Navigating the gluten-free boom

Article *in* JAAPA: official journal of the American Academy of Physician Assistants · August 2015

DOI: 10.1097/01.JAA.0000469434.67572.a4 · Source: PubMed

2 authors:

Glenn A Gaesser
Arizona State University
201 PUBLICATIONS **6,408** CITATIONS
SEE PROFILE

Siddhartha S Angadi
Arizona State University
44 PUBLICATIONS **190** CITATIONS
SEE PROFILE

Navigating the Gluten-Free Boom

Word count: 2,812

Glenn A. Gaesser, PhD

Siddhartha S. Angadi, PhD

Healthy Lifestyles Research Center

Exercise and Wellness Program

School of Nutrition and Health Promotion

Arizona State University

500 N 3rd Street

Phoenix, AZ 85004

Phone: 602-827-2283

fax: 602-496-1873

glenn.gaesser@asu.edu

Address correspondence to:

Glenn A. Gaesser, PhD (at address above)

Conflicts of Interest:

Glenn A Gaesser receives honoraria as chair of the Scientific Advisory Board of the Grain Foods Foundation and as a member of the Wheat Foods Council Advisory Board.

Siddhartha S Angadi has no conflicts of interest to declare.

Introduction

Gluten-free dieting has gained considerable popularity in the general population. According to a 2013 survey by the NPD Group, 30 percent of adults are interested in avoiding gluten or at least reducing the amount of gluten in their diets .[1] The gluten market is now $4.2 billion per year and is expected to reach $6.6 billion by 2017.[2] As of March 19, 2014, Amazon.com listed 9,881 entries for "gluten-free" books, more than double the number in 2012.[3] A Google search at the same time for "gluten-free" produced more than 20 million results. A 2013 survey by Mintel indicated that 65 percent of U.S. adults say they eat gluten-free products because they think they are healthier, and 27 percent of U.S. adults eat gluten-free products for weight loss purposes.[4] Celebrity endorsements also contribute to the heightened awareness of gluten-free eating, especially with regard to weight-loss.[5]

Despite the health claims for gluten-free eating, there is no published experimental evidence to suggest that the general population would be better off by avoiding gluten.[3,6] The purpose of this review is to briefly describe some of the research on the spectrum of gluten related disorders and the limited research on effects of gluten and gluten avoidance in otherwise healthy individuals.

The Spectrum of Gluten-Related Disorders

Gluten refers to a family of storage proteins (gliadins and glutenins) found in wheat and related grains such as barley and rye. The spectrum of gluten-related disorders includes celiac disease, non-celiac gluten sensitivity, and wheat allergy.[7,8]

Wheat Allergy

Wheat allergy is an IgE-mediated reaction to wheat proteins, with an estimated prevalence of approximately 0.1%.[7] Wheat allergy is treated with wheat avoidance and therefore is not as restrictive as a gluten-free diet as these patients do not typically become symptomatic upon consumption of gluten-containing grains such as rye and barley.[7] It is important to note that although symptoms of wheat allergy can be similar to celiac disease, it does not cause permanent gastrointestinal damage like celiac disease. Finally, wheat allergy typically develops during early infancy or toddlerhood, and children typically outgrow it between the ages of 3 to 5 years whereas celiac disease is a lifelong disorder.[7]

Celiac Disease

Celiac disease is a complex autoimmune pathology of the small intestine in genetically susceptible people that is caused by ingestion of gluten-containing grains.[9] As recently as 2000, prevalence of celiac disease was thought to be rare, ~1 in 10,000 to 1 in 4,800, based on epidemiological studies.[10] Currently the prevalence is thought to be much greater, approximately 1 percent worldwide.[11,12] Celiac disease is a unique model of autoimmunity in which some of the genes involved, the target auto antigen, and the environmental trigger (gluten) are known. The genetic predisposition observed in patients with celiac disease is related to human leukocyte antigen (HLA) Class II genes, namely, HLA-DQ2 and HLA-DQ8. These genes explain ~40% of the disease heritability. Because celiac disease prevalence increases with age, genes and gluten are probably not the only things responsible for celiac disease development. Diagnosis of celiac disease is primarily carried out through serological testing for anti-gliadin, anti-endomysium and anti-transglutaminase antibodies. These serological tests are

typically coupled with a small bowel biopsy for histopathological assessment of the gut. Lifelong adherence to a strict gluten-free diet is essential for treating celiac disease.[9,11,12]

Non-celiac Gluten Sensitivity (NCGS)

Non-celiac gluten sensitivity (also referred to as gluten sensitivity and non-celiac gluten intolerance), is associated with gastrointestinal symptoms such as gas, bloating and diarrhea, as well as extraintestinal symptoms such as fatigue, headaches, dizziness, and ataxia, which frequently improve with the adoption of a gluten-free diet. Prevalence of NCGS is unknown. One study of 5,896 patients from the University of Maryland Center for Celiac Research reported prevalence of NCGS at 6%,[13] which would indicate that approximately 18 million Americans may have NCGS. However, due to the inherent subjectivity in diagnosis of NCGS, definitive data on prevalence will be difficult to establish.

Gluten free diet in other disorders

A gluten-free diet has been shown to improve gastrointestinal and/or systemic symptoms in systemic lupus erythematosus, dermatitis herpetiformis, irritable bowel syndrome, rheumatoid arthritis, type 1 diabetes, thyroiditis, and psoriasis.[14,15] Although gluten-free diets have been used to treat autism spectrum disorders (ASD),[8,16] results are inconsistent,[17] and the American Academy of Pediatrics does not support the use of gluten-free diets as a primary treatment for individuals with ASD.[18]

Diagnosis of gluten-related disorders

Algorithms have been proposed for diagnosis of the spectrum of gluten-related disorders (see Figure 1).[13,19] Diagnostic criteria for celiac disease and wheat allergy have been established. Clinical diagnosis of NCGS is generally based on responses to a gluten-free diet.[7] It is clear that a gluten-free diet is essential for treating celiac disease. However, the treatment of NCGS is

less clear. In a recent double-blind cross-over trial of 37 women and men with NCGS and irritable bowel syndrome (IBS), gastrointestinal symptoms consistently improved when subjects consumed a diet low in fermentable, oligo-, di-, monosaccharides, and polyols (FODMAPs), but gluten-specific effects were observed in only 3 (8%) of the subjects.[20] Those subjects who consumed a low-FODMAP diet that was high in gluten had the same symptom profile as when they consumed the same diet with low gluten content. These results suggest that in those with NCGS and/or IBS, symptoms widely attributed to gluten *per se* may be due to FODMAPs. In order to improve treatment strategies for NCGS, t he results of this study on subjects with both NCGS and IBS need to be replicated and further research is necessary to determine the extent of symptomology due to gluten and FODMAPs. In healthy adults, one FODMAP prevalent in wheat—inulin—was reported to cause few gastrointestinal symptoms.[21]

Apart from the demonstrated effectiveness of a gluten-free diet for treating the spectrum of gluten-related disorders and the conditions mentioned above, evidence-based research supporting the merits of a gluten-free diet as a "healthier" option for the general population is lacking.

No evidence to support a weight-loss claim for a gluten-free diet

Despite the fact that an estimated 27 percent of US adults consume gluten-free products for weight loss,[4] no studies have been published to demonstrate that a gluten-free diet produces weight loss in persons without celiac disease or NCGS. Data on weight change in persons with celiac disease following a gluten-free diet are mixed.[22-25] Although body mass index status generally improves in celiac patients who follow a gluten-free diet,[22] this is not always the case. In two studies that included a total of 740 adults with celiac disease, 22 of 81 (27%) initially overweight subjects in one study[22] and 55 of 67 (82%) initially overweight subjects in another

study[23] gained weight after following a gluten-free diet for at least 2 years. Similar results have been documented in children.[24,25] In one study of 149 children with celiac disease who followed a gluten-free diet for at least one year, the percentage of overweight children increased from 11% to 21%.[24] Among 679 children with celiac disease who followed a gluten-free diet, body mass index increased by an average of 2 BMI units during a mean follow-up of 39.5 months.[25] The change in body mass index was correlated with the duration of follow-up. In this study, 15.8% of children moved from a normal body mass index into an overweight body mass index class, and 22% of initially overweight children gained weight. The authors concluded that weight maintenance counseling should be a key component of dietary education in this population.

The increased body weight observed in a significant percentage of celiac patients who adhere to a gluten-free diet is likely due to enhanced absorption of nutrients corresponding to healing of intestinal lining after gluten removal from the diet. The effect of a gluten-free diet on body weight in persons without celiac disease remains to be established. Gluten-free foods are not necessarily low-calorie; in fact some gluten-free foods contain more calories than the gluten-containing foods they are designed to replace.[6] A gluten-free diet may also result in lower intake of whole grains and dietary fiber.[6] This may also compromise weight control because consumption of both whole grains and dietary fiber has been reported to be inversely correlated with body mass index.[26]

Is there a downside to eliminating wheat from the diet?

Wheat is the most widely consumed grain in the United States and is by far the most important source of fructan-type resistant starches such as oligofructose and inulin.[27-28] These substances have a prebiotic action that helps create a healthy composition of gut bacteria[29-36] which may reduce risk of some cancers, inflammatory conditions, and cardiovascular disease.[34-

[35] Eliminating wheat from the diet without an established medical reason may have unintended consequences.

Because intense attention to gluten as a potential health issue is only a recent phenomenon, there is currently very little published research on the effects of gluten-free diets in otherwise healthy individuals. There is some evidence, however, to suggest that following a gluten-free diet reduces concentrations of beneficial gut bacteria.[37] Ten healthy subjects followed a gluten-free diet for one month by exchanging all gluten-containing foods with products certified to be gluten-free. The gluten-free diet reduced concentrations of beneficial bacteria in fecal samples of the subjects, including *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium prausnitzii* (which have been shown to be protective in animal models of inflammatory bowel disease[38]) *and Clostridium lituseburense*, and increased levels of pathogenic *enterobacteriaceae* and *Escherichia coli*.[37] Although conclusions from this study must be viewed with caution, they do suggest that following a gluten-free diet without a valid medical reason to do so may adversely affect composition of gut bacteria.

On the other hand, a gluten-rich diet may boost the numbers of beneficial gut bacteria.[39] While maintaining their habitual diet, 31 healthy adults consumed either 48 g/day of 100% whole-grain wheat breakfast cereal or 48 g/day of wheat-bran cereal for three weeks. The addition of 48 g/day of 100% whole-grain wheat breakfast cereal increased numbers of fecal *Bifidobacterium* by approximately10%, whereas wheat bran had no effect. The numbers of *Lactobacilli* in fecal samples were increased by 7.4% after the 100% whole-grain wheat condition, which was statistically significantly greater than the 5.0% improvement after the wheat-bran condition. A prebiotic effect of whole-grain wheat breakfast cereal may be one of

the mechanisms by which whole-grain foods confer health benefits,[29-36] which is consistent with the reduced cardiovascular disease risk associated with whole-grain food intake.[33-34]

Are there unrecognized health benefits of gluten?

Although limited in numbers, there are several studies that suggest gluten itself may have health benefits in addition to its energy value as a protein. For example, in 24 hyperlipidemic adults who consumed over a 2-week period an additional 60 g/day of gluten in the form of a specially made bread with a high gluten content, serum triglycerides were reduced by 13%.[40] In the same subjects, a diet with increased amounts of wheat fiber or wheat bran had no effect on triglycerides. In another study by the same researchers,[41] hyperlipidemic men and women consumed during a 4-week period either a control diet or a diet in which 11% of the carbohydrate in the control diet was replaced with wheat gluten. The increased gluten intake (78 g/day) reduced serum triglycerides by 19.2%, uric acid by 12.7%, and low-density lipoprotein (LDL) oxidation by 10.6%. The authors commented that the observed effects of added wheat gluten on serum triglycerides and oxidized LDL are comparable to those of monounsaturated fat and soy protein. Gluten may also have a positive effect on blood pressure. Various peptide fragments of gliadin extracted from wheat gluten have been shown to inhibit angiotensin I-converting enzyme (ACE),[42] which could help lower blood pressure. Whole grain diets have been shown to reduce blood pressure in mildly hyperchoelsterolemic adults ,[43] with wheat itself having a specific effect.[44] In addition to the contribution of the dietary fiber component of whole grains in blood pressure regulation,[45] gluten (via one of its constituent proteins gliadin) may also play a role.[42]

Gluten may also contribute to a healthy immune system, possibly due to the fact that ~40% of the amino acid composition of gluten is due to glutamine. The incidence of infections

following surgery has been shown to be reduced with glutamine supplementation.[46] In a pilot study of the effects of gluten supplementation on natural killer cell activity, five healthy volunteers who consumed 3 g per day wheat gluten hydrolysate for 6 days increased natural killer cell activity by 6% to 57%, whereas four control subjects receiving a placebo showed no improvement.[47] An increased concentration of natural killer cell activity could be expected to boost protection against tumor development and viral infections,[48] and these preliminary findings are consistent with the reports showing an association between whole-grain wheat consumption and reduced cancer risk.[49,50] It is important, however, to note the preliminary nature of these findings and more research needs to be done in this area.

Gluten-free options

With the explosion in the gluten-free market,[2] more gluten-free options are available. There are many gluten-free grains, seeds, flours and starches, for example, which can help consumers obtain adequate dietary fiber found in whole grains.[51] These include buckwheat, corn, arrowroot, amaranth, flax, millet, legume flours, mesquite flour, and nut flours. These safe options may enable those on a gluten-free diet to avoid some of the nutritional deficiencies, such as low intakes of thiamin, riboflavin, niacin, folate, and iron, which have been reported to be associated with gluten avoidance.[12,51] Gluten-free products may also have lower protein contents than the gluten-containing foods they are designed to replace.[52] By choosing foods that are nutrient dense, a gluten-free diet can be a well balanced diet. This does not, however, mean that a gluten-free diet is a healthier diet, as is commonly believed.[4] For individuals who require a gluten-free diet, it is recommended that they consult with a registered dietitian with expertise in celiac disease.

Guidelines established on August 5, 2013 by the Food and Drug Administration should help consumers who require a gluten-free diet be able to determine whether a product is really gluten-free (federal register website). In order to bear a label of "gluten-free," "without gluten," "free of gluten," or "no gluten," the product must have less than 20 ppm (parts per million) gluten. This level corresponds to the lower limit that can be consistently detected with currently available analytical tools, and is in agreement with recommendations in the scientific literature.[53] Food manufacturers were given until August 5, 2014 to bring their food labels into compliance. One additional point worth noting is that foods and beverages that do not inherently contain gluten (e.g., bottled water, fruits and vegetables) will be allowed to be labeled as "gluten-free." This has the potential to produce some confusion among consumers if confronted with an inherently gluten-free product that does not bear a "gluten-free" label.

Along with the growing numbers of people avoiding gluten, there has been an associated increase in internet sites catering to the demand for gluten-free products. More than 93% of individuals with digestive diseases seek Web-based health information.[54] However, nearly one-half of 98 internet sites that provided information on celiac disease had information that was judged to be less than 95% accurate.[54] Furthermore 20% of commercial, nonprofit, and professional websites provided information that was less than 90% accurate. Inaccuracies included information about the definition and prevalence of celiac disease, proper diagnosis of the disease, and various aspects of a gluten-free diet. Furthermore, 52% of websites contained less than 50% of the core information that is considered essential information about celiac disease. This reinforces our recommendation that people with celiac disease or documented NCGS work with their physician and a registered dietitian with expertise in celiac disease and gluten-free dieting.

Summary and Recommendations

Gluten-free diets are clearly indicated for patients with celiac disease. Notwithstanding the recent evidence suggesting that FODMAPs may be the underlying cause of symptoms in NCGS,[20] gluten-free diets appear to be indicated for these individuals as well. A gluten-free diet may also be beneficial for patients with other chronic auto-immune conditions.[14,15]

Despite recent surveys[4] showing that most U.S. adults think gluten-free products are healthier, and that more than one-quarter of U.S. adults are avoiding gluten for purposes of weight control, there is no published medical evidence to support health or weight loss claims for the general population.[3,6] Moreover, because whole-grain intake is associated with numerous health benefits,[33,34,49] and because wheat is the most widely consumed grain in America, going "gluten-free" may not only be unnecessary but may be an unhealthier alternative without careful attention to nutritional quality of gluten-free replacements. Gluten-free baked goods, for example, can be high in fat and total calories[12] and lower in protein.[52] Furthermore, gluten-free products may cost more than twice as much as their gluten-containing counterparts.[55] The continued usage of an inherently more expensive diet that lacks a meaningful evidence base is hard to explain. More research on the health effects of gluten is needed, including the conceivable unintended consequences of gluten avoidance, especially in otherwise healthy individuals.

References

1. Gluten-free diet appeals to 30 percent of adults, survey says. Huffington Post website. http://www.huffingtonpost.com/2013/03/06/gluten-free-diet_n_2818954.html. Accessed March 19, 2014.
2. Schultz EJ. Gluten-free food fad gaining momentum among marketers. Advertising Age, September 16, 2013. http://adage.com/article/news/gluten-free-food-fad-gaining-momentum-marketers/244174/. Accessed March 19, 2014.
3. Gaesser GA, Angadi SS. Gluten-free diet: Imprudent dietary advice for the general population? *J Acad Nutr Diet.* 2012;112:1330-1333.
4. Watson E. Health/weight-conscious consumers are driving the gluten-free market, not celiac, says Mintel. http://www.foodnavigator-usa.com/Markets/Health-weight-conscious-consumers-are-driving-the-gluten-free-market-not-celiacs-says-Mintel. Accessed March 19, 2014.
5. Miley Cyrus: Gluten-Free Diet is Responsible for Weight Loss. Huffington Post, http://www.huffingtonpost.com/2012/04/10/miley-cyrus-gluten-free-diet-weight-loss_n_1414641.html. Accessed March 19, 2014.
6. Marcason W. Is there evidence to support the claim that a gluten-free diet should be used for weight loss? *J Am Diet Assoc*. 2011;111:1786.
7. Pietzak M. Celiac disease, wheat allergy, and gluten sensitivity: when gluten free is not a fad. *J Parental Enterol Nutr*. 2012;36:68S-75S.
8. Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PHR, Hadjivassiliou, Kaukinen K,, Rostami K, Sanders DS, Schumann M, Ullrich R, Villalto D, Volta U, Catassi C, Fasano A. Spectrum

of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med.* 2012;10:13.

9. Briani C, Samaroo D, Alardini A. Celiac disease: from gluten to autoimmunity. *Autoimmunity Rev*. 2008;7:644-650.
10. Barton SH, Kelly DG, Murray JA. Nutritional deficiencies in celiac disease. *Gastroenterol Clin N Am* 2007;36:93-108.
11. Catassi C, Fassano A. Celiac disease. *Curr Opin Gastroenterol*. 2008;24:687-691.
12. Niewinski MM. Advances in celiac disease and gluten-free diet. *J Am Diet Assoc*. 2008;108:661-672.
13. Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PHR, Hadjivassiliou M, Kaukinen K, Rostami K, Sanders DS, Schumann M, Ullrich R, Villalta D, Volta U, Catassi C, Fasano A. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med*. 2012;10:13.
14. Green PH. Mortality in celiac disease, intestinal inflammation, and gluten sensitivity. *JAMA*. 2009;302:1225-1226.
15. El-Chammas K, Danner E. Gluten-free diet in nonceliac disease. *Nutr Clin Pract*. 2011;26:294-299.
16. de Magistris L, Familiari V, Pascotto A, Sapone A, Frolli A, Iardino P, Carteni M, De Rosa M, Francavilla R, Riegler G, Militerni R, Bravaccio C. Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. *J Pediatr Gastroenterol Nutr*. 2010;51:418-424.

17. Mulloy A, Lang R, O'Reilly M, Sigafoos J, Lancioni G, Rispoli M. Gluten-free and casein-free diets in the treatment of autism spectrum disorders; a systematic review. *Res Autism Specturm Disorders.* 2010;4:328-339.

18. Buie T, Campbell DB, Fuchs GJ 3rd, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics.* 2010;125 Suppl 1:S1-S18.

19. Lundin KEA, Alaedini A. Non-celiac gluten sensitivity. *Gastrointest Endoscopy Clin N Am.* 2012;22:723-734.

20. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of low-fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterol*. 2013;145:320-328.

21. Murray K, Wilkinson-Smith V, Hoad C, Costigan C, Cox E, Lam C, Marciani L, Gowland P, Spiller RC. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. *Am J Gastroenterol.* 2014;109:110-119.

22. Cheng J, Brar PS, Lee AR, Green PHR. Body mass index in celiac disease. Beneficial effect of a gluten-free diet. *J Clin Gastroenterol.* 2010;44:267-271.

23. Dickey W, Kearney N. Overweight in celiac disease: Prevalence, clinical characteristics, and effect of a gluten-free diet. *Am J Gastroenterol.* 2006;101:2356-2359.

24. Valletta E, Fornaro M, Cipolli M, Conte S, Bissolo F, Danchielli C. Celiac disease and obesity: need for nutritional follow-up after diagnosis. Eur J Clin Nutr. 2010;64:1371-1372.

25. Kabbani TA, Goldberg A, Kelly CP, Pallav K, Tariq S, Peer A, Hansen J, Dennis M, Leffler DA. Body mass index and the risk of obesity in coeliac disease treated with the gluten-free diet. *Aliment Pharmacol Ther*. 2012;35:723-729.

26. Gaesser GA. Carbohydrate quantity and quality in relation to body mass index. *J Am Diet Assoc*. 2007;107:1768-1780.

27. van Loo J, Coussement P, de Leenheer L, Hoebregs H, Smits G. On the presence of inulin and oligofructose as natural ingredients in the western diet. *Crit Rev Food Sci Nutr*. 1995;35:525-552.

28. Moshfegh AJ, Friday JE, Goldman JP, Ahuja JKC. Presence of inulin and oligofructose in the diets of Americans. *J Nutr*. 1999;129:1407S-1411S.

29. Neyrinck AM, Delzene NM. Potential interest of gut microbial changes induced by nondigestible carbohydrates of wheat in the management of obesity and related disorders. *Curr Opin Clin Nutr Metab Care*. 2010;13:722-728.

30. Gibson GR. Prebiotics as gut microflora management tools. *J Clin Gastroenterol*. 2008;42(suppl 2):S75-S79.

31. Delzenne NM, Cani PD. Gut microbiota and the pathogenesis of insulin resistance. *Curr Diab Rep*. 2011;11:154-159.

32. Jonnalagadda SS, Harnack L, Liu RH, McKeown N, Seal C, Liu S, Fahey GC. Putting the whole grain puzzle together: health benefits associated with whole grains – summary of American Society for Nutrition 2010 Satellite Symposium. *J Nutr*. 2011;141:1011S-1022S.

33. Harris KA, Kris-Etherton PM. Effects of whole grains on coronary heart disease risk. *Curr Atheroscler Rep*. 2010;12:368-376.

34. Slavin J. Why whole grains are protective: biological mechanisms. *Proc Nutr Soc*. 2003;62:129-134.

35. Fava F, Gitau R, Lovegrove J, Tuohy KM. The gut microflora and lipid metabolism: implications for human health. *Curr Med Chem*. 2006;13:3005–3021.

36. Rastall RA, Gibson GR, Gill HS, Guarner F, Klaenhammer TR, Pot B, Reid G, Rowland IR, Sanders ME. Modulation of the microbial ecology of the human colon by probiotics, prebiotics and synbiotics to enhance human health: an overview of enabling science and potential applications. *FEMS*. 2005;52:145–152.

37. De Palma G, Nadal I, Collado MC, Sanz Y. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. *Brit J Nutr*. 2009;102:1154-1160.

38. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev*. 2009;9:313-323.

39. Costabile A, Klinder A, Fava F, Napolitano A, Fogliano V, Leonard C, Gibson GR, Tuohy KM. Whole-grain wheat breakfast cereal has a prebiotic effect on the human gut microbiota: a double-blind, placebo-controlled, crossover study. *Brit J Nutr*. 2008;99:110-120.

40. Jenkins DJA, Kendall CWC, Vuksan V, Augustin LSA, Mehling C, Parker T, Vidgen E, Lee B, Faulkner D, Seyler H, Josse R, Leiter LA, Connelly PW, Fulgoni V. Effect of wheat bran on serum lipids: influence of particle size and wheat protein. *J Am Coll Nutr*. 1999;18:159-6.

41. Jenkins DJA, Kendall CWC, Vidgen E, Augustin LSA, van Erk M, Geelen A, Parker T, Faulkner D, Vuksan V, Josse RG, Leiter LA, Connelly PW. High-protein diets in hyperlipidemia: effect of wheat gluten on serum lipids, uric acid, and renal function. *Am J Clin Nutr*. 2001;74:57-63.

42. Thewissen BG, Pauly A, Celus I, Brijs K, Delcour JA. Inhibition of angiotensin I-converting enzyme by wheat gliadin hydrolysates. *Food Chem.* 2011;127:1653-1658.

43. Behall KM, Scholfield DJ, Hallfrisch J. Whole-grain diets reduce blood pressure in mildly hypercholesterolemic men and women. *J Am Diet Assoc*. 2006;106:1445-1449.

44. Tighe P, Duthie G, Vaughan N, Brittenden J, Simpson WG, Duthie S, Mutch W, Wahle K, Horgan G, Thies F. Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: a randomized controlled trial. *Am J Clin Nutr*. 2010;92:733-740.

45. Streppel MT, Arends LR, van't Veer P, Grobbee DE, Geleijnse JM. Dietary fiber and blood pressure: a meta-analysis of randomized placebo-controlled trials. *Arch Int Med.* 2005;165:150-156.

46. Novak F, Heyland DK, Avenall A, Drover JW, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med.* 2002;30:2022-2029.

47. Horiguchi N, Horiguchi H, Suzuki Y. Effect of wheat gluten hydrolysate on the immune system in healthy human subjects. *Biosci Biotechnol Biochem*. 2005;69:2445-2449.

48. Herberman RB, Oltaldo JR. Natural killer cells: their roles in defences against disease. *Science*. 1981;214:24-30.

49. Fardet A. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? *Nutr Res Rev*. 2010;23:65-134.

50. Reddy BS, Hirose Y, Cohen LA, Simi B, Cooma I, Rao CV. Preventive potential of wheat bran fractions against experimental colon carcinogenesis: implications for human colon cancer prevention. *Cancer Res.* 2000;60:4792-4797.

51. Case S. Gluten-free Diet: A Comprehensive Resource Guide. Regina, Saskatchewan, Canada: Case Nutrition Consulting, 2006.

52. Miranda J, Lasa A, Bustamante MA, Churruca I, Simon E. Nutritional differences between a gluten-free diet and a diet containing equivalent products with gluten. *Plant Foods Hum Nutr*. Published online March 1, 2014 (http://link.springer.com/article/10.1007%2Fs11130-014-0410-4)

53. Gibert A, Kruizinga AG, Neuhold S, Houben GF, Canela MA, Fasano A, Catassi C. Might gluten traces in wheat substitutes pose a risk in patients with celiac disease? A population-based probabilistic approach to risk estimation. *Am J Clin Nutr*. 2013;97:109-1016.

54. McNally SL, Donohue MC, Newton KP, Ogletree SP, Conner KK, Ingegneri SE, Kagnoff MF. Can consumers trust web-based information about celiac disease? Accuracy, comprehensiveness, transparency, and readability of information on the internet. *Interact J Med Res*. 2012;1:e1.

55. Stevens L, Rashid M. Gluten-free and regular foods: a cost comparison. *Can J Diet Prac Res*. 2008;69:147-150.