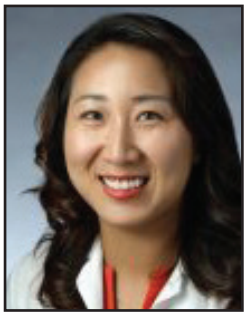
Arsenic Levels in Celiac Patients

Runa Diwadkar Watkins



Dana Hong

Elaine Lynne Leonard Puppa

Anca Safta

Samra Sarigol Blanchard

Background:

For persons with celiac disease, wheat, barley and rye trigger an autoimmune response in the small intestine, specifically destroying the villi of the duodenum and triggering systemic inflammation. To avoid this immune response, people with celiac disease substitute rice and rice products for wheat, barley and rye. Concerns regarding arsenic levels in rice have prompted the celiac community to question whether increased rice consumption puts them at an increased risk for arsenic toxicity. Some studies have suggested children may be at greater risk than adults. The purpose of this study was to evaluate the risk for increased arsenic levels in persons with celiac disease.

Methods:

A retrospective chart review of 60 charts was performed for patients seen at a Mid-Atlantic celiac clinic between July 2012 and June 2014. Arsenic levels in biopsy-proven pediatric and adult celiac patients were reviewed. Serum arsenic levels were compared to established normal values; the length of time patients were adherent to a gluten free diet was recorded. Pediatric celiac patients were compared to adult celiac patients.

Results:

Thirty-nine patients had arsenic levels reported. The duration of time between diagnosis to laboratory collection of arsenic levels ranged from four months to 10 years. The mean duration between diagnosis and laboratory collection was 2.35 years for the pediatric group and 3.31 years for the adult group. All patients had normal serum arsenic levels.

Conclusions:

Rice consumption did not increase risk for arsenic toxicity in a retrospective study of serum arsenic levels for patients with biopsy proven celiac disease, irrespective of the duration of gluten free diet.

Runa Diwadkar Watkins, MD[1] Dana Hong, MD[1] Elaine Lynne Leonard Puppa, RN, Med, MSN[1] Anca Safta, MD[2] Samra Sarigol Blanchard, MD[1] [1]Department of Pediatrics, University of Maryland, Baltimore, MD [2]Department of Pediatrics, Wake Forest University, Winston-Salem, NC

INTRODUCTION

Celiac disease is an autoimmune enteropathy triggered by gliadin proteins found in wheat, barley and rye, commonly referred to as glutens. The disease is characterized by increased intestinal permeability, systemic inflammation and damage to the villi of the small intestine resulting in impaired nutrient absorption.[1] The prevalence of celiac disease in the United States is approximately 1:133 individuals.[2] However, the majority of persons in the United States remain undiagnosed.[2] Typical symptoms include dyspepsia and diarrhea.[3,4] Atypical cases may present with a variety of symptoms including short stature, fatigue, rash, anemia, folate deficiency, osteoporosis, arthralgias and myalgias, migraine, peripheral neuropathy and seizure disorder.[4] The only treatment for celiac disease is strict elimination of any exposure to the gliadin proteins, as gluten consumption as low as 20 ppm (¼ tsp flour) may trigger the autoimmune response.[5]

Wheat, barley and rye constitute the staple grains of the United States. Although quinoa, amaranth, corn and other grains that do not contain gluten have recently come into the market, rice remains the staple grain of the celiac diet in most parts of the world. A 2012 Consumer Report article detailed concerns over arsenic levels in food in general, and rice in particular.[6] In addition, the Food and Drug Administration (FDA) began its own investigation into the levels of arsenic in rice in 2012.[7] Concerns over the quality of rice and results of accumulated consumption over time began to emerge from the celiac community.[8-12] A 2014 study estimated that rice-based foods contained potentially dangerous levels of arsenic with consumption of 0.45-0.46 µg per kg bodyweight.[13] Patients in our practice began to express concerns for the level of arsenic they were consuming, not just as rice itself, but also in their baked goods and other gluten free foods that contained rice flour and rice starch as a primary ingredient.

Arsenic is a metallic trace element widely distributed in the environment as a result of natural and human activity.[14] Its organic forms are believed to be essential to many forms of mammalian life.[15] The human body rapidly eliminates organic arsenic compounds such as those found in seafood.[16] However, the inorganic forms of arsenic are more problematic. The World Health Organization (WHO) categorizes inorganic arsenic as a class I human carcinogen.[17,18] Long-term exposure can lead to arsenicosis, a condition of arsenic toxicity due to chronic exposure. Arsenicosis can manifest itself in diseases involving the skin, cardiovascular, nervous, hepatic, hematologic, endocrine or renal systems.

Arsenic compounds occur in soils, and contamination can be widespread in the environment. Volcanoes disperse arsenic containing ash. Metal smelting, burning fossil fuels, pesticide production and use, and drilling of water wells may also mobilize arsenic in the soil.[6-7,19] Ground water dissolves the mineral from the soil creating a variety of salts across a wide range of conditions.[20]

For most people, diet is the largest source of exposure to arsenic with mean dietary intakes of total arsenic of 50 -60 mcg/day. Intake of inorganic arsenic ranges from 1-20 mcg/day when rice and/or infant rice cereal are included in the diet. Rice contains the highest level of inorganic arsenic and arsenic concentrations ranging from 0.05 to 0.4 mcg/g of rice.[7]

Arsenic accumulation in the rice plant increases markedly under flooded conditions due to the soluble nature of arsenic salts. Arsenic levels vary throughout the world with highest arsenic contamination found in ground water affecting Bangladesh, India, Vietnam, Thailand, and Nepal. Contamination of water is largely due to heavy industry contaminants. Within the United States, rice grown in the south-central US contains higher average total arsenic concentrations compared to California.[15] Brown rice contains higher levels of arsenic because the arsenic tends to concentrate in the area near the surface of the grain, the area polished off to create white rice. [21]

Children have dietary arsenic exposure from 2 to 3 times greater than that of adults and may be the most vulnerable.[22] Considering rice and rice based foods contain high levels of inorganic arsenic, pediatric celiac patients may be a particularly high-risk category.[23] In these patients, rice and rice based foods are the main edible substitutes of gluten based products.

The American Academy of Pediatrics (AAP) in November 2014 advised pediatric patients to reduce exposure to arsenic in rice, in response to FDA

advisory group which conducted a risk assessment regarding acceptable levels of arsenic in drinking water and diets.[24] The AAP recommended interim advice was directed, in particular, toward infant rice cereal, which is used as a thickening agent in feedings for infants and older children, and as a bland introductory food during weaning. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) in 2015 published a consensus statement that rice contains high levels of inorganic arsenic and its intake during childhood is likely to affect long-term health. The recommendation was to limit the intake of inorganic arsenic as long as possible and reduce intake of inorganic arsenic exposure from food by including a variety of grains such as oat, barley, wheat and maize in the diet.

Chronic and continued exposure to arsenic achieves steady-state concentrations in blood and urine as well as arsenic accumulating in hair and nails.[25] Urinary arsenic reflects arsenic excretion but may not reflect tissue burden. Blood arsenic levels better demonstrate both recent exogenous exposure and an individual's total internal arsenic burden.[25]

METHODS

A retrospective chart review of celiac clinic patients with arsenic orders placed between July 2012 and June 2014 was conducted. Physicians obtained routine nutritional and serologic markers to monitor the nutritional status and antibody levels of their patients diagnosed with celiac disease. Blood arsenic levels were ordered in conjunction with annual nutritional and serology follow up in established celiac patients or within six months for newly diagnosed celiac patients as part of routine care.

Blood arsenic level was selected as a marker to limit the number of extra procedures. The value of evaluating blood or urine arsenic has been shown to be equivocal in detecting chronic exposure and body's burden of the toxin.[25-26] Chronic and continued exposure to arsenic achieved steady state concentrations in blood and urine. However, urine arsenic levels reflect arsenic excretion and not actual tissue burden.[14] The blood arsenic levels may be a better indicator of recent exogenous exposure and tissue burden.

The review identified sixty unique patients on a gluten free diet from the University of Maryland Medical Center Division of Pediatric Gastroenterology and Nutrition. Inclusion criteria included an order for blood arsenic levels and a diagnosis of celiac disease with confirmatory small bowel biopsy. Demographics, diagnoses, method of diagnosis, date of diagnosis and lab values for arsenic level were reviewed for each patient. Four patients were excluded for lack of follow up visit and 15 patients were excluded as the laboratory studies were ordered but not resulted in the patient chart. Of the remaining 41 patients, the diagnosis of celiac disease was made by biopsy of small bowel on esophagogastroduodenoscopy (EGD) for 39 patients as recommended by NASPGHAN. The arsenic levels from lab panels of the 39 patients who met inclusion criteria were reviewed.

RESULTS

Demographics

Thirty-nine patients, ages ranging from 5 to 68 years of age, met the inclusion criteria for review. The mean age for the group was 20 years of age with a bimodal distribution. Twenty-two patients were pediatric patients, defined as less than 18 years of age. The median age of reviewed patients was 10 years old for the pediatric group and 30 years old for the adult group.

RESULTS

The span for duration of time from diagnostic biopsy to blood arsenic collection ranged from 4 months to 10 years. The mean duration period from diagnosis to collection of arsenic levels was 2.35 years for the pediatric group and 3.31 years for the adult group. All patients had normal serum arsenic levels (Table 1). Seven patients had rice exposure of greater than 6 years and the arsenic levels did not differ from the other patients with shorter exposure. This pilot study found no abnormal levels of serum arsenic in patients diagnosed with Celiac Disease, eating a gluten-free diet. Longer exposure to a rice containing diet, determined by an earlier age of diagnosis of Celiac Disease, demonstrated no

Table 1.

	Pediatric Patients	Adult Patients
Gender		
Male	8	3
Female	14	14
Age (years)		
<5	2	
6-11	12	
12-17	8	
18 and older		17
Range of age (years)	4-17	18-68
Median Age (years)	10	30
Mean Duration of Time from Diagnosis to Arsenic level (years)	2.35	3.31
Time range on a Gluten Free Diet (years)	0.5-12	0.75-10
Arsenic Level		
Undetectable	14	9
Low	8	8

increased risk of arsenic accumulation for either pediatric or adult celiac patients.

DISCUSSION

Although significant speculation regarding the potential risk of high arsenic exposure in persons can be found in the literature regarding persons with celiac disease due to their higher rice consumption on a gluten free diet, no published literature is available to substantiate the risk. Bioavailability of arsenic from rice can be very high due to the ability of rice to sequester arsenic absorbed from soil and water.[24-26] Existing arsenic levels in rice are often exacerbated by contaminated cooking water.[20,27] The American Academy of Pediatrics, FDA and NASPGHAN committee on nutrition recommends limiting the intake of rice in diet and to introduce variety of grains including oats, wheat and barley in vulnerable populations.[7,24,26,28] This limitation of rice intake by introducing variety of grains is not possible for celiac patients who have restricted diets where oats are limited and wheat, barley, or rye and oats are eliminated.[4]

This pilot study suggests that celiac patients who are on an exclusive gluten free diet may not need to have arsenic levels checked along with their other follow up laboratory studies. We did not see any abnormal serum arsenic values for celiac patients who were on exclusive gluten free diets for a longer duration of time. This study highlights the need for clinicians to be aware of the concerns that parents of celiac patients may be facing in the dietary restrictions but no further work up is

recommended based on this limited set of data from the pilot study.

This study should be interpreted within the context of its limitations. First, because of the retrospective design, we could not perform blood arsenic levels at time of diagnosis and later after therapy with a gluten free diet for comparison. Second, the gluten free diet of each celiac patient did not account for varied intake in amount of rice consumption for each patient or the origin of the rice. Variations existed in the definition of normal range of arsenic levels between lab facilities that were used to define cut off values. Standardization of laboratory collection at the same resulting facilities would eliminate this variability in comparison of values. Lastly, the power of the study can be improved if an increased number of subjects were included. Future studies should focus on improving the shortcomings as highlighted above. Newer concerns have also suggested arsenic levels possibly being higher in urine samples in those with a strictly gluten free diet. This value was not tested in our study, but would need to be considered in future studies as well.

Most studies of arsenic levels are laboratory based and do not allow for the complex interaction of systems involved in human digestion. Several other modifying effects from the environment influence the human body's ability to detoxify arsenic that may have influenced the results of this study. Folate and folic acid supplements have demonstrated the ability to lower blood arsenic levels in persons exposed to high levels of arsenic in the drinking water.[29] Arsenic, therefore, presents a greater threat to persons who are folate deficient. Likewise, antioxidants from brassicas and other vegetables have also shown protective effects in vitro and been hypothesized to provide a protective effect in the human diet.[16] The soil microbiome is known to degrade inorganic arsenic and the human microbiome has demonstrated a similar effect in vitro.[16,30] Based on these findings and interpretations, it is not useful to obtain nor follow serum arsenic levels in those with Celiac Disease.

CONCLUSION

In conclusion, the serum arsenic levels were found to be normal in our patients with Celiac Disease. Adherence to a strict gluten free diet did not pose a risk of elevated serum arsenic levels. It is suggested that elevated serum levels of arsenic is correlated with acute toxicity, which did not occur in our cohort. We strongly recommend that patients with Celiac Disease do use high quality rice products and future studies may point to checking urine arsenic levels after being on a strict gluten free diet for a long period of time. ■

References

1. Fasano, A. Leaky gut and autoimmune diseases. Clinical Review of Allergy and Immunology. 2012; 42(1):71-78.
2. Catassi C, K.D., Bhatti B, Sturgeon C, Helzlsouer K, Clipp SL, Gelfond D, Puppa E, Sferruzza A, Fasano A. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. Annals of Medicine. 2010; 42(7):530-8.
3. Accomando, S. and F. Cataldo. The global village of celiac disease. Digestive and Liver Disease. 2004; 34:492-498.
4. Fasano, A. Celiac Disease. New England Journal of Medicine. 2012; 367: 2419-26.
5. Hischenhuber C, C.R., Jarry B, et al. Safe amounts of gluten for patients with wheat allergy or coeliac disease. Aliment Pharmacol THer. 2006;23(559-75).
6. Food and Drug Administration. Arsenic in Rice: Summary analytical results from rice/ rice product sampling September, 2012. 2012.
7. Food & Drug Administration. Arsenic in Rice and Rice Products. U.S. Food and Drug Administration.Toxicology Profile for Arsenic, A.f.T.S.a.D. Registry, Editor. 2012.
8. Burkhardt, A. Arsenic in the gluten-free diet: facts and tips. http://theceliacmd.com/2015/03/arsenic-in-rice-the-gluten-free-diet-facts-and-tips/ 2015.
9. Celiac Community Foundation of Northern California. Statement on arsenic in rice. 2012; Available from: http://www.celiaccommunity.org/2012/statement-on-arsenic-in-rice/.
10. Fernstrom, M., Arsenic in gluten-free food: How worried should you be? http://drmadelynfernstrom.com/feed-items/arsenic-in-gluten-free-food-how-worried-should-you-be/ 2014.
11. Reports, C., How much arsenic is in your rice. Consumer Reports, 2014.
12. Munera-Picazo, S., et al. Inorganic and total arsenic contents in rice-based foods for children with celiac disease. Journal of Food Science. 2014; 79(1):T122-T128.
13. Munera-Picazo, S., F. Burló, and Á.A. Carbonell-Barrachina. Arsenic speciation in rice-based food for adults

(continued on page 18)

(continued from page 16)

with celiac disease. Food Additives & Contaminants: Part A. 2014;31(8): p. 1358-1366.
14. Klaassen, C.D. Mechanisms of Toxicity. 6 ed. Casarett and Doull's toxicology: the basic science of poisons. 2001, China: McGraw HIll. 35-82.
15. Underwood, E., Trace elements in human and animal nutrition 4e. 2012: Elsevier.
16. Da Sacco, L., A. Baldassarre, and A. Masotti. Diet's role in the toxicity of inorganic arsenic (iAs): A journey from soil to children's mouth. Journal of Geochemical Exploration. 2013;131: p. 45-51.
17. World Health Organization. Arsenic Fact Sheet. 2016, WHO: Geneva, Switzerland.
18. World Health Organization. Exposure to Arsenic: A Major Public Health Concern. 2010, WHO Document Production Service: Geneva, Switzerland.
19. Jayasumana, C., et al. Phosphate fertilizer is a main source of arsenic in areas affected with chronic kidney disease of unknown etiology in Sri Lanka. SpringerPlus. 2015;4(1): 1.
20. Ackerman, A.H., et al. Comparison of a chemical and enzymatic extraction of arsenic from rice and an assessment of the arsenic absorption from contaminated water by cooked rice. Environmental Science & Technology. 2005;39(14):5241-5246.
21. Signes-Pastor, A., M. Carey, and A. Meharg.Inorganic arsenic in rice-based products for infants and young children. Food Chemistry. 2016; 191: 128-134.
22. Kordas, K., et al. Low-level arsenic exposure: Nutritional and dietary predictors in first-grade Uruguayan children. Environmental Research. 2016; 147: 16-23.
23. Jara, E. and C. Winter.Dietary exposure to total and inorganic arsenic in the United States, 2006–2008. International Journal of Food Contamination. 2014;1(1):3.
24. American Academy of Pediatrics. AAP group offers advice to reduce infants' exposure to arsenic in rice. AAP News. 2014;35(10): p. 1.
25. Hall, M., et al. Blood arsenic as a biomarker of arsenic exposure: results from a prospective study. Toxicology. 2006; 225(2): 225-233.
26. Food and Drug Administration.Supporting Document for Draft Guidance for Industry on Inorganic Arsenic in Rice Cereals for Infants: Action Level. Agency for Toxic Substances and Disease, Editor. 2016, Food and Drug Administration.
27. Kippler, M., et al. Prospective evaluation of arsenic exposure in rural Bangladeshi children shows continuous exposure both via water and rice. in Arsenic Research and Global Sustainability: Proceedings of the Sixth International Congress on Arsenic in the Environment. 2016. Stockhelm, Sweden: CRC Press.
28. Hojsak, I., et al. Arsenic in rice: a cause for concern. Journal of pediatric gastroenterology and nutrition. 2015;60(1): p. 142-145.
29. Hall, M.N., et al. Folate, cobalamin, cysteine, homocysteine, and arsenic metabolism among children in Bangladesh. Environmental health perspectives. 2009;117(5): 825.
30. Van de Wiele, T., et al. Arsenic metabolism by human gut microbiota upon in vitro digestion of contaminated soils. Environmental Health Perspectives. 2010; 118(7):1004-1009.