Advances in Practice

Impact of different protein sources on health outcomes in adults with kidney disease

By Philippa Norton Feiertag, MEd, RD, CSR, LD. *Philippa is a clinical consultant with Clinical Computing, Inc. in Cincinnati, OH. She can be reached at feier@fuse.net*

Functional foods and the patient with renal failure

As consumers have become more aware of the link between diet and health, many have started to look at the health benefits of foods as well as their nutrient content. Foods, or food ingredients, that provide health benefits beyond basic nutrition are called functional foods, and the market for these items is growing due to increasing consumer demand, advances in food technology and rising healthcare costs (1).

Recently, attention has focused on the ability of non-digestible oligosaccharides, such as fructooligosaccharides (FOS) and isomaltooligosaccharides (IMO), to modify the bacterial composition of the large intestine (2). FOS found in wheat, onions, bananas, honey, garlic and leeks, and IMO present in fermented foods such as miso, soy sauce and sake, belong to a group of functional foods known as prebiotics (2,3). Prebiotics are non-digestible food ingredients that support growth and/or activity of beneficial bacteria present in the colon (4). Oligosaccharides resist digestion by gastric acid and pancreatic enzymes and stimulate growth of the *Bifidobacterium* population (5). Increased concentrations of bifidobacteria have been linked with lower blood urea levels, increased absorption of some vitamins and minerals, modulation of lipid metabolism, inhibition of some pathogens and stimulation of the immune system (2,6-8).

All of these effects can have a positive impact on health outcomes in patients with kidney disease, and several medical nutritional formulas used by this population incorporate FOS in the form of NutraFlora® (9,10). Since renal dietetics professionals may need to interpret information on functional foods and educate patients on their appropriate use as part of a healthy eating plan, this column will focus on the safety, physiologic effects and health benefits of oligosaccharides for patients with renal disease.

Safety and legal status of oligosaccharides

Oligosaccharides are a significant part of the European diet, where daily intake averages 10 g; Americans consume on average 2.5 g oligosaccharides per day (8,11). In most countries, oligosaccharides can be used without restriction in food formulations, and a panel of U.S. experts performing a Generally Recognized As Safe (GRAS) Self-Affirmation Evaluation reached the same conclusion in 1992 (12).

Approximate levels of FOS intake to optimize health status have been set at 3-10 g/day (1). A dose of 2.75 g FOS/day is sufficient to promote growth of bifidobacteria, while 10 g FOS daily is well tolerated and significantly increases the *Bifidobacterium* population in the colon (13,14). A medical nutrition product containing 3.7 g FOS per 8 fluid ounce serving has been used as the sole source of nutrients in patients undergoing hemodialysis; ingestion of up to 18.5 g FOS daily from this product was well tolerated by these patients (15).

IMO supplied to hemodialysis (HD) patients as a liquid preparation at a dose of 15 g twice daily for 28 days caused some abdominal bloating, but was generally well tolerated (3).

Physiologic effects of oligosaccharides

Oligosaccharides resist digestion by enzymes in the gastrointestinal tract and undergo fermentation by anaerobic bacteria in the colon to yield short chain fatty acids (acetate, butyrate and proprionate) and lactic acid (2,15).

Bifidobacteria are gram-positive anaerobic bacteria, which inhabit the mammalian colon and use FOS as their preferred energy source (15). Introduction of FOS into the diet increases acidity of the colon due to fermentative production of acetate and lactate by bifidobacteria (16,17). These acids, along with other anti-microbial substances produced by bifidobacteria, inhibit the growth of invasive pathogens including *Escherichia coli, Clostridium difficile, Vibrio cholerae* and *Salmonella, Listeria, Campylobacter* and *Shigella species* (9,17).

Butyric acid generated during fermentation of oligosaccharides has a powerful trophic effect on the cecum (16). As a result, both the surface area of the cecum and its blood supply increase, allowing a higher rate of solute transfer between the bloodstream and the lumen of the cecum. Short chain fatty acids yielded during fermentation may also inhibit hepatic cholesterol synthesis and redistribute cholesterol from the plasma to the liver, leading to a drop in plasma cholesterol levels (18).

Health benefits of oligosaccharides for patients with renal disease

Increased extra-renal nitrogen excretion:

Dietary protein restriction is implemented in patients with chronic kidney disease (CKD) to decrease plasma urea concentrations and delay the progression .

Animal studies indicate that a diet containing fermentable carbohydrates, including FOS, promotes the transfer of urea from the plasma into the cecum, resulting in a decrease in plasma urea concentration of approximately 30% (16,19). This accelerated

Continued on page 8

continued from page 7

urea transfer across the wall of the cecum has been attributed to the trophic effect of butyric acid, which increases both the surface area of the cecum and its blood supply.

Thus, deterioration in renal function may be delayed in patients with CKD and concerns regarding malnutrition during protein restriction may be reduced by prescribing a diet that incorporates FOS and a moderate protein restriction.

Enhanced absorption of some vitamins and minerals:

In patients with renal failure, absorption of vitamins and minerals is influenced by dietary restrictions, drug-nutrient interactions and uremic toxins (20). In addition, patients with stage 5 CKD, undergoing dialysis therapy, sustain loss of B vitamins during dialysis at a rate exceeding normal urinary excretion.

Animal studies indicate that the non-digestible oligosaccharides stimulate absorption of several minerals, including calcium, iron and magnesium (21). The decrease in colon pH, which results from growth of the *Bifidobacterium* population, increases solubilization of these minerals. In addition, FOS may increase the concentrations of proteins that bind these minerals, accelerating their transport into the bloodstream.

Bifidobacteria synthesize vitamins B1, B6 and folic acid (22). In animal studies, increased *Bifidobacterium* concentration in the cecum and colon is associated with a 40% increase in mean serum folate levels.

Improved lipid profile:

Cardiovascular disease is another important contributor to mortality in patients with CKD (23,24). Lipid disturbances in this population include elevated lipoprotein (a) and very low-density lipoprotein (VLDL) in CKD, stages 1 through 4, and hypertriglyceridemia with decreased high-density lipoprotein (HDL) in stage 5 CKD maintenance dialysis patients (25).

Increased intake of indigestible carbohydrates, including oligosaccharides, has been associated with decreasing plasma triglycerides in normolipidemic human subjects and with reduction in cholesterol levels in hyperlipidemic subjects (18). FOS also reduces de novo fatty acid synthesis in the liver and VLDL production by inhibiting lipogenic enzymes including acetyl-coA carboxylase and fatty acid synthase (26).

The effect of IMO on lipid profiles has been examined in patients undergoing maintenance HD (3). These patients received 30 g IMO daily for 4 weeks and their lipid profiles at the end of the study were compared with those of age- and sex-matched controls who had similar initial lipid profiles, but who did not receive IMO. After the study, patients who had received IMO showed reductions in total cholesterol (17.6%) and triglycerides (18.4%), and increased HDL-cholesterol (39.1%). Thus, IMO was effective in lowering total cholesterol and triglycerides and in raising HDL-cholesterol in HD patients.

Decreased risk of infection:

Infection is a leading cause of death in maintenance HD patients and this population is at significantly greater risk for developing nosocomial infections than other hospitalized patients (27,28). *Clostridium difficile* - associated diarrhea imposes a serious financial burden due to increased healthcare costs, and causes increased morbidity and mortality (29).

When the *Bifidobacterium* population in the colon grows as a result of FOS ingestion, bowel acidity increases (9). This environment has an inhibitory effect on the growth of *Clostridium difficile* and other pathogens (10,17). Consequently, FOS has the potential to decrease both infection rates and associated healthcare costs.

Stimulation of the immune system:

In addition to decreasing infection risk, Bifidobacteria increase the ability to fight infection by impacting the immune system (30). Approximately 70% of the body's immune system is localized in the gastrointestinal tract. Animal studies suggest that growth of the *Bifidobacterium* population as a result of FOS ingestion is accompanied by increased immunoglobulin A (IgA) secretion by Peyer's patch cells in the intestinal mucosa (31). IgA antibodies form the first line of immune defense by inhibiting attachment of microbes to the mucosal epithelial lining, and may also neutralize viruses intracellularly (32,33).

Thus, non-digestible oligosaccharides have a range of potential beneficial effects, and manipulating intestinal microbial populations through diet is a growing area of research. FOS have attracted considerable commercial interest as prebiotics and can be synthesized from sucrose (34).

By keeping abreast of research findings, registered dietitians can educate other healthcare professionals and patients about the roles of functional foods in promoting health. Most importantly, renal dietetics professionals can provide recommendations to their patients for incorporating these foods into their eating plan to optimize health outcomes and decrease risk of disease.

REFERENCES

1. Position of the American Dietetic Association: Functional foods. *J Am Diet Assoc.* 1999; 99:1278-1285.
2. Chow J. Probiotics and prebiotics: A brief overview. *J Ren Nutr.* 2002;12:76-86.
3. Wang HF, Lim PS, Kao MD, Chan EC, Lin LC, Wang NP. Use of isomaltooligosaccharide in the treatment of lipid profiles and constipation in hemodialysis patients. *J Ren Nutr.* 2001;11:73-79.
4. Roberfroid MB. Prebiotics and probiotics: Are they functional foods? *Am J Clin Nutr.* 2000;71 (suppl 6):1682S-1687S.
5. Cummings JH, Macfarlane GT, Englyst HN. Prebiotic digestion and fermentation. *Am J Clin Nutr.* 2001;73 (suppl 2):415S-420S.

Continued on page 9

continued from page 8

6. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J Nutr.* 1995;125:1401-1412.
7. Krause LJ, Forsberg CW, O'Connor DL. Feeding human milk to rats increases Bifidobacterium in the cecum and colon which correlates with enhanced folate status. *J Nutr.* 1996;126:1505-1511.
8. Niness KR. Inulin and oligofructose: What are they? *J Nutr.* 1999;129 (suppl 7):1402S-1406S.
9. Ross Products Division Abbott Laboratories Inc. Fructooligosaccharides. April 2002.
10. GTC Nutrition Company. *NutraFlora® and its role in medical nutrition therapy.* 1999.
11. Moshfegh AJ, Friday JE, Goldman JP, Ahuja JK. Presence of inulin and oligofructose in the diets of Americans. *J Nutr.* 1999;129 (suppl 7):1407S-1411S.
12. Coussement PA. Inulin and oligofructose: Safe intakes and legal status. *J Nutr.* 1999; 129 (suppl 7):S1412-S1417.
13. Roberfroid MB. Prebiotics and synbiotics: Concepts and nutritional properties. Br *J Nutr.* 1998; 80 (suppl):S197-S202.
14. Bouhnik Y, Vahedi K, Achour L, Attar A, Salfati J, Pochart P, Marteau P, Flourie B, Bornet F, Rambaud JC. Short-chain fructo-oligosaccharide administration dose-dependently increases fecal bifidobacteria in healthy humans. *J Nutr.* 1999;129:113-116.
15. Cockram DB, Hensley MK, Rodriguez M, Agarwal G, Wennberg A, Ruey P, Ashbach D, Herbert L, Kunau R. Safety and tolerance of medical nutritional products as sole sources of nutrition in people on hemodialysis. *J Ren Nutr.* 1998;8:25-33.
16. Younes H, Alphonse JC, Hadj-Abdelkader M, Remesy C. Fermentable carbohydrate and digestive nitrogen excretion. *J Ren Nutr.* 2001;11:139-148.
17. Gibson GR, Wang X. Regulatory effects of bifidobacteria on the growth of other colonic bacteria. *J Appl Bacteriol.* 1994;77:412-420.
18. Pereira DI, Gibson GR. Effects of consumption of probiotics and prebiotics on serum lipid levels in humans. *Crit Rev Biochem Mol Biol.* 2002;37:259-81.
19. Remesy C, Demigne C. Specific effects of fermentable carbohydrates on blood urea flux and ammonia absorption in the rat cecum. *J Nutr.* 1989;119:560-565.
20. Makoff R. Vitamin replacement therapy in renal failure patients. *Miner Electrolyte Metab.* 1999;25:349-351.
21. Scholz-Ahrens KE, Schaafsma G, van den Heuvel E, Schrezenmeir J. Effects of prebiotics on mineral metabolism. *Am J Clin Nutr.* 2001;73 (suppl 2):459S-464S.
22. Crittenden RG, Martinez NR, Playne MJ. Synthesis and utilization of folate by yoghurt starter cultures and probiotic bacteria. *Int J Food Microbiol.* 2003;80:217-222.
23. National Kidney Foundation Task Force on Cardiovascular Disease Executive Summary. Controlling the epidemic of cardiovascular disease in chronic renal disease. Available at: http://www.kidney.org/professionals/pysfile/cardiointro.cfm. Accessed January 18,2004.
24. Pennell JP. Optimizing medical management of patients with pre-end-stage renal disease. *Am J Med.* 2001;111:559-568.
25. Wheeler DC. Cardiovascular risk factors in patients with chronic renal failure. *J Ren Nutr.* 1997;7:182-186.
26. Delzenne NM, Kok N. Effects of fructans-type prebiotics on lipid metabolism. *Am J Clin Nutr.* 2001;73 (suppl 2):456S-458S.
27. Hung YM, Lee SSJ. Analysis of early and late mortality of chronic hemodialysis patients in a hemodialysis center of southern Taiwan. *Dialysis and Transplantation.* 2003;32:198-205.
28. D'Agata EM, Mount DB, Thayer V, Schaffner W. Hospital-acquired infections among chronic hemodialysis patients. *Am J Kidney Dis.* 2000;35:1083-1088.
29. Miller MA, Hyland M, Ofner-Agostini M, Gourdeau M, Ishak M; Canadian Hospital Epidemiology Committee. Canadian Nosocomial Infection Surveillance Program. Morbidity, mortality, and healthcare burden of nosocomial *Clostridium difficile*- associated diarrhea in Canadian hospitals. *Infect Control Hosp Epidemiol.* 2002;23:137-140.
30. Bengmark S. Pre-, pro- and synbiotics. *Curr Opin Clin Nutr Metab Care.* 2001;4:571-579.
31. Hosono A, Ozawa A, Kato R, Ohnishi Y, Nakanishi Y, Kimura T, Nakamura R. Dietary fructooligosaccharides induce immunoregulation of intestinal IgA secretion by murine Peyer's patch cells. *Biosci Biotechnol Biochem.* 2003;67:758-764.
32. Lamm ME. Current concepts in mucosal immunity. IV. How epithelial transport of IgA antibodies relates to host defense. *Am J Physiol.* 1998;274:G614-G617.
33. Lamm ME. Interaction of antigens and antibodies at mucosal surfaces. *Annu Rev Microbiol.* 1997;51:311-340.
34. Kaplan H, Hutkins RW. Fermentation of fructooligosaccharides by lactic acid bacteria and Bifidobacteria. *Appl Environ Microbiol.* 2000;66:2682-2684.