), also determine the percentage dry weight of stools. In this study, which used not only a qualitative measurement (Bristol stool form scale) but also a quantitative measurement (dry weight of feces), lactulose gave more a favorable result than the fiber mixture with respect to softer and more wet feces.

High fiber intake has been advocated as a treatment option for chronic childhood constipation. Early reports showed a positive relation between low fiber intake and the risk of constipation.[28-31] Other reports from the Netherlands and Brazil did not confirm this relation.[32,33] Table 5 shows that patients in our study already received 77% to more than 100% of the recommended fiber intake per day according to age, just by drinking the yogurt.

Table 5 Supplement of fiber mix with yogurt drink containing 10 g/125 mL

Weight, kg	Age, y (maximum)	Recommended dose, g (min max)	Fiber in yogurt dose received	Recommended daily dose provided in yogurt drink, %
<15	3	8 – 13	10	77 to >100
15 – 20	5	10 – 15	20	>100
>20	12	17 – 22	30	>100

Recommended fiber intake is (age in years +5 [minimum] to 10 [maximum] g).[36]

Possibly adding more fiber to the diet than the advised daily allowance is not accompanied by additional effects on stool frequency and consistency.[34] This may be an important observation, inasmuch it has been shown that starting and maintaining high-fiber diets in pediatric patients is difficult.[35]

In conclusion, the results of this study show that a fluid fiber mixture in the treatment of childhood constipation is feasible and has overall results comparable with those of treatment with lactulose.

References

1. Benninga MA, Voskuijl WP, Taminiau JA. Childhood constipation: is there new light in the tunnel? J Pediatr Gastroenterol Nutr 2004;39:448 – 64.
2. Voskuijl W, de Lorijn F, Verwijs W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. Gut 2004;53:1590 – 4.
3. Dupont C, Leluyer B, Maamri N, et al. Double-blind randomized evaluation of clinical and biological tolerance of polyethylene glycol 4000 versus lactulose in constipated children. J Pediatr Gastroenterol Nutr 2005;41:625 – 33.
4. Floch MH. The pharmacology of dietary fiber for laxation. Am J Gastroenterol 1987;82:1295 – 6.
5. Edwards CA, Tomlin J, Read NW. Fiber and constipation. Br J Clin Pract 1988;42:26 – 32.
6. Muller-Lissner SA. Effect of wheat bran on weight of stool and gastrointestinal transit time: a meta-analysis. BMJ (Clin Res Ed) 1988;296:615 – 7.
7. Staiano A, Simeone D, Del Giudice E, et al. Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. J Pediatr 2000;136:41 – 5.
8. Loening-Baucke V, Miele E, Staiano A. Fiber (glucomannan) is beneficial in the treatment of childhood constipation. Pediatrics 2004;113:e259 – 64.
9. Hillemeier C. An overview of the effects of dietary fiber on gastrointestinal transit. Pediatrics 1995;96:997 – 9.
10. Anti M, Pignataro G, Armuzzi A, et al. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. Hepatogastroenterology 1998;45:727 – 32.
11. Mate-Jimenez J, Gomez-Cedenilla A. Dietary fiber and the gut: action in gastrointestinal disorders. Methods Find Exp Clin Pharmacol 1996;18 (Suppl B):3 – 6.
12. Voderholzer WA, Schatke W, Muhldorfer BE, et al. Clinical response to dietary fiber treatment of chronic constipation. Am J Gastroenterol 1997;92:95 – 8.
13. McRorie J, Pepple S, Rudolph C. Effects of fiber laxatives and calcium docusate on regional water content and viscosity of digesta in the large intestine of the pig. Dig Dis Sci 1998;43:738 – 45.
14. Teuri U, Korpela R. Galacto-oligosaccharides relieve constipation in elderly people. Ann Nutr Metab 1998;42:319 – 27.
15. Rumessen JJ, Hamberg O, Gudmand-Hoyer E. Interval sampling of end-expiratory hydrogen (H2) concentrations to quantify carbohydrate malabsorption by means of lactulose standards. Gut 1990;31:37 – 42.
16. McIntyre A, Young GP, Taranto T, et al. Different fibers have different regional effects on luminal contents of rat colon. Gastro- enterology 1991;101:1274 – 81.
17. Alles MS, Hautvast JG, Nagengast FM, et al. Fate of fructo- oligosaccharides in the human intestine. Br J Nutr 1996;76:211 – 21.
18. Molis C, Flourie B, Ouarne F, et al. Digestion, excretion, and energy value of fructooligosaccharides in healthy humans. Am J Clin Nutr 1996;64:324 – 8.
19. Loening-Baucke V. Modulation of abnormal defecation dynamics by biofeedback treatment in chronically constipated children with encopresis. J Pediatr 1990;116:214 – 22.

20. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920 – 4.
21. Snedecor GW, Cochran WG. Statistical Methods. Ames: Iowa State University Press; 1989.
22. Tolia V, Lin CH, Elitsur Y. A prospective randomized study with mineral oil and oral lavage solution for treatment of faecal impaction in children. Aliment Pharmacol Ther 1993;7:523 – 9.
23. Loening-Baucke V. Prevalence, symptoms and outcome of constipation in infants and toddlers. J Pediatr 2005;146:359 –63.
24. Schumann C. Medical, nutritional and technological properties of lactulose: an update. Eur J Nutr 2002;41 (Suppl 1):17 – 25.
25. Klaschik E, Nauck F, Ostgathe C. Constipation: modern laxative therapy. Support Care Cancer 2003;11:679 – 85.
26. Maffei HV. Chronic functional constipation: which supplementary fiber to choose? J Pediatr (Rio J) 2004;80:167 – 8.
27. Loening-Baucke V. Polyethylene glycol without electrolytes for children with constipation and encopresis. J Pediatr Gastroenterol Nutr 2002;34:372 – 7.
28. Liebl BH, Fischer MH, Van Calcar SC, et al. Dietary fiber and long- term large bowel response in enterally nourished nonambulatory profoundly retarded youth. JPEN J Parenter Enteral Nutr 1990;14:371 – 5.
29. Roma E, Adamidis D, Nikolara R, et al. Diet and chronic con- stipation in children: the role of fiber. J Pediatr Gastroenterol Nutr 1999;28:169 – 74.
30. Morais MB, Vitolo MR, Aguirre AN, et al. Measurement of low dietary fiber intake as a risk factor for chronic constipation in children. J Pediatr Gastroenterol Nutr 1999;29:132 – 5.
31. Morais MB, Maffei HV. Constipation. J Pediatr (Rio J) 2000;76 (Suppl 1):S147 – 56.
32. Mooren GC, van der Plas RN, Bossuyt PM, et al. The relationship between intake of dietary fiber and chronic constipation in children. Ned Tijdschr Geneeskd 1996;140:2036 – 9.
33. Aguirre AN, Vitolo MR, Puccini RF, et al. Constipation in infants: influence of type of feeding and dietary fiber intake. J Pediatr (Rio J) 2002;78:202 – 8.
34. Macfarlane S, Macfarlane GT, Cummings JH. Prebiotics in the gastrointestinal tract. Aliment Pharmacol Ther 2006;24:701 – 14.
35. McClung HJ, Boyne L, Heitlinger L. Constipation and dietary fiber intake in children. Pediatrics 1995;96:999 – 1000.
36. Marlett JA, McBurney MI, Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. J Am Diet Assoc 2002;102:993 – 1000.

CHAPTER 7

Changes in fecal short chain fatty acids and colonic microbiota composition in constipated children treated with either a multi-fiber mixture or lactulose.

Freddy TM Kokke*[1], Petra AMJ Scholtens*[2], Guenther Boehm[3], Jules JM Tolboom[4], Marc A Benninga[5], Jan Knol[2], Roderick HJ Houwen[1]

1. Department of Pediatric Gastroenterology, Wilhelmina Children's Hospital, Utrecht, The Netherlands
2. Danone Research, Wageningen, The Netherlands
3. Danone Research, Friedrichsdorf, Germany
4. Department of Pediatrics and Pediatric Gastroenterology, Radboud University Hospital, Nijmegen, The Netherlands
5. Department of Pediatric Gastroenterology, Emma Children's Hospital / Academic Medical Center, Amsterdam, The Netherlands

both authors were equally involved in this study

(not published)

Abstract

AIM

Constipation is a common problem in children. Prebiotics are often advocated as first line therapy because their fermentation results in a laxative effect. However, little is known about changes in concentration of fecal short chain fatty acids (SCFA) and composition of microbiota in constipated children. The aim of the current study was to explore these changes after ingestion of either a multi-fiber mixture or lactulose in constipated children aged 1-13 years.

METHODS

In a double-blind, randomized, controlled study, constipated children received a yoghurt drink with either a multi-fiber mixture or lactulose. At week 0 and 3 fecal samples were collected and analyzed by gas chromatography for quantization of SCFA and fluorescent *in situ* hybridization (FISH) for bifidobacteria and *Clostridium* spp.

RESULTS

Fecal samples of 101 children were available. Concentration of total SCFA decreased (non significant) and concentration of acetate increased (non significant) in both treatment groups. The concentration of other SCFA decreased, reaching statistical significance for butyrate (13.4 to 10.2 mmol/kg wet weight feces, p=0.05), and isovalerate (3.2 to 2.7, p=0.04) in the multi-fiber group and for propionate (11.7 to 11.4, p=0.05), valerate (2.1 to 1.7, p=0.02) and isovalerate (3.3 to 2.6, p=0.04) in the lactulose group. The decrease in total SCFA in both groups was comparable (-6.3 and -7.1 resp., p=0.81). Changes in concentration of individual SCFA in time were comparable between the 2 treatment groups. A significant increase in bifidobacteria in the multi-fiber (from 7.34×10^9 to 11.7×10^9, $p<0.01$) and in the lactulose group (from 5.67×10^9 to 15.9×10^9, $p<0.01$) as well as a significant decrease in total *Clostridium* spp. counts in the multi-fiber (from 1.77×10^9 to 1.16×10^9, p=0.05) and in the lactulose treatment group (from 2.35×10^9 to 1.10×10^9, $p<0.01$ resp.) was observed. Changes in bacterial counts were significantly higher in the lactulose group (resp. p=0.03 and p=0.04).

CONCLUSION

Ingestion of either a multi-fiber mixture or lactulose in constipated children results in comparable effects on total fecal SCFA and bifidobacteria and *Clostridia*. Changes in concentration of individual fecal SCFA are comparable after treatment except for a significant decrease for butyrate and isovalerate (multi-fiber

group) and for propionate, valerate and isovalerate (lactulose group). Furthermore, both the multi-fiber and lactulose affect the composition of the colonic microbiota in constipated children, with a significant increase in total bifidobacteria, and significant decrease in total *Clostridium* spp. These changes are significantly larger in the lactulose group.

Introduction

Childhood constipation is a frequent encountered condition, characterized by infrequent and painful defecation and often accompanied by the involuntary loss of feces.[1] Lactulose is often used in the treatment of childhood constipation. Its action is based on its fermentation by bacteria in the colon resulting in the production of short chain fatty acids (SCFA). The subsequent increase in osmolality leads to higher intra-luminal water content and a larger feces volume. Stools, therefore, become softer and stool frequency increases.[2] Interestingly, lactulose can also be considered as a prebiotic as it affects the microbiota of the host by selectively stimulating the growth of a limited number of bacteria strains in the colon like bifidobacteria and lactobacillus at the cost of possibly harmful bacteria like *Clostridia*.[2–5]

SCFA are responsible for the increase in the intra-luminal osmotic load resulting in osmotic as well as mechanical stimulation of colonic motility.[6,7] Ingestion of lactulose in healthy volunteers leads to an overall increase of fecal SCFA.[8] In addition a shift in the composition of SCFA is seen with an increase of acetic acid and a decrease of propionic acid, butyric acid, and valeric acid.[8] Like lactulose, prebiotics such as inulin and oligofructose also stimulate the colonic production of SCFA and favour the growth of indigenous Lactobacilli and bifidobacteria.[8,9] The same holds for other dietary carbohydrates like resistant starches.[10]

In constipated children, *Clostridia* were found to be present in higher counts than in non-constipated patients and that this could be reversed by administration of prebiotics.[11] In addition, it has been suggested that *Clostridia* may play a role in the onset of constipation. Jonsson *et al.* showed that *Clostridia* produce medium-chain fatty acids that increase colonic water absorption resulting in constipation.[12] Stimulating the growth of Bifidobacteria at the cost of *Clostridia* through fermentation of prebiotics could therefore have a potential additional laxative effect.

Like lactulose, dicoman 5, glucomannan, and cocoa husk exert the same dual effect in the colon: a laxative effect through SCFA production and a shift in composition of colonic microbiota. They have therefore been investigated in therapeutic trials in (childhood) constipation.[13-16] Instead of a single-fiber supplement, an alternative approach could be the use of a multi-fiber mixture with both short chain (galacto-oligosaccharides (GOS)) and long chain fiber (inulin, soy polysaccharide (SP) and resistant starch (RS)). The fermentation of the described multifiber mixture should occur sequentially during colonic transit and may promote higher levels of SCFA.[17] Therefore it could be expected that long chain fibers in vivo produce SCFA more distal in the colon, while fermentation of short chain oligosaccharides, such as GOS, will be completed in the proximal colon, as is the case for the disaccharide lactulose.[18-21] The fermentation of such a multi-fiber mixture, containing long chain dietary fibers, might take more time to complete.

Therefore the aim of the current study was to explore changes in fecal SCFA production and changes in composition of the colonic microbiota after ingestion of either a multi-fiber mixture or lactulose in constipated children aged 1-13 years.

Materials and methods

The results presented in this paper are part of a larger study aimed at the clinical efficacy and safety of a dietary multi-fiber mixture in the treatment of childhood constipation. A detailed description of the materials and methods has already been published.[22] In short, the study had a double blind, randomized, controlled design. Constipated children aged 1-13 years were included and randomized to receive a yoghurt drink containing a multi-fiber mixture (3.0g trans-galacto oligosaccharides (polymerization degree 2-7), 3.0g inulin (Frutafit EXL; polymerization degree 20-60), 1.6g soy fiber and 0.33g resistant starch RS3 (Novelose 330) per 100mL) or a yoghurt drink containing 8g of lactulose per 100mL. The intake of the yoghurt drink increased with body weight. Fecal samples were collected before the start of the study (week 0) and three weeks thereafter (week 3) in plastic tubes. The fecal samples were immediately stored at -20°C and analyzed within 14 days.

LABORATORY ANALYSIS

Short chain fatty acids

Short chain fatty acids (acetic, propionic, and n-butyric acids, iso-butyric, n-valeric, and iso-valeric acids) content of the fecal samples was determined by a Varian 3800 gas chromatograph (Varian, Inc., Walnut Creek, CA) equipped with a flame ionization detector as described earlier.[23]

Fluorescent in situ hybridization (FISH) for bifidobacteria and Clostridium spp. (Clostridium histolyticum / Clostridium lituseburense)

Collected feces was stored at -20°C, fecal samples were thawed on ice, suspensions were made by weighing 1 gram of feces and adding 9 ml of PBS (phosphate buffered saline, pH 7.4) and homogenizing for 10 minutes in a stomacher (IUL Instruments, Barcelona, Spain). One milliliter of homogenized fecal suspension was directly fixed in 3 mL freshly prepared 4% (wt/vol) paraformaldehyde in PBS and incubated overnight at 40°C. Fixed samples were separated into aliquots and stored at -20°C to be used for the microbiota analysis. The composition of the colonic microbiota was analyzed with fluorescent in situ hybridization (FISH) as described previously.[24] Fecal samples were applied to gelatin-coated glass slides 8-well object slides with square-shaped wells (1 cm^2 per well; CBN Labsuppliers, Drachten, the Netherlands), air dried and hybridized with 10 ng/mL Cy3-labelled *Bifidobacterium* specific probe Bif164,[25] Cy3-labelled *Clostridium histolyticum* / *Clostridium lituseburense* specific probe Chis150/Clit135,[25] or incubated and stained with 0,25 ng/mL 4',6-diamidino-2-phenylindole (DAPI) for total cell counts. Slides were automatically counted using an Olympus AX70 epifluorescence microscope and image analysis software. The percentage of bifidobacteria per sample was determined by analyzing 25 randomly chosen microscopic positions.[26] At each position, the number of bifidobacteria and *Clostridia* spp. was determined by counting all cells with a DAPI filter set and counting all bifidobacteria and *Clostridia* spp. using a Cy3 filter set (SP100 and 41007, resp.; Chroma Technology Corp., Brattleboro, VT).

Data analysis

Data were checked for normality by visual inspection of the normal probability curves, and with the Shapiro-Wilk test of normality. Due to a skewed distribution of the data, non-parametric tests were performed to assess statistical significant differences between the groups. For the differences in time within the treatment group, paired tests were performed with the Wilcoxon Signed Ranks test. Differences between the groups in the change from week 0 to week 3 were assessed with Mann-Whitney *U* tests. The results are presented as medians with the minimum and maximum values, unless mentioned otherwise.

Results

SCFA

In total, 135 patients were randomized. Fecal samples of 101 children were available (45 in the multi-fiber group and 56 in the lactulose group (figure 1). The population characteristics were comparable between the two groups (table 1).

Figure 1 Flow chart of participants

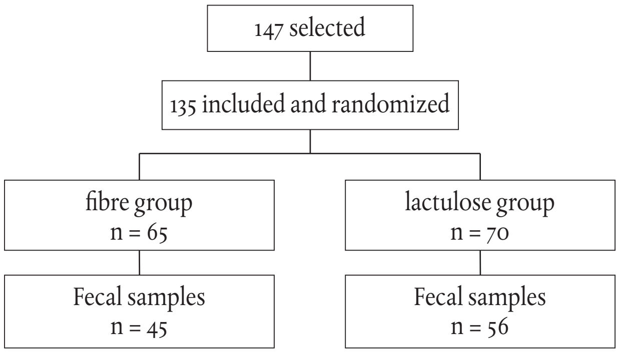


Table 1 Baseline characteristics of constipated children from the multi-fiber and lactulose group.

Characteristics	Multi-fiber	Lactulose	P
Boys / Girls	20/25	24/32	0.88
Weight (kilogram)	8-46 (median: 22)	12-51 (median: 20)	0.85
Age (years)	1-13 (median: 5)	1-13 (median: 5)	0.69
Duration complaints (weeks)	1-72 (median: 12)	1-104 (median:12)	0.79

The concentration of total SCFA (the sum of acetate, propionate, butyrate, iso-butyrate, valerate, and iso-valerate expressed in mmol/kg wet weight feces) slightly decreased in both treatment groups. This change was not significant in the multi-fiber group (89.8 in week 0 and 83.5 in week 3, p=0.50) nor in the lactulose group (83.7 in week 0 and 79.6 in week 3, p=0.74). In addition, the decrease in total SCFA in the multi-fiber and lactulose group was comparable (-6.3 and -7.1 mmol/kg wet weight feces resp.; p=0.81).

A non significant increase in acetate was seen in both treatment groups. Other SCFA molecules showed a decrease that reached statistical significance for butyrate and isovalerate in the fiber mixture group and for propionate, valerate and isovalerate in the lactulose group (table 2). Changes in the concentrations of individual SCFA in time were comparable between the 2 treatment groups (data not shown).

Table 2 Absolute concentration of individual fecal SCFA before (week 0) and after treatment (week 3) for the multi-fiber group and lactulose group.

Multi-fiber	median week 0	median week3	p-value
Acetate	46.0	50.0	0.76
Propionate	16.5	16.3	0.67
Butyrate	13.38	10.19	0.05
Isobutyrate	2.1	1.8	0.07
Valerate	2.6	2.2	0.15
Isovalerate	3.2	2.7	0.04
Total SCFA	89.8	83.5	0.50
Lactulose	**median week 0**	**median week 3**	**p-value**
Acetate	41.0	54.5	0.11
Propionate	11.7	11.4	0.05
Butyrate	10.8	10.0	0.08
Isobutyrate	2.1	1.9	0.11
Valerate	2.1	1.7	0.02
Isovalerate	3.3	2.6	0.04
Total SCFA	83.7	79.6	0.74

Concentration of SCFA is expressed in mmol/kg wet weight feces.

MICROBIOTA

A significant increase in total bifidobacteria was observed in the multi-fiber (from 7.34×10^9 to 11.7×10^9, $p<0.01$) as well as in the lactulose group (from 5.67×10^9 to 15.9×10^9, $p<0.01$). Also a significant decrease of total *Clostridium* spp. was observed in the multi-fiber (from 1.77×10^9 to 1.16×10^9, $p=0.05$) as well as in the lactulose treatment group (from 2.35×10^9 to 1.10×10^9, $p<0.01$ resp.) (table 3). The increase in bifidobacteria counts and the decrease in the *Clostridium* spp. counts was significantly greater in the lactulose as compared to the multi-fiber group (resp. $p=0.03$ and $p=0.04$).

Table 3 Bacterial counts before (week 0) and after treatment (week 3) in the multi-fiber group and lactulose group.

Multi-fiber	median week 0	median week 3	p-value
Total bacteria	$3.03x10^{10}$	$3.18x10^{10}$	0.80
Bifidobacteria	$7.34x10^{9}$	$11.7x10^{9}$	<0.01
Clostridia	$1.77x10^{9}$	$1.16x10^{9}$	0.05
Lactulose	median week 0	median week 3	p-value
Total bacteria	$3.74x10^{10}$	$3.55x10^{10}$	0.41
Bifidobacteria	$5.67x10^{9}$	$15.9x10^{9}$	<0.01
Clostridia	$2.35x10^{9}$	$1.10x10^{9}$	<0.01

Quantity of bacteria is expressed in CFU (colony forming units)

Discussion

The current study shows that in constipated children aged 1-13 years neither the ingestion of a multi-fiber supplement (containing galacto-oligosaccharides (GOS), inulin, soy polysaccharides (SP), and resistant starch [RS3]) nor lactulose did result in a significant change in total fecal SCFA although significant changes were found in some of the individual SCFA. In addition, the effectiveness for inducing these SCFA changes was not different between the multi-fiber mixture and lactulose. In both groups a significant increase in total bifidobacteria and a significant decrease in total *Clostridium* spp. were found, lactulose being more effective in inducing these changes.

Our initial hypothesis was that the multi-fiber mixture would give better results in constipated children with respect to laxation, SCFA production and induction of changes in bacterial species, as fermentation of long chain fibers in the multi-fiber mixture were thought to occur throughout the colon, while lactulose is degraded in the proximal colon [19]. However, no differences in SCFA production were found between both products, and although lactulose was slightly more efficient in inducing softer stools in the clinical study, the overall laxative effect was comparable [22]. In the current study the increase in bifidobacteria and decrease in *Clostridia* species was larger in the lactulose group, despite the relatively large amount of long chain fibers (63%) in the mixture that were hypothesized to induce a greater bacterial response. These unexpected results might be partly explained by the small amount (3 grams) and a less efficient induction by GOS of changes in the microbiota in comparison with lactulose (8 grams). For example it was found that the increase in bifidobacteria was 8 times greater with lactulose as with its synthetic derivate lactitol [8]. Finally our hypothesis of extended fermentation, supposedly resulting in a better effect for the fiber mixture, could have been wrong.

These results have to be scrutinized even more, as only 5% of the SCFA produced in the colon appear in the feces due to colonic uptake. Consequently this measurement is a poor indication of SCFA production in the (proximal) colon.[27,28] For example, for inulin and oligofructose using a dose of 15g/day, no effects on fecal concentrations were found, most likely because most of the SCFA formed during fermentation had been absorbed or utilized by the colonic mucosa.[29] Thus, as we found here, ingestion of prebiotics does not necessarily lead to an increase in the concentration of fecal SCFA.

With both the multi-fiber mixture and lactulose the total number of bacteria per gram fecal material remained stable at the level of $3.0\text{-}3.7 \times 10^{10}$ known to be normal for children.[30] However, within this stable bacterial population we found an increase in bifidobacteria and a decrease in *Clostridia* species upon the treatment of constipation with lactulose or the multi-fiber mix. Interestingly, an observational study has shown that constipated children harbor higher *Clostridia* when compare to healthy children.[11] Although it cannot be excluded that it is a secondary effect of the constipation this might suggest that *Clostridia* species contribute to constipation, as has been suggested before.[12] If *Clostridia* have a causative role in constipation, the impact of both interventions on this bacterial group may partly explain the symptom improvement, apart from the other laxative effects of these prebiotics.

In conclusion, a yoghurt drink with either a multi-fiber mixture or lactulose was shown to induce a shift in the microbiota in the colon, which might be beneficial. Total SCFA concentration, as measured in the feces, was not affected, although some changes in individual SCFA molecules were found.

Acknowledgements

The authors would like to thank the families for their participation in the study, Marieke Majoor for the help in the practical execution of the study, and Esmeralda van der Linde for the laboratory analyses.

References

1. van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol 2006; 101:2401-9.
2. Schumann C. Medical, nutritional and technological properties of lactulose. An update. Eur J Nutr 2002; 41 Suppl 1:I17-25.
3. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 1995; 125:1401-12.
4. Roberfroid MB. Functional foods: concepts and application to inulin and oligofructose. Br J Nutr 2002; 87 Suppl 2:S139-43.
5. Macfarlane S, Macfarlane GT, Cummings JH. Review article: prebiotics in the gastrointestinal tract. Aliment Pharmacol Ther 2006; 24:701-14.
6. Cummings JH. Constipation, dietary fibre and the control of large bowel function. Postgrad Med J 1984; 60:811-9.
7. Jenkins DJ, Jenkins AL, Wolever TM, Rao AV, Thompson LU. Fiber and starchy foods: gut function and implications in disease. Am J Gastroenterol 1986; 81:920-30.
8. Ballongue J, Schumann C, Quignon P. Effects of lactulose and lactitol on colonic microflora and enzymatic activity. Scand J Gastroenterol Suppl 1997; 222:41-4.
9. Guarner F. Inulin and oligofructose: impact on intestinal diseases and disorders. Br J Nutr 2005; 93 Suppl 1:S61-5.
10. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol 2006; 40:235-43.
11. Zoppi G, Cinquetti M, Luciano A, Benini A, Muner A, Bertazzoni Minelli E. The intestinal ecosystem in chronic functional constipation. Acta Paediatr 1998; 87:836-41.
12. Jonsson G, Midtvedt AC, Norman A, Midtvedt T. Intestinal microbial bile acid transformation in healthy infants. J Pediatr Gastroenterol Nutr 1995; 20:394-402.
13. Cucchiara S, Devizia B, Staiano A, et al. [Treatment of chronic functional constipation in children by administration of vegetable fiber (Dicoman 5)]. Minerva Pediatr 1989; 41:147-52.
14. Staiano A, Simeone D, Del Giudice E, Miele E, Tozzi A, Toraldo C. Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. J Pediatr 2000; 136:41-5.
15. Loening-Baucke V, Miele E, Staiano A. Fiber (glucomannan) is beneficial in the treatment of childhood constipation. Pediatrics 2004; 113:e259-64.
16. Castillejo G, Bullo M, Anguera A, Escribano J, Salas-Salvado J. A controlled, randomized, double-blind trial to evaluate the effect of a supplement of cocoa husk that is rich in dietary fiber on colonic transit in constipated pediatric patients. Pediatrics 2006; 118:e641-8.
17. Stewart ML, Timm DA, Slavin JL. Fructooligosaccharides exhibit more rapid fermentation than long-chain inulin in an in vitro fermentation system. Nutr Res 2008; 28:329-34.
18. Rumessen JJ, Hamberg O, Gudmand-Hoyer E. Interval sampling of end-expiratory hydrogen (H_2) concentrations to quantify carbohydrate malabsorption by means of lactulose standards. Gut 1990; 31:37-42.
19. Alles MS, Hautvast JG, Nagengast FM, Hartemink R, Van Laere KM, Jansen JB. Fate of fructo-oligosaccharides in the human intestine. Br J Nutr 1996; 76:211-21.

20. Molis C, Flourie B, Ouarne F, et al. Digestion, excretion, and energy value of fructooligosaccharides in healthy humans. Am J Clin Nutr 1996; 64:324-8.
21. Heijnen ML, Deurenberg P, van Amelsvoort JM, Beynen AC. Retrograded (RS3) but not uncooked (RS2) resistant starch lowers fecal ammonia concentrations in healthy men. Am J Clin Nutr 1997; 65:167-9.
22. Kokke FT, Scholtens PA, Alles MS, et al. A dietary fiber mixture versus lactulose in the treatment of childhood constipation: a double-blind randomized controlled trial. J Pediatr Gastroenterol Nutr 2008; 47:592-7.
23. Knol J, Scholtens P, Kafka C, et al. Colon microflora in infants fed formula with galacto- and fructo-oligosaccharides: more like breast-fed infants. J Pediatr Gastroenterol Nutr 2005; 40:36-42.
24. Harmsen HJ, Wildeboer-Veloo AC, Raangs GC, et al. Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. J Pediatr Gastroenterol Nutr 2000; 30:61-7.
25. Langendijk PS, Schut F, Jansen GJ, et al. Quantitative fluorescence in situ hybridization of Bifidobacterium spp. with genus-specific 16S rRNA-targeted probes and its application in fecal samples. Appl Environ Microbiol 1995; 61:3069-75.
26. Jansen GJ, Wildeboer-Veloo AC, Tonk RH, Franks AH, Welling GW. Development and validation of an automated, microscopy-based method for enumeration of groups of intestinal bacteria. J Microbiol Methods 1999; 37:215-21.
27. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev 2001; 81:1031-64.
28. Kien CL, Schmitz-Brown M, Solley T, Sun D, Frankel WL. Increased colonic luminal synthesis of butyric acid is associated with lowered colonic cell proliferation in piglets. J Nutr 2006; 136:64-9.
29. Nyman M. Fermentation and bulking capacity of indigestible carbohydrates: the case of inulin and oligofructose. Br J Nutr 2002; 87 Suppl 2:S163-8.
30. Tiihonen K, Ouwehand AC, Rautonen N. Human intestinal microbiota and healthy ageing. Ageing Res Rev 2010;9:107-16.

CHAPTER 8

General discussion

Constipation in childhood is a very common problem. In most cases it is short lived and can be treated easily. When constipation is diagnosed in a child a few organic diseases, like Hirschsprung's disease, must be ruled out first, which can generally be done by taking a thorough history and performing a complete physical examination. When, as in most constipated children, no organic cause can be found, a diagnosis of functional constipation is made. No further investigations are needed and a trial with laxative treatment for a limited amount of time is standard care. In this thesis, we reported the results of further research into the diagnosis and treatment of constipation in otherwise healthy children and in pediatric CF patients. The main focus in this thesis was the use of dietary fiber as a treatment option.

Low dietary fiber and fluid intake are considered to be important factors in the development of childhood constipation. A lower absolute fiber intake in children with constipation was indeed described in several studies. In contrast, others could not find this difference between constipated children and controls with respect to fiber intake. When scrutinizing these studies, it became clear that those studies that did find a correlation between low fiber (and/or fluid) intake and constipation generally expressed the intake in g/day, while those studies that could not find a correlation expressed intake in g/MJ/day. In **chapter 3** we therefore evaluated dietary fiber, fluid and energy intake in constipated children and in healthy controls from a single cohort and expressed fiber and fluid intake both in g/day and in g/MJ/day. Although we found that absolute intake of fiber and fluid was significantly lower in constipated children compared to healthy controls, fiber and fluid intake expressed as g/MJ/day did not differ. These different outcomes, depending on the unit used (g/day or g/MJ/day), could be an explanation for the contradictory results found in the literature. It also suggests that fiber intake is probably not very important in the development or resolution of childhood constipation. So it seems unwise to advice a drastic increase in the intake of fiber in constipated children, as this is difficult for children to comply to, and the effect is doubtful.

In the diagnosis of childhood functional constipation many clinicians order a plain abdominal radiograph to assess the presence of retained stool or enlargement of the distal gastrointestinal tract to confirm the diagnosis, to evaluate the severity of constipation, to evaluate success of treatment or to help convince the parents that constipation is indeed the cause of their child's complaints. To date 3 scoring systems have been described to assess the severity of fecal loading on an abdominal radiograph.[1-3] Sofar, a fourth scoring method, described by Starreveld et al,[4] was used in adults only. In **chapter 4** we evaluated this scoring method and compared it with the most widely used Barr score. Both the Starreveld and the Barr scoring method appeared to be of limited value in the diagnosis of pediatric constipation. As similar results were obtained when re-evaluating other scoring systems the abdominal radiograph should not be a part of the routine work-up of pediatric constipation. However both our study and most other studies evaluating the use of an abdominal radiograph in the diagnosis of pediatric constipation have used controls that were recruited from an outpatient clinic for pediatric gastroenterology and had abdominal complaints, so some of the controls could in fact have had an overfilled colon, but without meeting the diagnostic criteria for constipation. Scientifically more convincing results could have been obtained when a control group was used not having gastrointestinal complaints.[5]

Diagnosing constipation in pediatric cystic fibrosis patients can be a challenge for pediatric gastroenterologists as in cystic fibrosis patients two patterns of defecation disorders exist: constipation and the distal intestinal obstruction syndrome (DIOS). Recently, criteria for constipation and DIOS in pediatric CF patients were published by the ESPGHAN CF Working Group.[6] Constipation was defined as [1] abdominal pain and/or distension or [2a] a reduced frequency of bowel movements in the last few weeks and/or [2b] increased consistency of stools in the last few weeks, while [3] the symptoms are relieved by the use of laxatives. DIOS was defined as the combination of [1] complete intestinal obstruction, as evidenced by vomiting of bilious material and/or fluid levels in small intestine on an abdominal radiograph with [2] a fecal mass in the ileocecal area and [3] abdominal pain and/or distension. In **Chapter 5**, using these criteria, we found that almost half of the CF patients had a history of constipation, while 20% patients were constipated at the reference date (January 1st, 2006). Meconium ileus and low total fat absorption were independently associated with constipation. However, fiber intake was not associated with constipation in CF as was also found in a study from Belgium.[7] Furthermore, no differences in the fluid intake between patients with or without constipation were found. In practice this should lead to a high suspicion of constipation in every CF patient with abdominal complaints, especially in those with a history of meconium ileus or when fatty feces are described. A liberal use of laxatives, preferably polyethylene glycols, is recommended. Parents should be instructed to adapt the dose in case of abdominal pain or change in defecation pattern in their child as managing chronic disease should be performed in a partnership between clinician and patient and / or parents.[8,9]

As discussed above, several scoring methods exist to assess fecal loading on a plain abdominal radiograph. In the current study both the Barr and Leech score appeared of limited value in the diagnosis of constipation in CF patients. Consequently, an abdominal radiography can not be recommended as a standard diagnostic tool in the regular gastrointestinal follow-up of CF patients.

Until recently, with the introduction of polyethylene glycols, lactulose was the most widely used laxative in the treatment of adult and childhood constipation. Lactulose, a disaccharide, is a fiber that is quickly and completely fermented in the cecum. At the outset of our studies we hypothesized that a mixture containing a combination of fibers that are quickly and totally fermented, and fiber that is partially, more slowly fermented, could led to better results in the treatment of childhood constipation. In this mixture fermentation would proceed during the passage through the complete colon (in contrast to lactulose where fermentation takes place in the proximal colon) and would therefore continue to have a laxative effect up to the distal parts of the colon.

Chapter 6 describes the outcome of a prospective, randomized, double blind trial with this fiber mixture versus lactulose, the total amount (in grams) of either laxative being the same. Fiber mixture and lactulose led to a comparable outcome in the treatment of childhood constipation. However, duration of the study might have been too short or power calculation too optimistic to reveal differences between the two treatments. The results of this study however show that the use of a fiber mixture dissolved in a yoghurt drink in the treatment of childhood constipation is feasible.

Nevertheless we were concerned by the refusal of a considerable number of children to continue the use of the fiber mixture or the lactulose because of the taste and/or quantity to consume. Similar problems were encountered when using milk of magnesia as a laxative[10] but not with glucomannan[11] or polyethylene glycol (PEG; this can be considered as artificial long non-branching non-fermentable fiber with a molecular weight between 3350 and 4000).[10,12,13] However, in a trial comparing lactulose and PEG 3350 (with electrolytes), bad taste was reported significantly more often in the PEG group.[14] This emphasizes that taste matters in children taking laxatives. In this respect the introduction of tasteless polyethylene glycol without electrolytes, is certainly an improvement. As polyethelene glycol also outperformed lactulose in several recent trials, it seems appropriate to promote PEG instead of lactulose or (a) dietary fiber (mixture) in the future.[14,15]

Dietary fiber exerts its laxative action mainly by the production of short chain fatty acids (SCFA) during fermentation in the colon. Additionally, some fibers stimulate growth of certain genera present in the colonic microbiota. So far, little is known about SCFA production and changes in microbiota composition after supplementing dietary fiber in (constipated) children. In **Chapter 7** we therefore investigated the changes in fecal short chain fatty acids production and colonic microbiota composition in constipated children treated with either the multi-fiber mixture or lactulose. The study showed that in constipated children aged 1-13 years neither the ingestion of a multi-fiber supplement nor lactulose did result in a significant change in total fecal SCFA (a non-significant decrease in total fecal SCFA was found in both groups) although significant changes were found in some of the individual SCFA. However, less than 5% of bacterial derived SCFA appears in, whereas 95% is metabolized in the colon or absorbed by colonocytes.[16,17] Consequently the measurement of fecal SCFA, although easy to sample, is rather a poor indication of the production in the (more proximal) colon.[16,17,18] Measuring exact local production of SCFA would have been better, but sampling is difficult without invasive techniques. However, stabile isotope methodology is now being developed in specialised laboratories, so site of production and fate of SCFA in the human body can be studied in the near future.[19,20]

Finally, a statistical significant increase in total bifidobacteria (from 7.34×10^9 to 11.7×10^9 in the multifiber group; $p<0.01$ and 5.67×10^9 to 15.9×10^9 in the lactulose group; $p<0.01$) and a significant decrease in total *Clostridium* spp. (from 1.77×10^9 to 1.16×10^9, in the multifiber group; $p=0.05$) and 2.35×10^9 to 1.10×10^9 in the lactulose group; $p<0.01$ were found. These changes were significantly larger in the lactulose group suggesting that the rapid and complete fermentation of lactulose in the cecum is more efficient in stimulating the growth of bifidobacteria at the expense of Clostridia species, than fermentation of the fiber mixture that is thought to be completed slowly and throughout the colon. It also seems likely that the changes in the colonic microbiota were induced by the prebiotic effect of the laxatives used in the study (the fiber mixture or lactulose) and were not secondary to a better fecal flow, as polyethylene glycol, which is at least equivalent to lactulose with respect to its laxative potential, does not induce this shift in colonic microbiota.[21] It remains questionable whether the supposed beneficial effects of an increased number of bifidobacteria in constipated children should tip the balance in favour of laxatives with prebiotic potential. PEG without electrolytes does have a taste advantage,[22] and might be marginally more effective on a weight/weight basis than lactulose,[23] while evidence for the proposed advantages of a bifidogenic agent in constipated, but otherwise healthy individuals is still lacking.[24] In summary, therefore this thesis suggests that the role of dietary fiber in the treatment of childhood constipation is more limited than assumed previously.

References

1. Barr RG, Levine MD, Wilkinson RH, Mulvihill D. Chronic and occult stool retention: a clinical tool for its evaluation in school-aged children. Clin Pediatr (Phila) 1979; 18:674-9.
2. Blethyn AJ, Verrier Jones K, Newcombe R, Roberts GM, Jenkins HR. Radiological assessment of constipation. Arch Dis Child 1995; 73:532-3.
3. Leech SC, McHugh K, Sullivan PB. Evaluation of a method of assessing faecal loading on plain abdominal radiographs in children. Pediatr Radiol 1999; 29:255-8.
4. Starreveld JS, Pols MA, Van Wijk HJ, Bogaard JW, Poen H, Smout AJ. The plain abdominal radiograph in the assessment of constipation. Z Gastroenterol 1990; 28:335-8.
5. Jackson CR, Lee RE, Wylie AB, Adams C, Jaffray B. Diagnostic accuracy of the Barr and Blethyn radiological scoring systems for childhood constipation assessed using colonic transit time as the gold standard. Pediatr Radiol 2009; 39:664-7.
6. Houwen RH, van der Doef HP, Sermet I, et al. Defining DIOS and Constipation in Cystic Fibrosis With a Multicentre Study on the Incidence, Characteristics, and Treatment of DIOS. J Pediatr Gastroenterol Nutr 2010; 50:38-42.
7. Proesmans M, De Boeck K. Evaluation of dietary fiber intake in Belgian children with cystic fibrosis: is there a link with gastrointestinal complaints? J Pediatr Gastroenterol Nutr 2002; 35:610-4.
8. Robinson A, Thompson DG, Wilkin D, Roberts C. Guided self-management and patient-directed follow-up of ulcerative colitis: a randomised trial. Lancet 2001; 358:976-81.
9. Kennedy AP, Nelson E, Reeves D, et al. A randomised controlled trial to assess the effectiveness and cost of a patient orientated self management approach to chronic inflammatory bowel disease. Gut 2004; 53:1639-45.
10. Loening-Baucke V. Polyethylene glycol without electrolytes for children with constipation and encopresis. J Pediatr Gastroenterol Nutr 2002; 34:372-7.
11. Staiano A, Simeone D, Del Giudice E, Miele E, Tozzi A, Toraldo C. Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. J Pediatr 2000; 136:41-5.
12. Youssef NN, Peters JM, Henderson W, Shultz-Peters S, Lockhart DK, Di Lorenzo C. Dose response of PEG 3350 for the treatment of childhood fecal impaction. J Pediatr 2002; 141:410-4.
13. Pashankar DS, Loening-Baucke V, Bishop WP. Safety of polyethylene glycol 3350 for the treatment of chronic constipation in children. Arch Pediatr Adolesc Med 2003; 157:661-4.
14. Voskuijl W, de Lorijn F, Verwijs W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. Gut 2004; 53:1590-4.
15. Dupont C, Leluyer B, Maamri N, et al. Double-blind randomized evaluation of clinical and biological tolerance of polyethylene glycol 4000 versus lactulose in constipated children. J Pediatr Gastroenterol Nutr 2005; 41:625-33.
16. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev 2001; 81:1031-64.

17. Kien CL, Schmitz-Brown M, Solley T, Sun D, Frankel WL. Increased colonic luminal synthesis of butyric acid is associated with lowered colonic cell proliferation in piglets. J Nutr 2006; 136:64-9.
18. Nyman M. Fermentation and bulking capacity of indigestible carbohydrates: the case of inulin and oligofructose. Br J Nutr 2002; 87 Suppl 2:S163-8.
19. Meesters RJ, van Eijk HM, ten Have GA, et al. Application of liquid chromatography-mass spectrometry to measure the concentrations and study the synthesis of short chain fatty acids following stable isotope infusions. J Chromatogr B Analyt Technol Biomed Life Sci 2007; 854:57-62.
20. Pouteau E, Nguyen P, Ballevre O, Krempf M. Production rates and metabolism of short-chain fatty acids in the colon and whole body using stable isotopes. Proc Nutr Soc 2003; 62:87-93.
21. Bouhnik Y, Neut C, Raskine L, et al. Prospective, randomized, parallel-group trial to evaluate the effects of lactulose and polyethylene glycol-4000 on colonic flora in chronic idiopathic constipation. Aliment Pharmacol Ther 2004; 19:889-99.
22. Humphreys MR, Reinberg YE. Contemporary and emerging drug treatments for urinary incontinence in children. Paediatr Drugs 2005; 7:151-62.
23. Kokke FT, Scholtens PA, Alles MS, et al. A dietary fiber mixture versus lactulose in the treatment of childhood constipation: a double-blind randomized controlled trial. J Pediatr Gastroenterol Nutr 2008; 47:592-7.
24. Macfarlane S, Macfarlane GT, Cummings JH. Review article: prebiotics in the gastrointestinal tract. Aliment Pharmacol Ther 2006; 24:701-14.

Summary

Chapter 1 addresses general aspects of childhood constipation, an important health problem with a median prevalence of 9% worldwide, which is characterized by infrequent and often painful defecation. In less than 5% of constipated children an organic cause can be found (e.g. M. Hirschsprung, cerebral palsy, cystic fibrosis or the use of constipation promoting drugs) while in the remainder no organic disease is found after thorough investigation. In this latter group of patients, with so-called functional constipation, behavioral as well as dietary factors are considered to be important. One of the dietary factors that are implicated is dietary fiber, which is the main topic of this thesis.

Chapter 2 reviews the general role of dietary fiber in childhood and its applications in pediatric gastroenterology. Dietary fiber is the carbohydrate fraction in food that cannot be digested in the small intestine, but will be -partially- fermented by bacteria in the colon subsequently. Fiber and its fermentation products, short chain fatty acids (SCFA), will increase fecal bulk, decrease intestinal transit time and soften the stools, and as such have a laxative effect. As fiber might also have other health benefits, such as reducing the energy density of food, generally an ample fiber intake (0.5 g/kg/day) is recommended for toddlers and older children. However, only a minority of the children will actually consume this amount.

Low dietary fiber and fluid intake indeed are often considered as important causative factors in the development of childhood constipation but studies investigating this association have been contradictory. Several studies found an association between fiber intake and the constipation in otherwise healthy children, whereas others could not find this association.

Chapter 3 now describes the results of a study comparing dietary fiber and fluid intake in constipated and healthy children. This study shows for the first time that, depending on the unit used (g/day vs. g/MJ/day), results regarding the association between dietary fiber intake and childhood constipation differ. When dietary fiber intake is expressed in gram per day, intake was significantly lower in the constipated children while, when expressed in gram per megajoule energy intake per day, the intake was similar in constipated and healthy controls. The same was found with respect to water intake. We suggest that these different outcomes, depending on the unit used, can be an explanation for the contradic-

tory results found in literature. Finally, neither the constipated nor the healthy controls did meet Dutch recommendations for dietary fiber intake, suggesting that these recommendations might be too high.

The diagnosis of constipation in childhood is made by careful history taking in combination with a thorough physical examination. Sometimes a plain abdominal radiograph is made additionally.

In **Chapter 4** we investigated whether this practice can contribute to the diagnostic process by evaluating two scoring methods for fecal loading on an plain abdominal radiograph (Starreveld and Barr) in pediatric patients with or without constipation. Accuracy as measured by the area under the receiver operator characteristics curve for the Starreveld score was 0.54 and for the Barr score 0.38, indicating poor discriminating power. Inter-observer agreement was 0.49-0.52 (Starreveld) and 0.44 (Barr), which is considered moderate and intra-observer agreement was 0.52-0.71 (Starreveld) and 0.62- 0.76 (Barr) which is considered moderate to good. This study therefore showed that both the Starreveld and Barr scoring method to assess fecal loading on a plain abdominal radiograph is of limited value in the diagnosis of childhood constipation. It also confirmed what earlier studies, investigating several scoring methods (i.e. Barr, Leech and Blethyn score), found: the original publications all show good to excellent results while most studies trying to duplicate these results failed to do so. Given these results we conclude that the abdominal radiograph should not be part of the routine work up of childhood constipation.

Slow intestinal transit is a common problem in patients with Cystic Fibrosis (CF) frequently causing constipation. As the exact prevalence of constipation in CF is unknown, in **Chapter 5** we investigated all pediatric CF patients that were under our care at 1-1- 2006. In 46 out of 230 CF patients (20%) constipation was present at that moment, while 107 (47%) had a history of constipation. A low fat absorption and a history of meconium ileus were independent risk factors for constipation in CF, while fiber and fluid intake were not associated. We also investigated whether a routine abdominal radiograph, scored according to Barr and Leech, could help in making the diagnosis of constipation in CF patients, which is now done primarily by history taking and physical examination. We found that in CF patients the inter- and intra-observer variability of the Barr and Leech scores were poor to moderate.
So, constipation appears to be a significant medical issue in pediatric CF patients while in this patient group too it seems inappropriate to include an abdominal radiography in the regular follow-up.

Chapter 6 describes the results of a randomized, double-blind, prospective controlled trial comparing a mixture containing 4 different types of dietary fiber with lactulose in the treatment of childhood constipation. The laxative effect of both lactulose and the fiber mixture is primarily obtained through fermentation in the colon. Our hypothesis was that the mixture, containing fibers of different length, would perform better, because fermentation is expected to take place in the complete colon in contrast to the very short lactulose molecule that is fermented in the proximal part of the colon. The study showed, however, no difference between the groups with respect to defecation frequency and fecal incontinence frequency. Also abdominal pain and flatulence scores were comparable, as were the necessity of step-up medication during the treatment period and taste scores. However, duration of the study might have been too short or the groups too small (42 versus 55) to reveal differences between the two treatments. Fermentation of fiber and lactulose in the colon will result in the generation of SCFA and in a modification of the composition of the bacterial species in the colon, i.e. an increase in the number of bifodobacteria and a reduction of clostridium species.

In **Chapter 7** we investigated whether either the fiber mixture or lactulose (see chapter 6) was more efficient in inducing SCFA production and changes in the colon microbiota. We found that after 3 weeks treatment the fecal concentration of total SCFA had slightly (non-significantly) decreased in both the fiber mixture and lactulose group. However a significant increase in bifidobacteria in the multi-fiber and in the lactulose group, as well as a significant decrease in total *Clostridium* species counts in the multi-fiber and in the lactulose treatment group were observed. These changes were significantly larger in the lactulose group suggesting that the rapid and complete fermentation of lactulose in the proximal colon is more efficient in stimulating the growth of bifidobacteria at the expense of Clostridia species, than a fiber mixture that is thought to be fermented throughout the colon.

In **Chapter 8** we conclude that the role of dietary fiber in the genesis of constipation is at least questionable and the role in the resolution of childhood constipation limited, although several studies have shown that dietary fiber performs better than placebo. The polyethylene glycol preparations in use nowadays in the treatment of childhood constipation are good treatment alternatives that have been proven to be superior to lactulose and dietary fiber.

Samenvatting

In **hoofdstuk 1** worden algemene aspecten besproken van obstipatie op de kinderleeftijd, een belangrijk gezondheidsprobleem met een wereldwijde mediane prevalentie van 9%. Obstipatie wordt gekarakteriseerd door een infrequente en vaak pijnlijke ontlasting. In minder dan 5% van de gevallen kan een organische oorzaak gevonden worden (bijvoorbeeld ziekte van Hirschsprung, spasticiteit, cystic fibrosis of het gebruik van obstipatie bevorderende medicatie); bij het overgrote deel van de patienten wordt na uitgebreid onderzoek geen organische oorzaak gevonden. Bij deze groep, met zogenaamde functionele obstipatie, worden zowel gedrags- als dieetfactoren van groot belang geacht. Eén van deze dieetfactoren is voedingsvezel, het onderwerp waar dit proefschrift met name over gaat.

In **hoofdstuk 2** wordt een overzicht gegeven van de rol van voedingsvezel en haar toepassingen op de kinderleeftijd. Voedingsvezel zijn de koolhydraat bestanddelen van voedsel die niet verteerd kunnen worden in de dunnedarm en vervolgens -deels- worden gefermenteerd door bacteriën in de dikke darm. De voedingsvezels zelf en de produkten van de fermentatie van deze vezels, de zogenaamde korte keten vetzuren, vergroten het volume van de ontlasting, verminderen de darmpassagetijd en zorgen voor een zachtere consistentie. Door deze combinatie ontstaat een laxerend effect. Omdat voedingsvezel nog andere gezondheidseffecten kan hebben, zoals een verlaging van de energiedichtheid van de voeding, wordt een ruime vezelinname geadviseerd voor peuters, kleuters en oudere kinderen. Echter maar een klein deel van de kinderen zal deze hoeveelheid ook echt iedere dag eten .

Een lage vezel- en vochtinname wordt vaak beschouwd als een belangrijke factor bij het ontstaan van obstipatie op de kinderleeftijd, maar op basis van de studies die deze associatie tot nu toe onderzochten kon geen duidelijke conclusie getrokken worden. Sommige studies vonden namelijk wel een associatie tussen vezelinname en obstipatie bij verder gezonde kinderen, terwijl anderen deze associatie niet konden bevestigen.

Hoofdstuk 3 beschrijft de resultaten van een studie welke de vezel- en vochtinname vergelijkt tussen geobstipeerde en gezonde kinderen. Deze studie toont voor de eerste keer aan dat, afhankelijk van de manier waarop de inname wordt uitgedrukt (g/dag of gram/MJ/dag), de associatie tussen vezelinname en obstipatie wel of niet gevonden kan worden. Wanneer de vezelinname werd uitgedrukt in gram per dag was de vezelinname van geobstipeerde kinderen significant lager, terwijl wanneer deze werd uitgedrukt in gram per megajoule per dag de vezelinname van geobstipeerde en gezonde kinderen vergelijkbaar was. Hetzelfde resultaat werd gevonden voor de waterinname. We denken dat deze uitkomst, waarbij de resultaten afhankelijk zijn van de gebruikte eenheid, een verklaring kunnen zijn voor de elkaar tegensprekende literatuur. Tenslotte voldoen noch de geobstipeerde kinderen noch de gezonde controles aan de Nederlandse aanbevelingen voor voedingsvezelinname, wat suggereert dat deze aanbevelingen te hoog zouden kunnen zijn.

De diagnose obstipatie op de kinderleeftijd wordt gesteld door een nauwkeurige anamnese en goed lichamelijk onderzoek. Soms wordt tevens een buikoverzichtsfoto gemaakt. In **Hoofstuk 4** hebben wij onderzocht of dit een aanvulling kan zijn op het gebruikelijke diagnostisch proces door twee methoden om de hoeveelheid faeces op buikoverzichtsfoto's te beoordelen (Starreveld en Barr) te evalueren bij kinderen met en zonder obstipatie. De nauwkeurigheid zoals gemeten met een zogenaamde ROC (receiver operator characteristics) curve was 0.54 voor de Starreveld methode en 0.38 voor de Barr methode, hetgeen betekent dat het onderscheidend vermogen slecht is. De overeenstemming tussen de verschillende beoordelaars van de buikoverzichtsfoto's was 0.49-0.52 voor de Starreveld methode en 0.44 voor de Barr methode wat als matig kan worden beschouwd. De overeenstemming tussen twee evaluaties met een maand tussenpauze van elke beoordelaar was 0.52-0.71 voor de Starreveld methode en 0.62-0.76 voor de Barr methode, wat matig tot goed is. Deze studie toont aan dat zowel de Starreveld als de Barr methoden om de hoeveelheid ontlasting op de buikoverzichtsfoto te beoordelen van beperkte waarde zijn bij het stellen van de diagnose obstipatie op de kinderleeftijd. De studie bevestigt ook wat met eerder onderzoek al werd gevonden: de eerste publicatie van een bepaalde methode om de hoeveelheid faeces op een buikoverzichtsfoto te beoordelen laat een goede of uitstekende correlatie zien tussen kliniek (wel of geen obstipatie) en de beoordeling van de foto, terwijl studies die dit willen dupliceren daar meestal niet toe in staat zijn. Daarom stellen wij vast dat de buikoverzichtsfoto geen deel dient uit te maken van de routine diagnostiek bij obstipatie op de kinderleeftijd.

Een langzame passagetijd is een veel voorkomend probleem bij patienten met Cystische Fibrose (CF) wat ook frequent aanleiding geeft tot obstipatie. Omdat de exacte prevalentie van obstipatie bij CF onbekend is onderzochten we in **Hoofdstuk 5** alle pediatrische CF patienten die op 1 januari 2006 in ons centrum behandeld werden. Bij 46 van de 230 CF patienten (20%) was er op dat moment sprake van obstipatie, terwijl bij 107 CF patienten (47%) er in het verleden sprake was geweest van obstipatie. Een lage vetabsorptie en een meconiumileus in de voorgeschiedenis verhoogden het risico op obstipatie bij CF patienten, terwijl vezel- en vochtinname niet geassocieerd waren met obstipatie. We onderzochten verder of het routinematig maken van een buikoverzichtsfoto en beoordeeld volgens de Barr en Leech methode, zou kunnen helpen bij het stellen van de diagnose obstipatie bij CF patienten, wat tot nu toe nu gebeurt middels anamnese en lichamelijk onderzoek. We vonden dat bij CF patienten de bruikbaarheid van de Barr en Leech methode matig tot slecht was. Derhalve is het ook bij deze patiëntengroep niet nuttig standdaard buikoverzichtsfoto te maken.

Hoofdstuk 6 beschrijft de resultaten van een gerandomiseerde, dubbelblinde, prospectief gecontroleerde trial. In deze studie werd een mengsel met 4 verschillende soorten voedingsvezels vergeleken met lactulose bij de behandeling van obstipatie op de kinderleeftijd. Het laxerend effect van zowel het vezelmengsel als lactulose wordt vooral bereikt door fermentatie in de dikke darm. Onze hypothese was dat het mengsel, met vezels van verschillende lengte, het beter zou doen, omdat verwacht werd dat de fermentering in de gehele dikke darm zou plaatsvinden, in tegenstelling tot het lactulose waarvan bekend is dat het al volledig gefermenteerd wordt in het begin van de dikke darm. De studie toonde echter aan dat er geen verschil was tussen de beide groepen met betrekking tot de ontlastingsfrequentie en het aantal malen dat er sprake was van fecale incontinentie. Verder was de mate van buikpijn en flatulentie in de beide groepen vergelijkbaar, net zoals de noodzaak om extra laxantia (Transipeg®) te geven. Ook was er geen verschil in smaak. De duur van de studie kan echter te kort zijn geweest of de groepen toch te klein (42 versus 55) om verschillen tussen beide interventies te kunnen vinden.

Fermentering van vezels en lactulose in de dikke darm resulteert in de vorming van korte keten vetzuren en in een verandering van de verhouding tussen bacterie soorten in de dikke darm, met een toename van het aantal bifidobacteriën en een afname van *Clostridium* bacteriesoorten. In **Hoofstuk** 7 hebben wij onderzocht of het vezelmengsel of juist de lactulose (zie hoofdstuk 6) efficiënter is in het induceren van deze veranderingen. Wij vonden dat met beide interventies de totale faecale concentratie van korte keten vetzuren lager, maar niet significant lager, werd. Wel werd in beide groepen een significante toename van het aantal bifidobacteriën en een significante afname van het aantal *Clostridium* bacteriën gevonden. Deze verschillen waren in de lactulose groep significant groter dan in de vezel groep, wat suggereert dat de snelle en complete fermentering van lactulose in het proximale colon efficiënter is om de groei van bifidobacteriën ten koste van de *Clostridia* te stimuleren, dan het vezelmengsel waarvan gedacht wordt dat het over de gehele lengte van de dikke darm gefermenteerd wordt.

In **Hoofdstuk 8** concluderen we dat voedingsvezel geen grote rol speelt bij het ontstaan van obstipatie. Verder is de rol van vezel bij de behandeling van obstipatie beperkt, hoewel enkele studies hebben laten zien dat vezel beter werkt dan placebo.

Curriculum vitae

Freddy Kokke werd geboren op 28 mei 1958 in Utrecht als vierde in een gezin met alleen jongens. Zijn vader heette Jo en zijn moeder heet Ada. Vader werkte bij de Nederlandse Spoorwegen wat aanleiding gaf tot regelmatige verhuizingen; iets dat ook in zijn latere leven zo gebleven is.

Zijn lagere school bracht hij door in Enschede (klas 1 tot en met 5) en Culemborg (klas 6), de middelbare school in Utrecht. Het Atheneum B diploma behaalde hij in 1976 (Bonifatiuscollege). De studie Technische Natuurkunde in Delft werd opgepakt maar bleek niet de juiste keuze. Uit die tijd stamt zijn vriendschap met Michael Taen. In verband met uitloten voor de studie geneeskunde deed hij 2 jaar fysiotherapie op de Haagse Academie voor Lichamelijke Opvoeding. In 1979 kon hij eindelijk beginnen aan de studie Geneeskunde in Nijmegen. Hij maakte daar o.a. de Pierson rellen van zeer nabij mee. Twee wetenschappelijke stages deed hij: één in de geschiedenis van de geneeskunde en één in de kinderneurologie.

Na het behalen van de artsenbul startte hij onmiddellijk als AGNIO in het Academisch Ziekenhuis Maastricht in het oude St Annadal Ziekenhuis (Prof. Dr. René Kuijpers en Prof. Dr. Carlos Blanco). Na acht maanden AGNIO mocht hij zich AGIO noemen en kwam via een uitwisselingsconstructie met de Beatrix Kinderkliniek (Prof. Dr. Hugo Heymans en Prof. Dr. Albert Okken) naar het Academisch Ziekenhuis Groningen. Daar raakte hij toen bevriend met Ruurd van Elburg. Op 31 januari 1993 voltooide hij de opleiding en was enkele maanden Research Fellow Voedselallergie bij Prof. Dr. Hugo Heymans en werkte samen met Dr. Ruurd van Elburg. Mede dankzij de hulp van Prof. Dr. Hans Büller verhuisde hij met zijn gezin voor twee jaar naar Baltimore. Daar, in de School of Medicine van de Johns Hopkins University, Department of Gastroenterology (Prof. Mark Donowitz) deed hij aan de bench basaal wetenschappelijk onderzoek naar de transporter familie NHE (sodium-hydrogen exchanger). In 1995 keerde hij terug naar Groningen en werd fellow Kindergastroenterologie, later Kindergastroenteroloog en lid van het Kinderlevertransplantatieteam. In 1999 besloot hij naar een grote perifere opleidingskliniek te gaan in Arnhem (Dr. Frank Brus). Daar werkte hij zeven jaren met veel plezier om, na een vraag van Dr. Roderick Houwen, te solliciteren naar een baan als Kindergastroenteroloog in het WKZ Utrecht (Prof. Dr. Jan Kimpen). Inmiddels werkt hij daar al weer ruim vijf jaar aanvankelijk als kinderarts-MDL, nu gecombineerd met de tijdelijke functie Chef de Clinique van de afdeling Kikker (kinder-MDL en kinderchirurgie).

Hij is getrouwd met Marike Visser, woont op fietsafstand in Soesterberg en heeft vijf kinderen.

Dankwoord

Tot slot mijn dankwoord.

Op de allereerste plaats wil ik alle kinderen en ouders bedanken die deelnamen aan het onderzoek. Zij hebben zich erg ingespannen om de flesjes leeg te drinken, de voedingsdagboekjes in te vullen, de ontlasting te verzamelen en deze te beoordelen aan de hand van de Bristol Stool Form Scale.

Verder wil ik natuurlijk mijn promotor en copromotoren bedanken.

Professor Kimpen, beste Jan, nu al weer vijf jaar geleden heb jij mij de kans gegeven in het WKZ te komen werken en om op mijn leeftijd nog te promoveren waarvoor hartelijk dank. Als leeftijdsgenoten kennen we elkaar al een aardige tijd. Bij mij in herinnering komt een scene in de oudbouw van het toenmalige Academisch Ziekenhuis Groningen op de gang van afdeling Observatie (de boxen afdeling): 3 kalende mannen (Jan Kimpen, Maarten Hoekstra en Wim van Aalderen) in vrolijk overleg met elkaar. Heel even flitste het door me heen of ik niet ook mijn haardos moest veranderen… Weliswaar zit je nu aan de overkant van het WKZ maar je bent nog steeds makkelijk toegankelijk, dat is zeer te waarderen.

Beste Marc, we hebben elkaar ontmoet in 1994 (of 1995) tijdens een AGA congres; Jan Taminiau en Hans Büller stelden je aan mij voor. Daarna een hernieuwde kennismaking bij de start van het onderzoeksproject in Arnhem in 2000. Regelmatig heb je de rit gemaakt naar Arnhem (soms Wageningen) om de voortgang te bespreken met mij en de anderen. Voor de hele onderzoeksfase en een groot deel van de artikelen ben jij onmisbaar geweest. Een memorabele herinnering tijdens de First European Meeting on Pediatric Gastrointestinal Motility op Capri in 2001: we deelden een hotelkamer en daar heb ik ontdekt dat jouw leven dag en nacht voortduurt. Overdag wetenschap bedrijven en 's nachts golf kijken op TV. Een andere herinnering: dankzij jouw overredingskracht kregen we de taxichauffeur zo ver om een wijk in het centrum van Napels in te rijden waar zelden of nooit een toerist komt... Anderen voor mij hebben al gesproken over je tomeloze energie: waar haal je dat energie-elixer toch vandaan?

Beste Roderick, na Marc heb jij het stokje als het ware overgenomen en voor een ander deel van mijn proefschrift een zeer belangrijke rol gespeeld. Bij het schrijven heb je mij enorm geholpen waarbij een uitspraak van Goethe zeer toepasselijk is: "In der Beschränkung zeigt sich der Meister". Met een paar woorden kun jij precies dat zeggen waar ik vele zinnen voor nodig had; bijzonder leerzaam. En als spin-off van jouw inspanningen ken je nu niet alleen mijn huis maar ook het tuinhuisje van binnen. Voor al je hulp heel veel dank. Het eerste beeld van jou dat bij me opkomt, is een gezellig diner in Boston tijdens het First World Congress of Paediatric Gastroenterology, Hepatology and Nutrition in 2000 terwijl je kreeft eet met een slabbertje om. Een ander karakteristiek beeld: wanneer je doceert met de linkerhand in de zij waarbij de pols als steunpunt dient en in de rechter hand de onvermijdelijke White Board stift waarmee je in enkele zwieren weer de lever en galwegen tekent voor ons onwetenden. Tenslotte nog een laatste beeld: wanneer je in mijn kamer bent en altijd even terloops, vóór je de deur uitgaat, in de spiegel kijkt (ja, je haar zit goed). Je bent een nuchtere intellectueel die toch graag de sterren telt: je zou jouw specialisme ook gastrologie kunnen noemen. Zoals beloofd gaan we samen nog een keer sterren tellen.

Beste Ruurd en Michael, Ik noem jullie in één adem; dat hangt samen met jullie ceremoniële taak. Met jullie beiden heb ik een langjarige vriendschap die soms zwijgend is maar dan ook weer luid. Gelukkig kunnen jullie het ook samen goed vinden. Jullie hebben me met de laatste fase van het voorbereiden van het proefschrift enorm geholpen. Ik heb er vertrouwen in dat de vriendschap blijft voortbestaan.

Beste Marieke, met een redelijk budget was het mogelijk een nurse practitioner aan te stellen. Je hebt me veel werk uit handen genomen en hebt huisbezoeken gebracht bij de patiënten, flessen geteld en schriften bijgehouden. In die periode heb je veel meegemaakt maar mij altijd geholpen bij de noodzakelijke onderzoeksklussen. Gelukkig zien we elkaar nog steeds zo nu en dan, bijvoorbeeld bij Heleen en Gerrit, en dat moeten we zo houden.

Beste Jules, je bent vanaf het allereerste begin betrokken geweest bij het onderzoek en hebt een belangrijke bijdrage geleverd aan de voortgang van het onderzoek en het klinische artikel waarvoor dank. Ook bij jou komt meteen een herinnering naar boven: tijdens mijn co-schap kindergeneeskunde in het St. Radboud Ziekenhuis hield je een voordracht nadat je net uit Londen was teruggekeerd. Met de jou eigen humor vertelde je op geweldige wijze over je avontuur daar, wat je had opgestoken en dat je "John" had mogen zeggen tegen Prof. Walker-Smith. Na mijn terugkeer uit Baltimore nodigde jij mij meteen uit om over virale gastro-enteritis op het NVK Congres in Veldhoven te spreken. Later, toen ik in Arnhem werkte, bezocht ik je regelmatig in het St. Radboud Ziekenhuis op de vrijdagmiddag. Eerst met een grote groep mensen vergaderen, het Eetteam, gevolgd door het overleg met zijn tweeën over "lastige" patiënten. Het zal je wellicht plezieren dat ik nu op mijn kamer een klok heb hangen die elk uur een ander gezang laat horen van een vogel uit het Amazone gebied. Ik denk wel eens: zou Jules die ook kunnen herkennen?

Beste Theo, jij kwam samen met Jules naar onze bijeenkomsten in Arnhem. Dat was het logische gevolg van jouw samenwerking met Jules in de zorg van chronische obstipatie patiënten. Dit, terwijl je vakgebied de kinderreumatologie is. Ik herinner me de levendige discussies over klinische karakteristieken van obstipatie patiënten tussen jou en Marc. Jij hebt aan het klinische stuk een belangrijke bijdrage geleverd waarvoor dank.

Beste Martine, Petra en Jan, dat ik jullie samen noem heeft alles te maken met jullie herkomst: Numico Research, tegenwoordig Danone Research. Martine en Petra, jullie hebben in de startfase van het onderzoek veel tijd geïnvesteerd in het onderzoek om het op gang te helpen. Jullie waren ook direct betrokken bij het verwerven van de fondsen. Martine had altijd veel ideeën en heeft me op het juiste moment (winter Barcelona 2006) aangespoord om door te gaan omdat het waardevol onderzoek was. Petra heeft veel voorwerk verricht in de beginfase met het ontwerpen van CRF, dagboekjes etc. Ook heeft zij de stagiaires diëtetiek begeleid die de data, beschreven in hoofdstuk 3, hebben gegenereerd. Tenslotte Jan, jij hebt een bijdrage geleverd door op de achtergrond mee te denken en belangrijke input gehad in hetgeen in hoofdstuk 7 wordt weergegeven.

Beste collega's van het Rijnstate Ziekenhuis Arnhem: jullie moet ik bedanken voor de hulp bij het includeren van geschikte patiënten voor deelname aan het onderzoek. Op de 7 jaar in Arnhem kijk ik met veel plezier terug. Bedankt voor deze leerzame, gezellige en collegiale periode in mijn leven.

Beste Hubert, binnenkort promoveer jij ook. Het was goed om af en toe met je te praten over alles wat met promoveren samenhangt: van de statistiek tot sponsoring, van schrijfkunst tot peer review. Succes bij jouw verdediging.

Beste Ingrid en Marie-Jeanne, bij de laatste loodjes hebben jullie me ondersteund bij allerlei administratieve bezigheden van sponsorbrieven sturen tot stickers uitdraaien. Bedankt, en we gaan gewoon verder waar we nu gebleven zijn.

Beste Janneke, jouw proefschrift heb ik menigmaal ter hand genomen om te zien hoe jij bepaalde zaken had opgelost. Bovendien hebben we elkaar regelmatig over praktische zaken rond de promotie gesproken. We zullen in de nabije toekomst professioneel anders naast elkaar komen te staan: op wetenschappelijk terrein ga ik vast nog veel van je leren.

Beste Hans en Gerrit, jullie zeer bedankt voor de omslag en lay-out van het proefschrift. Vorm en inhoud zijn onlosmakelijk.

Beste Victorien en Cathelijne, jullie zijn de eerste fellows kinder-MDL die ik samen met Roderick heb opgeleid. Dat was voor mij zeker zo leerzaam. Ik verheug me in de toekomstige voortgezette samenwerking met jullie. Cathelijne binnenkort als kinderarts-MDL en Victorien als staflid van de afdeling kinder-MDL in het WKZ.

Beste Anemone, met veel plezier werk ik samen met je en ook met jou heb ik van gedachten kunnen wisselen over het proces dat promoveren heet. Ik bedank jou en Michiel ("dedication is all") ook voor de gezelligheid buiten het werk bijvoorbeeld op de Amsterdamse grachten.

Beste Winnie, Janet, Ellen, Marianne. Jullie hebben ieder op eigen wijze bijgedragen door jullie betrokkenheid bij de afronding van het boekje. Hoe de toekomstige werksituatie precies vorm zal gaan krijgen, nu jullie onderdeel van de nieuwe afdeling Kameleon worden, weet ik niet maar jullie blijven voor mij de "gastro dames". Ook Ellen en Debbie bedankt voor de goede atmosfeer die jullie meebrengen in het kamertje naast mij.

Beste Sarah, je bent al weer een half jaar fellow bij onze kinder-MDL afdeling maar we kennen elkaar natuurlijk in het bijzonder van het werk op afdeling Kikker. Je bent een loyale collega en ik hoop op een vruchtbare samenwerking en veel interessante nieuwe gezichtspunten met jouw specifieke kennis.

Beste Amani, jij bent een belofte voor de toekomst. Ik kan later tenminste zeggen: met haar heb ik vroeger nog geluncht.

Beste collega's in het WKZ, waarbij ik dat breder wil trekken en ook de kinderchirurgen expliciet wil noemen: ik dank jullie voor het vertrouwen dat jullie aan een "zij-instromer" hebben gegeven. Ik zal me blijven inspannen om aan de 3 pijlers van het academisme (onderzoek, onderwijs en zorg) mijn eigen passende bijdrage te leveren. Enkele mensen uit deze grote groep collega's wil ik in het bijzonder bedanken voor de samenwerking tot nu toe: dat zijn Frederique, Esther en Atty met wie ik samenwerk in het richting geven van de (nieuwe) functie MHZE (medisch hoofd zorg eenheid). En tenslotte Claudia en Nanja, voor de goede samenwerking op Kikker waarbij we niet schuwen de goed en de minder goed lopende zaken op Kikker bij de naam te noemen.

Tenslotte wil ik het huidig MT-team, Edward Nieuwenhuis, Lieke Sanders, Julianne Meijers en Ernest Müter bedanken voor het getoonde vertrouwen en ik hoop op een voortgezette vruchtbare samenwerking in het WKZ naar de toekomst toe.

Lieve familie, Hans en Jolan, Jos en Ida, Vincent en Trien. De banden worden nu we ouder worden weer wat aangehaald. En wat is er nou leuker dan om samen met jullie te eten bij "Mijn broer"? De volgende keer ben ik aan de beurt voor dit jaarlijks uitje. In de toekomst zullen we nog wel eens vaker op elkaar aangewezen zijn. Dat zie ik met vertrouwen tegemoet.

Lieve moeder en vader, bedankt voor jullie hulp om te komen tot waar ik nu ben. En ma, de beste sponsor is dichterbij dan ik dacht!

Lieve Sanne, Stas, Ezra, Nard en Kjelt. Dit jaar hoeft er als surprise met Sinterklaas geen boekje meer gemaakt te worden voor mij. Het is nu immers af en er mogen geen grappen meer over gemaakt worden. Verheug jullie maar op de vakantie die we binnen afzienbare tijd weer een keer met zijn allen zullen gaan hebben. Wat een team.

Lieve Marike, wat ben ik blij dat ik het proefschrift nog ruimschoots voor je vijftigste verjaardag heb afgekregen. Dat was echter niet gelukt zonder jouw hulp en steun. De volgende vijftig jaar zal ik weer wat meer aandacht aan je besteden...

… Let’s party …

Publications

De Bie CI, Hummel TZ, Kindermann A, Kokke FTM, Damen GM, Kneepkens CMF, Van Rheenen PF, Schweizer JJ, Hoekstra JH, Norbruis OF, Tjon a Ten WE, Vreugdenhil AC, Deckers-Kocken JM, Gijsbers CFM, J. C. Escher JC, De Ridder L. The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited.
Aliment Pharmacol Ther 2011;33:243-50.

Kokke FT, Sittig JS, de Bruijn A, Wiersma T, Van Rijn RR, Kimpen JL, Houwen RH, Fischer K, Benninga MA. Starreveld scoring method in diagnosing childhood constipation.
Pediatr Radiol 2010; 40: 1789-93

Van der Doef HP, Kokke FT, Beek FJ, Woestenenk JW, Froeling SP, Houwen RH. Constipation in pediatric cystic fibrosis patients: an underestimated medical condition.
J Cyst Fibrosis 2010;9:59-63.

Kokke FT, Scholtens PA, Alles MS, Decates TS, Fiselier TJ, Tolboom JJ, Kimpen JL, Benninga MA.
A dietary fiber mixture versus lactulose in the treatment of childhood constipation: a double-blind randomized controlled trial.
J Pediatr Gastroenterol Nutr 2008;47: 592–7.

De Ridder L, Rings EH, Damen GM, Kneepkens CM, Schweizer JJ, Kokke FT, Benninga MA, Norbruis OF, Hoekstra JH, Gijsberts CF, Escher JC.
Infliximab dependency in pediatric Crohn's disease: Long-term follow-up of an unselected cohort.
Inflamm Bowel Dis 2008;14:353-8.

Kokke FT, Taminiau JA, Benninga MA
The role of dietary fiber in childhood and its applications in pediatric gastroenterology.
Nestle Nutr Workshop Ser Pediatr Program. 2005;56:111-20; discussion 120-6. Review.

De Moor JMH, Brons E, Kokke FTM, Vos H en Tolboom JJM
Extreme voedselselectiviteit na levertransplantatie bij een 5-jarig meisje; gedragstherapeutische behandeling.
Ned Tijdschr Geneeskd 2004;148:791-4.

Visser G, Rake JP, Kokke FT, Nikkels PG, Sauer PJ, Smit GP
Intestinal function in glycogen storage disease type I.
J Inherit Metab Dis. 2002;25:261-7.

Waalkens HJ, Kokke FTM, Rings EHHM, Sieders E, Peeters PMJG, Koetse HA, Slooff MJH en Bijleveld CMA
Levertransplantatie op de kinderleeftijd.
Tijdsch Kindergeneeskd 2000;68:137-42.

Wormmeester L, Sanchez de Medina F, Kokke F, Tse CM, Khurana S, Bowser J, Cohen ME, Donowitz M
Quantitative contribution of NHE2 and NHE3 to rabbit ileal brush-border Na^+/H^+ exchange.
Am J Physiol 1998;274:C1261-72.
Kokke FTM, Elsawy T, Bengtsson U, Wasmuth JJ, Jabs EW, Tse CM, Donowitz M, Brand SR
A NHE3-related pseudogene is on human chromosome 10; the functional gene maps to 5p15.3.
Mammalian Genome 1996;7:235-6
Van Elburg RM, Uil JJ, Kokke FTM, Mulder AM, Van de Broek WGM, Mulder CJJ, Heymans HSA
Repeatability of the sugarabsorptiontest, using lactulose and mannitol, for measuring intestinal permeability for sugars.
J Pediatr Gastroenterol Nutr 1995;20:184-8.
Donowitz M, Kokke FT, Saidi R
Evaluation of patients with chronic diarrhea.
N Engl J Med 1995;332:725-9.
Kokke FTM, Van Elburg RM, Van Overbeek FM, Heymans HSA
Een nieuwe koek, vrij van koemelkeiwit, kippeeiwit, lactose en gluten, voor kinderen met voedselovergevoeligheid.
Ned Tijdschr Geneeskd 1994;138:2549-52.
Van Elburg RM, Kokke FTM, Uil JJ, Mulder CJJ, De Monchy JGR, Heymans HSA
Meting van de selectieve darmpermeabiliteit met een nieuwe, eenvoudige suikerabsorptietest.
Ned Tijdschr Geneeskd 1993;137:2091-5.
Kokke FTM, van der Heide DH, Boelen-van der Loo WJC
Postoperatieve pijnbestrijding in drie Nederlandse ziekenhuizen: een pilotstudy.
Tijdschr Kindergeneeskd 1993;61:48-51.
Kokke FTM, Maertzdorf WJ
First European conference on pain in children.
Tijdschr Kindergeneeskd 1990;58:183-4.

Abstracts

Van Meegen MA, Kokke F, Dik P, Fockens P, Benninga MA
A seminal vesicle cyst palpable in the rectum.
Endoscopy 2006;38(S2):E7.
Kokke FTM, Nath S, Yun CCH, Weyer M, Wormmeester L, Schwiebert E, Cutting C, Guggino W, Tse CM, Donowitz M
Is CFTR the Na^+/H^+ exchanger associated regulatory protein involved in inhibition of brush border Na^+/H^+ exchange by cAMP?
Gastroenterology 1996;110:A338.

Wormmeester L, Kokke FTM, Kambadur R, Tse CM, Yun CCH, Bowser J, Ko W,Cohen ME, Donowitz M
Quantitation of rabbit ileal brush border Na^+/H^+ exchangers (NHE) in up and down regulation of intestinal Na^+ absorption.
Gastroenterology 1996;110:A375.
Kokke FTM, Van Elburg RM, Van Overbeek FM, Koerts B, Uil JJ, Mulder CJJ, Heymans HSA
Assessment of the sugar absorption test combined with a H_2-breathtest in inflammatory bowel disease: preliminary results.
Neth J Med 1994;44:A36.

Books and contributions

Richtlijn. Diagnostiek en behandeling van IBD bij kinderen
2007 ISBN 978-90-8523-179-0.
Eds. Escher JC, Hagemeijer JW, de Ridder L, Rings EHHM
Zuiden Communications B.V.
2007, Alphen aan den Rijn
Waalkens HJ en Kokke FTM
Hoofdstuk 37 Maag-darmbloedingen
In: Werkboek Kindergastro-enterologie 2e Editie
Eds. Kneepkens CMF, Taminiau JAJM en Polman HA
2002, Amsterdam
Donowitz M, Levine SA, Yun CHC, Brant SR, Nath S, Yip J, Kokke FTM, Hoogerwerf S, Montgomery J, Bianchini L, Pouyssegur J, Tse CM
Molecular studies of members of the mammalian Na+/H+-exchanger gene family.
In: Molecular Biology of Membrane Transport Disorders.
Eds. Schultz SG, Andreoli TE, Brown AM, Fambrough DM, Hoffman JF, Welsh MJ
Plenum Press, New York, 1996
Kokke FTM, Saidi RF, Watson A, Donowitz M
Chronic diarrhea.
Chapter 6.8 p.478-84.
In: The Principles and Practice of Medicine 23/E.
Eds. Stobo, Hellmann, Ladenson, Petty, and Traill, s. 23th ed. Appleton & Lange, Stamford,1996
Kokke FTM
Pijn en pijnbestrijding.
In: Therapiecompendium Kindergeneeskunde.
Eds. De Vries TW, Heymans HSA,
Groningen. 1991;24-9.

Kokke FTM
Zwavel in de Nederlandse medische therapie 1800-1850.
Scripta Tironum. Nummer 4.
De Moulin D en de Knecht-van Eekelen A eds. Instituut voor Geschiedenis der Geneeskunde KU Nijmegen, 1985.

List of abbreviations

AUC	Area Under the Curve
BSFS	Bristol Stool Form Scale
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
DAPI	4',6-diamidino-2-phenylindole
DIOS	Distal Intestinal Obstruction Syndrome
DNCFS	Dutch National Food Consumption Survey
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FAP	Functional Abdominal Pain
FISH	Fluorescent in situ Hybridization
FNRFI	Functional Non-retentive Fecal Incontinence
FOS	Fructo-oligosaccharides
G	Gram
GOS	Galacto-oligosaccharides
IBS	Irritable Bowel Syndrome
ICC	Intra-class Correlation Coefficient
MJ	Megajoule
NPV	Negative Predictive Value
PBS	Phosphate Buffered Saline
PEG	Polyethylene Glycol
PPV	Positive Predictive Value
ROC	Receiver Operator Characteristic
rRNA	ribosomal Ribo Nucleic Acid
RS	Resistant starch
SCFA	Short Chain Fatty Acid
SWO	Stichting Wetenschappelijk Onderzoek