NIH Consensus Development Conference

Lactose Intolerance and Health

Program and Abstracts

February 22–24, 2010

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Presented by

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH
Office of Medical Applications of Research, NIH

Cosponsors

National Institute of Diabetes and Digestive and Kidney Diseases, NIH
Division of Nutrition Research Coordination, NIH
National Institute on Aging, NIH
Office of Dietary Supplements, NIH

Partners

United States Department of Agriculture

The Agency for Healthcare Research and Quality and the Centers for Disease Control and Prevention provided additional conference development support.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

About the Program

The National Institutes of Health (NIH) Consensus Development Program has been organizing major conferences since 1977. The Program generates Evidence-based consensus statements addressing controversial issues important to healthcare providers, policymakers, patients, researchers, and the general public. The NIH Consensus Development Program holds an average of three conferences a year. The Program is administered by the Office of Medical Applications of Research within the NIH Office of the Director. Typically, the conferences have one major NIH Institute or Center sponsor, with multiple cosponsoring agencies.

Topic Selection

NIH Consensus Development and State-of-the-Science Conference topics must satisfy the following criteria:

- Broad public health importance. The severity of the problem and the feasibility of interventions are key considerations.
- Controversy or unresolved issues that can be clarified, or a gap between current knowledge and practice that can be narrowed.
- An adequately defined base of scientific information from which to answer conference questions such that the outcome does not depend primarily on subjective judgments of panelists.

Conference Type

Two types of conferences fall under the purview of the NIH Consensus Development Program: State-of-the-Science Conferences and Consensus Development Conferences. Both conference types utilize the same structure and methodology; they differ only in the strength of the evidence surrounding the topic under consideration. When it appears that there is very strong evidence about a particular medical topic, but that the information is not in widespread clinical practice, a Consensus Development Conference is typically chosen to consolidate, solidify, and broadly disseminate strong Evidence-based recommendations for general practice. Conversely, when the available evidence is weak or contradictory, or when a common practice is not supported by high-quality evidence, the State-of-the-Science label is chosen. This highlights what evidence about a topic is available and what directions future research should take, and alerts physicians that certain practices are not supported by good data.

Conference Process

Before the conference, a systematic evidence review on the chosen topic is performed by one of the Agency for Healthcare Research and Quality's Evidence-based Practice Centers. This report is provided to the panel members approximately 6 weeks prior to the conference, and posted to the Consensus Development Program Web site once the conference begins, to serve as a foundation of high-quality evidence, upon which the conference will build.

The conferences are held over 2-1/2 days. The first day and a half of the conference consist of plenary sessions, in which invited expert speakers present information, followed by "town hall forums," in which open discussion occurs among the speakers, panelists, and the general public in attendance. The panel then develops its draft statement on the afternoon and evening of the second day, and presents it on the morning of the third day for audience commentary. The panel considers these comments in executive session and may revise its draft accordingly. The conference ends with a press briefing, during which reporters are invited to question the panelists about their findings.

Panelists

Each conference panel comprises 12 to 16 members, who can give balanced, objective, and informed attention to the topic. Panel members:

- Must not be employees of the U.S. Department of Health and Human Services.
- Must not hold financial or career (research) interests in the conference topic.

- May be knowledgeable about the general topic under consideration, but must not have published on or have a publicly stated opinion on the topic.
- Represent a variety of perspectives, to include:
  - Practicing and academic health professionals
  - Biostatisticians and epidemiologists
  - Clinical trialists and researchers
  - Non-health professionals with expertise in fields relevant to the specific topic (ethicists, economists, attorneys, etc.)
  - Individuals representing public-centered values and concerns

In addition, the panel as a whole should appropriately reflect racial and ethnic diversity. Panel members are not paid a fee or honorarium for their efforts. They are, however, reimbursed for travel expenses related to their participation in the conference.

Speakers

The conferences typically feature approximately 21 speakers: 3 present the information found in the Evidence-based Practice Center's systematic review of the literature; the other 18 are experts in the topic at hand, have likely published on the topic, and may have strong opinions or beliefs on the topic. Where multiple viewpoints on a topic exist, every effort is made to include speakers who address all sides of the issue.

Conference Statements

The panel's draft report is released online late in the conference's third and final day. The final report is released approximately 6 weeks later. During the intervening period, the panel may edit its statement for clarity and correct any factual errors that might be discovered. No substantive changes to the panel's findings are made during this period.

Each Consensus Development or State-of-the-Science Conference Statement reflects an independent panel's assessment of the medical knowledge available at the time the statement is written; as such, it provides a "snapshot in time" of the state of knowledge on the conference topic. It is not a policy statement of the NIH or the Federal Government.

Dissemination

Consensus Development and State-of-the-Science Conference Statements have robust dissemination:

- A press briefing is held on the last day of the conference to assist journalists in preparing news stories on the conference findings.
- The statement is published online at consensus.nih.gov.
- The conference statement is published in a major peer-reviewed journal.
- Print copies are mailed to a wide variety of targeted audiences and are available at no charge through a clearinghouse.

Contact Us

For conference schedules, past statements, and evidence reports, please contact us:

NIH Consensus Development Program
Information Center
P.O. Box 2577
Kensington, MD 20891

1-888-NIH-CONSENSUS (888-644-2667)
consensus.nih.gov

Upcoming Conferences

NIH Consensus Development Conference:	**Vaginal Birth After Cesarean: New Insights** *March 8–10, 2010*
NIH State-of-the-Science Conference:	**Preventing Alzheimer's Disease and Cognitive Decline** *April 26–28, 2010*
NIH Consensus Development Conference:	**Inhaled Nitric Oxide Therapy for Premature Infants** *October 27–29, 2010*

To receive registration notifications and updates about conferences and other program activities, please join the NIH Consensus Development Program Information Network at **consensus.nih.gov/alerts.htm.**

Recent Conferences

NIH State-of-the-Science Conference:	**Enhancing Use and Quality of Colorectal Cancer Screening** *February 2–4, 2010*
NIH State-of-the-Science Conference:	**Diagnosis and Management of Ductal Carcinoma In Situ (DCIS)** *September 22–24, 2009*
NIH State-of-the-Science Conference:	**Family History and Improving Health** *August 24–26, 2009*
NIH Consensus Development Conference:	**Management of Hepatitis B** *October 20–22, 2008*
NIH Consensus Development Conference:	**Hydroxyurea Treatment for Sickle Cell Disease** *February 25–27, 2008*
NIH State-of-the-Science Conference:	**Prevention of Fecal and Urinary Incontinence in Adults** *December 10–12, 2007*
NIH State-of-the-Science Conference:	**Tobacco Use: Prevention, Cessation, and Control** *June 12–14, 2006*
NIH State-of-the-Science Conference:	**Multivitamin/Mineral Supplements and Chronic Disease Prevention** *May 15–17, 2006*
NIH State-of-the-Science Conference:	**Cesarean Delivery on Maternal Request** *March 27–29, 2006*
NIH State-of-the-Science Conference:	**Manifestations and Management of Chronic Insomnia in Adults** *June 13–15, 2005*
NIH State-of-the-Science Conference:	**Management of Menopause-Related Symptoms** *March 21–23, 2005*

To access previous conference statements, videocasts, evidence reports, and other conference materials, please visit **consensus.nih.gov.**

General Information

Continuing Education

The NIH Consensus Development Program aspires to offer continuing education credits to as many conference attendees as possible. If your preferred credit type is not listed, please check to see if your credentialing body will honor other types of credit.

Please note that continuing education credits are not available for Webcast viewers.

Continuing Medical Education

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME®) through the joint sponsorship of the Centers for Disease Control and Prevention (CDC) and the NIH. The CDC is accredited by the ACCME to provide continuing medical education for physicians.

The CDC designates this educational activity for a maximum of 13.5 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Continuing Education Designated for Non-Physicians

Non-physicians will receive a certificate of participation.

Dietitians

Registered Dietitians (RDs) and Dietetic Technicians Registered (DTRs) may receive up to 13.5 CPEUs for attending this activity.

Continuing Nursing Education

The CDC is accredited as a provider of continuing nursing education (CNE) by the American Nurses Credentialing Center's Commission on Accreditation.

This activity provides 13.0 contact hours.

Continuing Education Contact Hours

The CDC is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the certified health education specialists (CHES) to receive 13.0 Category 1 contact hours in health education, CDC provider number GA0082.

Continuing Nutrition Education (CNE)

The Certification Board for Nutrition Specialists, an arm of the American College of Nutrition, authorizes the award of 13.5 Continuing Nutrition Education (CNE) credits for full attendance at the NIH Consensus Development Conference: Lactose Intolerance and Health, February 22-24, 2010. For more information about the American College of Nutrition, please visit their web site at: **www.americancollegeofnutrition.org.**

Financial Disclosures

CDC, our planners, and our presenters wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters with the exception of the following:

Planning Committee	Company	Financial relationship
Winston Price, M.D., FAAP	National Dairy Council	Honorarium, speaker, consultant
Speakers	**Company**	**Financial Relationship**
Catherine M. Gordon, M.D., M.Sc.	Gilead Sciences	Honorarium, consultant
	Pfizer, Inc./Merck & Co., Inc.	Salary, Associate Director – Clinical Investigator Training Program, Harvard/MIT with Pfizer/Merck
Susan L. Johnson, Ph.D.	Dannon	Honorarium, board member
Jeanette Newton Keith, M.D.	National Dairy Council/International Dairy Foods Association	Honorarium, speaker's bureau
	A.S.P.E.N. Rhoads Research Foundation	Grant funding, investigator
	Proctor & Gamble	Grant funding, investigator
	Sprim International	Honorarium, consulting
	NPS Pharmaceuticals	Honorarium, consulting, Drug Safety Monitoring Board
	CTK Clinical Consultants	Family relationship, spouse
David S. Newburg, Ph.D.	Glycosyn, Inc.	Stock, board
	Mead Johnson Nutrition	Honorarium, speaking and teaching
	Wyeth (now Pfizer, Inc.)	Honorarium, speaking and teaching
Mary Ellen Sanders, Ph.D.	Proctor & Gamble	Fee for service, consultant
	Yakult	Fee for service, consultant
	Wyeth (now Pfizer, Inc.)	Fee for service, consultant
	Cadbury Global	Fee for service, consultant
	Danisco	Fee for service, consultant
	Ganeden Biotech, Inc.	Fee for service, consultant
	Dannon/Danone	Fee for service, consultant
	Mead Johnson Nutrition	Fee for service, consultant
	Clif Bar & Company	Fee for service, consultant
	Kraft Foods	Fee for service, consultant
	Nutrition 21	Fee for service, consultant
Andrew Szilagyi, M.D., FRCPC	Novartis	Honorarium, speaker
	Ferring Pharmaceuticals	Honorarium, consultant
	Abbott	Honorarium, speaker
Janet E. Taylor, M.D., M.P.H.	AstraZeneca Pharmaceuticals	Honorarium, speaker, consultant

Planning Committee Members and Speakers	Company	Financial Relationship
Richard J. Grand, M.D.	Solvay Pharmaceuticals	Honorarium, consultant
Josef Neu, M.D.	Mead Johnson Nutrition	Research grant, researcher
	Abbott	Honorarium, consultant
	Nestle	Honorarium, researcher
	Life Sciences, Environs	Consultant
	Medela Medical	Honorarium, advisory board
Dennis A. Savaiano, Ph.D.	Ritter Pharmaceuticals	Stock, consulting fees
Connie M. Weaver, Ph.D.	Pharmavite	Honorarium, advisory board
	Wyeth (now Pfizer, Inc.)	Honorarium, advisory board
	Cadbury Schweppes	Honorarium, advisory board
	Sara Lee	Honorarium, board member
	GTC Biotherapeutics	Honorarium, board member

Presentations will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of Dr. Mary Ellen Sanders's discussion on probiotics. She will be discussing evidence for the use of live microbes to help lactose maldigesters to be able to consume lactose-containing dairy products with fewer symptoms/discomfort. These products are generally not labeled for this function.

There is no commercial support for this activity.

Policy on Panel Disclosure

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

Videocast

Live and archived videocasts may be accessed at **videocast.nih.gov**. Archived videocasts will be available approximately 1 week after the conference.

Dining

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:30 p.m., in Building 38A, Level B1, across the street from the main entrance to the Natcher Conference Center.

Online Content

All materials issuing from the NIH Consensus Development Program are available at **consensus.nih.gov.** Additionally, remote participants will have the opportunity to provide comments on the panel statement by visiting **consensus.nih.gov/comments.htm** from 8:30 a.m. to 11:30 a.m. on Wednesday, February 24, 2010.

Contents

Background

Lactose intolerance is the inability to digest significant amounts of lactose, a sugar found in milk and other dairy products. Lactose intolerance is caused by a shortage of the enzyme lactase, which is produced by expression of the lactase-phlorizin hydrolase gene by the cells that line the small intestine. Lactase breaks milk sugar down into two simpler forms of sugar called glucose and galactose, which are then absorbed into the bloodstream. Infants of every racial and ethnic group worldwide produce lactase and successfully digest lactose provided by human milk or by infant formulas. However, by the time many of the world's children reach the age of 3-4 years, expression of intestinal lactase ceases. Most affected individuals–referred to as lactase nonpersisters–in the United States belong to minority groups, especially Asians, African Americans, Hispanics, Native Americans, Alaskan Natives, and Pacific Islanders.

Consumption of lactose-containing products by lactase nonpersisters may cause gas production, bloating, abdominal pain, and diarrhea. These symptoms of lactose intolerance are caused by intestinal bacteria's fermentation of undigested lactose and often cause individuals to avoid lactose-containing products. Lactose intolerance can be diagnosed by drinking one to two large glasses of milk after fasting and measuring breath hydrogen levels a few hours later. Other diagnostic tools include analyzing an intestinal biopsy sample or determining the genetic makeup of the chromosomal region coding for lactase. However, many individuals mistakenly ascribe symptoms of a variety of intestinal disorders to lactose intolerance without undergoing testing. This becomes intergenerational when self-diagnosed lactose-intolerant parents place their children on lactose-restricted diets in the belief that the condition is hereditary.

Healthcare providers are concerned that many lactose-intolerant individuals are avoiding dairy products, which constitute a readily accessible source of calcium and are fortified with vitamin D and other nutrients. Therefore, these individuals may not be meeting recommended intakes of these essential nutrients. Insufficient intakes of calcium carry a risk of decreased bone mineral density. This may have effects on bone health and increase the risk of fracture throughout the lifecycle, especially in postmenopausal women. Very low intake of vitamin D can lead to the development of rickets, especially in those of African descent and other highly pigmented individuals. Although milk alternative products are typically fortified with vitamin D and other nutrients, they are often more expensive and less widely available than conventional products.

The public health burden from deficiencies attributable to lactose intolerance is difficult to quantify. Additionally, it is challenging to identify and manage lactase nonpersisters. Questions remain as to the amount, if any, of lactose that can be tolerated by lactose nonpersisters and how best to assist these individuals in meeting recommended intakes. To examine these important issues, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the Office of Medical Applications of Research of the National Institutes of Health has convened Consensus Development Conference from February 22 to 24, 2010, to assess the available scientific evidence related to the following questions:

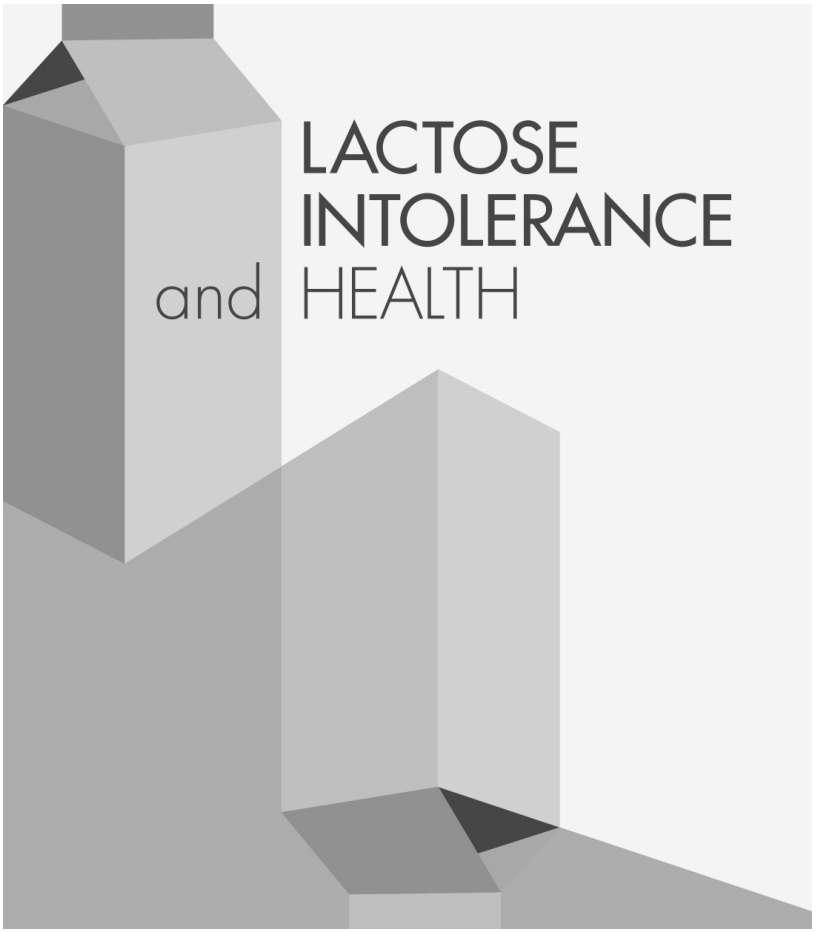
- What is the prevalence of lactose intolerance, and how does this prevalence differ by race, ethnicity, and age?
- What are the health outcomes of dairy exclusion diets?

- What amount of daily lactose intake is tolerable in subjects with diagnosed lactose intolerance?
- What strategies are effective in managing individuals with diagnosed lactose intolerance?
- What are the future research needs for understanding and managing lactose intolerance?

About the Artwork

The conference artwork is a stylized representation of two milk cartons: one, a mirror image of the other. Infants of every racial and ethnic group worldwide produce the enzyme lactase, allowing them to successfully digest the lactose provided by human milk or by infant formulas. However, by the time many of the world's children reach the age of 3–4 years, expression of intestinal lactase ceases. Some affected individuals—referred to as lactase nonpersisters—may experience gastrointestinal symptoms with the consumption of lactose-containing foods such as dairy products.

The image was conceived and created by Bryan Ewsichek of the National Institutes of Health Division of Medical Arts and is in the public domain. No permission is required to use the image. Please credit "Bryan Ewsichek/NIH Medical Arts."



Agenda

Monday, February 22, 2010

8:30 a.m. Opening Remarks
Alan E. Guttmacher, M.D.
Acting Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

8:40 a.m. Charge to the Panel
Jennifer M. Croswell, M.D., M.P.H.
Acting Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health

8:50 a.m. Conference Overview and Panel Activities
Frederick J. Suchy, M.D.
Panel and Conference Chairperson
Professor of Pediatrics
Chief of Pediatric Hepatology
The Jack and Lucy Clark Department of Pediatrics
Mount Sinai School of Medicine of New York University
Mount Sinai Kravis Children's Hospital

Overview of Topic

9:00 a.m. Early Feeding, Human Milk, and the Transition
Josef Neu, M.D.
Professor
Department of Pediatrics
University of Florida College of Medicine

9:20 a.m. Nutritive Value of Milk and Alternative Sources
Nancy F. Krebs, M.D., M.S.
Professor of Pediatrics and Head of Section of Nutrition
Department of Pediatrics
Health Sciences Center
University of Colorado at Denver

9:40 a.m. Cellular and Molecular Biology of Lactase
Eric Sibley, M.D., Ph.D.
Associate Professor
Divison of Pediatrics-Gastroenterology
Stanford University School of Medicine

Monday, February 22, 2010 *(continued)*

10:00 a.m. **Discussion**
Participants with questions or comments for the speakers should proceed to the designated microphones and wait to be recognized by the panel chairperson. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted on the computers in the registration area. Please be aware that all statements made at the microphone or submitted later are in the public domain.

10:30 a.m. What Is Lactose Intolerance and How To Measure It
Richard J. Grand, M.D.
Professor of Pediatrics
Harvard Medical School
Program Director
Clinical and Translational Study Unit
Director
Center for Inflammatory Bowel Disease
Children's Hospital Boston

10:50 a.m. Clinical Presentation and Approach: But What if It Is Not Lactose Intolerance?
Lin Chang, M.D.
Codirector
Center for Neurobiology of Stress
Professor of Medicine
David Geffen School of Medicine
University of California, Los Angeles

11:10 a.m. **Discussion**

I. What Is the Prevalence of Lactose Intolerance, and How Does This Prevalence Differ by Race, Ethnicity, and Age?

11:30 a.m. Population Genetics: Evolutionary History of Lactose Tolerance in Africa
Sarah A. Tishkoff, Ph.D.
Associate Professor
Departments of Genetics and Biology
David and Lyn Silfen University
University of Pennsylvania

11:50 a.m. Lactose Intolerance and Ethnic Prevalence
Wilma J. Wooten, M.D., M.P.H.
President
San Diego Chapter
National Medical Association
San Diego County Health Officer

Monday, February 22, 2010 *(continued)*

I. What Is the Prevalence of Lactose Intolerance, and How Does This Prevalence Differ by Race, Ethnicity, and Age? *(continued)*

12:10 p.m. **Lunch**
Panel Executive Session

1:10 p.m. Aging: Lactose Intolerance and Calcium Absorption in the Elderly
Richard J. Wood, Ph.D.
Associate Professor
Department of Nutrition
School of Public Health & Health Sciences
University of Massachusetts

1:30 p.m. Evidence-based Practice Center (EPC) Presentation I: Methods of Systematic Review and the Prevalence of Lactose Intolerance and Differences by Race, Ethnicity, and Age
Timothy J. Wilt, M.D., M.P.H.
Codirector
Minnesota Evidence-based Practice Center
Core Investigator
Minneapolis Veterans Affairs Center for Chronic Disease Outcomes Research
Professor of Medicine
University of Minnesota School of Medicine

1:50 p.m. **Discussion**

II. What Are the Health Outcomes of Dairy Exclusion Diets?

2:30 p.m. Consequences of Excluding Dairy, Milk Avoiders, Calcium Requirements in Children
Connie M. Weaver, Ph.D.
Distinct Professor and Head
College of Consumer and Family Sciences
Department of Foods and Nutrition
Purdue University

2:50 p.m. Consequences of Excluding Dairy or of Avoiding Milk in Adults
Robert P. Heaney, M.D., FACP, FACN
John A. Creighton University Professor
Osteoporosis Research Center
Professor of Medicine
School of Medicine
Creighton University

Monday, February 22, 2010 *(continued)*

II. What Are the Health Outcomes of Dairy Exclusion Diets? *(continued)*

3:10 p.m. Evidence-based Practice Center Presentation II:
The Bone Health Outcomes of Dairy Exclusion Diets
Timothy J. Wilt, M.D., M.P.H.
Codirector
Minnesota Evidence-based Practice Center
Core Investigator
Minneapolis Veterans Affairs Center for Chronic Disease Outcomes Research
Professor of Medicine
University of Minnesota School of Medicine

3:30 p.m. **Discussion**

III. What Amount of Daily Lactose Intake Is Tolerable in Subjects With Diagnosed Lactose Intolerance?

4:00 p.m. Adaptation to Lactose Intolerance
Andrew Szilagyi, M.D., FACN, FRCPC
Assistant Professor of Medicine
McGill University School of Medicine
Department of Medicine
Division of Gastroenterology
The Sir Mortimer B. Davis Jewish General Hospital

4:20 p.m. Dosing, Symptoms and Tolerable Doses of Lactose
Dennis A. Savaiano, Ph.D.
Professor and Dean
College of Consumer and Family Sciences
Department of Foods and Nutrition
Purdue University

4:40 p.m. Evidence-based Practice Center Presentation III: The Tolerable Amount of Lactose Intake in Subjects With Diagnosed Lactose Intolerance
Michael Levitt, M.D.
Professor
Minneapolis Veterans Affairs Medical Center
Division of Gastroenterology
Department of Medicine
University of Minnesota

5:00 p.m. **Discussion**

5:30 p.m. **Adjournment**

Tuesday, February 23, 2010

IV. What Strategies Are Effective in Managing Individuals With Diagnosed Lactose Intolerance?

8:30 a.m. Prebiotics and Lactose Intolerance
David S. Newburg, Ph.D.
Associate Professor of Pediatrics
Harvard Medical School
Director
Program in Glycobiology, Pediatric Gastroenterology and Nutrition
Massachusetts General Hospital

8:50 a.m. Strategies for Managing Individuals With Diagnosed Lactose Intolerance: Probiotics
Mary Ellen Sanders, Ph.D.
Consultant
Dairy and Food Culture Technologies
Executive Director
International Scientific Association for Probiotics and Prebiotics

9:10 a.m. Treatment Recommendations in Adults With Diagnosed Lactose Intolerance
Jeanette N. Keith, M.D.
Associate Professor
Department of Nutrition Sciences
Department of Medicine
The University of Alabama at Birmingham

9:30 a.m. Treatment Recommendations in Children
Catherine M. Gordon, M.D., M.Sc.
Director
Children's Hospital Bone Health Program
Adolescent/Young Adult Medicine and Endocrinology
Children's Hospital Boston
Associate Professor of Pediatrics
Harvard Medical School

9:50 a.m. **Discussion**

10:30 a.m. Evidence-based Practice Center Presentation IV: Effective Strategies for the Management of Individuals With Diagnosed Lactose Intolerance
Aasma Shaukat, M.D., M.P.H.
Investigator
Minneapolis Veterans Affairs Medical Center
Division of Gastroenterology
Department of Medicine
University of Minnesota

Tuesday, February 23, 2010 *(continued)*

IV. What Strategies Are Effective in Managing Individuals With Diagnosed Lactose Intolerance? *(continued)*

10:50 a.m. Behavioral Factors Related to Lactose Intolerance and Bone Consequences
Susan L. Johnson, Ph.D.
Associate Professor
Department of Pediatrics
Section of Nutrition
University of Colorado Denver
Anschutz Medical Center

11:10 a.m. Psychological Impacts: Strategies Effective in Managing Individuals Diagnosed With Lactose Intolerance
Janet E. Taylor, M.D., M.P.H.
Psychiatrist
Private Practice

11:30 a.m. **Discussion**

Noon **Adjournment**

Wednesday, February 24, 2010

9:00 a.m. **Presentation of the Draft Consensus Statement**
The panel chairperson will read the draft statement to the assembled audience.

9:30 a.m. **Public Discussion**
The panel chairperson will call for questions and comments from the audience on the draft statement, beginning with the introduction and continuing through each subsequent section, in turn. Please confine your comments to the section under discussion. The chairperson will use discretion in proceeding to subsequent sections so that comments on the entire statement may be heard during the time allotted. Participants with comments should proceed to the designated microphones and wait to be recognized by the panel chairperson. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted on the computers in the registration area. For participants viewing the remote Webcast, comments may be submitted online at ***consensus.nih.gov/comments.htm.*** *Comments will not be accepted after 11:30 a.m. Please be aware that all statements made at the microphone or submitted later are in the public domain.*

11:00 a.m. **Adjournment**

Panel Meets in Executive Session
The public portion of the conference ends at 11:00 a.m. The panel meets in its last executive session to review public comments on the draft statement.

Wednesday, February 24, 2010 *(continued)*

2:00 p.m. **Press Telebriefing**

The panel will provide a summary of its findings to the press and will answer questions from reporters via telebriefing. Only members of the press are permitted to ask questions of the panel during this time. Interested conference participants who are not members of the press may call in (from a remote location) to listen to the live telebriefing. Please go to ***consensus.nih.gov*** *for instructions on joining the call.*

The panel's draft statement will be posted to ***consensus.nih.gov*** *as soon as possible after the close of proceedings, and the final statement will be posted 4 to 6 weeks later.*

Panel

Panel Chairperson: **Frederick J. Suchy, M.D.**
Panel and Conference Chairperson
Professor of Pediatrics
Chief of Pediatric Hepatology
Jack and Lucy Clark Department of Pediatrics
Mount Sinai School of Medicine of New York University
Mount Sinai Kravis Children's Hospital
New York, New York

Patsy M. Brannon, Ph.D., R.D.
Professor
Division of Nutritional Sciences
Cornell University
Ithaca, New York

Thomas O. Carpenter, M.D.
Director
Yale Center for X-linked Hypophosphatemia
Professor
Department of Pediatrics
Yale School of Medicine
New Haven, Connecticut

Jose R. Fernandez, Ph.D.
Associate Professor
Department of Nutrition Sciences
Division of Physiology and Metabolism
The University of Alabama at Birmingham
Birmingham, Alabama

Vicente Gilsanz, M.D., Ph.D.
Director
Radiology Department
Children's Imaging Research Program
Children's Hospital Los Angeles
Los Angeles, California

Jeffrey B. Gould, M.D., M.P.H.
Robert L. Hess Professor in
Pediatrics-Neonatology
Stanford University
Stanford, California

Karen Hall, M.D., Ph.D.
Research Scientist
Geriatric Research, Education, and
Clinical Center
Veterans Affairs Ann Arbor Healthcare System
Clinical Associate Professor
Department of Internal Medicine
University of Michigan Medical School
Ann Arbor, Michigan

Siu L. Hui, Ph.D.
Professor
Department of Medicine
Division of Biostatistics
Senior Biostatistician
Center for Aging Research
Indiana University School of Medicine
Senior Scientist
Regenstrief Institute
Indianapolis, Indiana

Joanne Lupton, Ph.D.
Distinguished Professor
William W. Allen Endowed Chair in
Human Nutrition
Department of Nutrition and Food Science
Texas A&M University
College Station, Texas

Julie Mennella, Ph.D.
Member
Monell Chemical Senses Center
Philadelphia, Pennsylvania

Natalie J. Miller
Graduate Student
Combined Veterinary Medicine (VMD) and Ph.D. Program
School of Veterinary Medicine
University of Pennsylvania
Co-founder
Cares4Pets
Philadelphia, Pennsylvania

Stavroula Kalis Osganian, M.D., Sc.D., M.P.H.
Assistant Professor
Harvard University
Director
Clinical Research Program
Children's Hospital Boston
Boston, Massachusetts

Deborah E. Sellmeyer, M.D.
Associate Professor of Medicine
Director
Metabolic Bone Center
Johns Hopkins Bayview Medical Center
Baltimore, Maryland

Marshall A. Wolf, M.D.
Professor of Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Speakers

Lin Chang, M.D.
Codirector
Center for Neurobiology of Stress
Professor of Medicine
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, California

Catherine M. Gordon, M.D., M.Sc.
Director
Children's Hospital Bone Health Program
Adolescent/Young Adult Medicine
and Endocrinology
Children's Hospital Boston
Associate Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Richard J. Grand, M.D.
Professor of Pediatrics
Harvard Medical School
Program Director
Clinical and Translational Study Unit
Director
Center for Inflammatory Bowel Disease
Children's Hospital Boston
Boston, Massachusetts

Alan E. Guttmacher, M.D.
Acting Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Robert P. Heaney, M.D., FACP, FACN
John A. Creighton University Professor
Osteoporosis Research Center
Professor of Medicine
School of Medicine
Creighton University
Omaha, Nebraska

Susan L. Johnson, Ph.D.
Associate Professor
Department of Pediatrics
Section of Nutrition
University of Colorado Denver
Anschutz Medical Center
Denver, Colorado

Jeanette N. Keith, M.D.
Associate Professor
Department of Nutrition Sciences
Department of Medicine
The University of Alabama at Birmingham
Birmingham, Alabama

Nancy F. Krebs, M.D., M.S.
Professor of Pediatrics and Head of
Section of Nutrition
Department of Pediatrics
Health Sciences Center
University of Colorado at Denver
Aurora, Colorado

Michael Levitt, M.D.
Professor
Minneapolis Veterans Affairs
Medical Center
Division of Gastroenterology
Department of Medicine
University of Minnesota
Minneapolis, Minnesota

Josef Neu, M.D.
Professor
Department of Pediatrics
University of Florida College of Medicine
Gainesville, Florida

David S. Newburg, Ph.D.
Associate Professor of Pediatrics
Harvard Medical School
Director
Program in Glycobiology, Pediatric
Gastroenterology and Nutrition
Massachusetts General Hospital
Charlestown, Massachusetts

Mary Ellen Sanders, Ph.D.
Consultant
Dairy and Food Culture Technologies
Executive Director
International Scientific Association for Probiotics and Prebiotics
Centennial, Colorado

Dennis A. Savaiano, Ph.D.
Professor and Dean
College of Consumer and Family Sciences
Department of Foods and Nutrition
Purdue University
West Lafayette, Indiana

Aasma Shaukat, M.D., M.P.H.
Investigator
Minneapolis Veterans Affairs Medical Center
Division of Gastroenterology
Department of Medicine
University of Minnesota
Minneapolis, Minnesota

Eric Sibley, M.D., Ph.D.
Associate Professor
Divison of Pediatrics-Gastroenterology
Stanford University School of Medicine
Stanford, California

Andrew Szilagyi, M.D., FACN, FRCPC
Assistant Professor of Medicine
McGill University School of Medicine
Department of Medicine
Division of Gastroenterology
The Sir Mortimer B. Davis Jewish General Hospital
Montreal, Quebec
Canada

Janet E. Taylor, M.D., M.P.H.
Psychiatrist
Private Practice
New York, New York

Sarah A. Tishkoff, Ph.D.
Associate Professor
Departments of Genetics and Biology
David and Lyn Silfen University
University of Pennsylvania
Philadelphia, Pennsylvania

Connie M. Weaver, Ph.D.
Distinct Professor and Head
College of Consumer and Family Sciences
Department of Foods and Nutrition
Purdue University
West Lafayette, Indiana

Timothy J. Wilt, M.D., M.P.H.
Codirector
Minnesota Evidence-based Practice Center
Core Investigator
Minneapolis Veterans Affairs Center for Chronic Disease Outcomes Research
Professor of Medicine
University of Minnesota School of Medicine
Minneapolis, Minnesota

Richard J. Wood, Ph.D.
Associate Professor
Department of Nutrition
School of Public Health & Health Sciences
University of Massachusetts
Amherst, Massachusetts

Wilma J. Wooten, M.D., M.P.H.
President
San Diego Chapter
National Medical Association
San Diego County Health Officer
San Diego, California

Planning Committee

Planning Committee Chairperson:

Gilman D. Grave, M.D.
Chief
Endocrinology, Nutrition, and Growth Branch
Acting Director
Center for Research for Mothers and Children
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Lisa Ahramjian, M.S.
Communications Specialist
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Stephanie Chang, M.D., M.P.H.
Medical Officer
Evidence-based Practice Centers Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality
Rockville, Maryland

Richard J. Grand, M.D.
Professor of Pediatrics
Harvard Medical School
Program Director
Clinical and Translational Study Unit
Director
Center for Inflammatory Bowel Disease
Children's Hospital Boston
Boston, Massachusetts

Judy Hannah, Ph.D.
Health Science Administrator
Geriatrics and Clinical Gerontology Program
National Institute on Aging
National Institutes of Health
Bethesda, Maryland

Van S. Hubbard, M.D., Ph.D.
Rear Admiral, U.S. Public Health Service
Director
Division of Nutrition Research Coordination
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Wendy L. Johnson-Askew, Ph.D., M.P.H.
Public Health Nutrition and Health Policy Advisor
Division of Nutrition and Research Coordination
National Institutes of Health
Bethesda, Maryland

Barnett S. Kramer, M.D., M.P.H.
Associate Director for Disease Prevention
Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Kelli K. Marciel, M.A.
Communications Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Planning Committee members provided their input at a meeting held October 7–9, 2008. The information provided here was accurate at the time of that meeting.

Lata S. Nerurkar, Ph.D.
Senior Advisor for the Consensus Development Program
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Josef Neu, M.D.
Professor of Pediatrics
Director of Neonatology Fellowship Training Program
Department of Pediatrics
Division of Neonatology
University of Florida College of Medicine
Gainesville, Florida

Mary Frances Picciano, Ph.D.
Senior Nutrition Research Scientist
Office of Dietary Supplements
National Institutes of Health
Bethesda, Maryland

Winston Price, M.D., FAAP
Past President
National Medical Association
Executive Clinical Dean
American University of Antigua College of Medicine
Alpharetta, Georgia

Susan C. Rossi, Ph.D., M.P.H.
Deputy Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Mona Jaffe Rowe, M.C.P.
Associate Director
Office of Science Policy, Analysis, and Communications
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Dennis A. Savaiano, Ph.D.
Professor and Dean
Department of Foods and Nutrition
College of Consumer and Family Sciences
Purdue University
West Lafayette, Indiana

Eric Sibley, M.D., Ph.D.
Associate Professor
Pediatrics–Gastroenterology
Stanford School of Medicine
Stanford, California

Frederick J. Suchy, M.D.
Panel and Conference Chairperson
Herbert H. Lehman Professor and Chairperson
The Jack and Lucy Clark Department of Pediatrics
Mount Sinai School of Medicine
New York University
Pediatrician-in-Chief
Mount Sinai Hospital
New York, New York

Connie M. Weaver, Ph.D.
Distinct Professor and Head
Department of Foods and Nutrition
College of Consumer and Family Sciences
Purdue University
West Lafayette, Indiana

Karen K. Winer, M.D.
Medical Officer
Endocrinology, Nutrition, and Growth Branch
Center for Research for Mothers and Children
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Planning Committee members provided their input at a meeting held October 7–9, 2008. The information provided here was accurate at the time of that meeting.

Educational Planners

Lisa Ahramjian, M.S.
Communications Specialist
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Jennifer M. Croswell, M.D., M.P.H.
Acting Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Candace Kirksey, M.A., M.P.H., CPH, CHES
Continuing Education Consultant; CECH Reviewer
Training Services Division
Office of Workforce and Career Development
Centers for Disease Control and Prevention
Atlanta, Georgia

Susan Lukacs, D.O., M.S.P.H.
Medical Officer
Office of Analysis and Epidemiology
Infant, Child, and Women's Health Statistics Branch
National Center for Healthcare Statistics
Centers for Disease Control and Prevention
Hyattsville, Maryland

Kelli K. Marciel, M.A.
Communications Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Trish Reynolds, R.N., M.S.
Writer-Editor/Media Liaison
Office of Communications and Public Liaison
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
Bethesda, Maryland

Barbara Riley, M.S.C.M., B.S.N., R.N., LNC
Nurse Planner; Continuing Education Consultant
Training Services Division
Office of Workforce and Career Development
Centers for Disease Control and Prevention
Atlanta, Georgia

Abstracts

The abstracts are designed to inform the panel and conference participants, as well as to serve as a reference document for any other interested parties. We would like to thank the speakers for preparing and presenting their findings on this important topic.

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Please note that where multiple authors are listed on an abstract, the underline denotes the presenting author.

Early Feeding, Human Milk, and the Transition

Josef Neu, M.D.

Lactose, a disaccharide that comprises the monosaccharide glucose and galactose, is the primary carbohydrate found exclusively in mammalian milk. Lactase, the enzyme that splits the bond linking the glucose and galactose moieties of lactose, is localized primarily to the tips of the small intestinal villi. In premature babies, infants, and young children, congenital lactase deficiency is rare, but other forms of aberrations in the lactase enzyme occur and affect tolerance to the disaccharide. Studies from the 1970s demonstrated relatively low activities of lactase from intestine from fetuses or abortuses when compared to the other disaccharidases.[1] This so-called "developmental lactase deficiency" has been used as a premise to add non-lactose-containing carbohydrates to formulas designed for premature infants. Using stable isotope technology and breath hydrogen excretion in premature babies, one study validated a "deficiency" of lactose absorption in premature infants.[2] It showed that lactose does reach the colon, and that fermentation in the colon likely takes place, with beneficial effects. It was concluded that despite less than 100% efficiency of lactose digestion, replacement of lactose with other sugars may not be necessary for routine feeding of preterm infants. In another set of studies, lactase activity increased significantly over time.[3] Infants who were started on relatively early enteral feedings had greater lactase activity at 10 days of age (by 100%) and 28 days of age (by 60%) than the group started on delayed feedings. At 10 days of age, lactase activity was greater in human milk-fed versus formula-fed infants. It was concluded that early feeding increases intestinal lactase activity in preterm infants.

In the past few years, with improved understanding of intestinal microflora and host interactions, the role of lactose as a potential prebiotic in lactase-deficient and nonpersistent subjects is being considered.[4] Bacterial metabolism of colonic lactose lowers the fecal pH, which has a beneficial effect, favoring certain organisms in lieu of potential pathogens.

Many perceptions of what constitutes lactose intolerance in infants and how to treat these entities have been debated. Lactose-free and reduced lactose formulas are widely available for use in infants. However, the majority of lactase deficiencies in infants are transient and due to diarrheal illness. In most cases of acute gastroenteritis, enough lactose digestion and absorption are preserved so that low-lactose and lactose-free formulas have no clinical advantages compared with standard lactose-containing formulas except in severely undernourished children, in whom lactose-containing formulas may worsen the diarrhea and lactose-free formula may be advantageous.[5] The American Academy of Pediatrics has reviewed breast feeding in cases of diarrhea and has concluded that breast-fed infants should be continued on human milk in all cases.[6] Although lactose-free cow milk protein-based formulae are readily available and popular, the data to support that they have a positive impact on several outcomes including colic, growth, and development are lacking.[7]

References

1. Antonowicz I, Lebenthal E. Developmental pattern of small intestinal enterokinase and disaccharidase activities in the human fetus. *Gastroenterology*. 1977;72:1299–1303.

2. Kien CL, McClead RE, Cordero L Jr. *In vivo* lactose digestion in preterm infants. *Am J Clin Nutr.* 1996;64(5):700–705.

3. Shulman RJ, Schanler RJ, Lau C, Heitkemper M, Ou CN, Smith EO. Early feeding, feeding tolerance, and lactase activity in preterm infants. *J Pediatr.* 1998;133(5):645–649.

4. Szilagyi A. Redefining lactose as a conditional prebiotic. *Can J Gastroenterol.* 2004;18:163–167.

5. Kukuruzovic RH, Brewster DR. Milk formulas in acute gastroenteritis and malnutrition: a randomized trial. *J Paediatr Child Health.* 2002;38:571–577.

6. Heyman MB, Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. *Pediatrics.* 2006;118(3):1279–1286.

7. Heubi J, Karasov R, Reisinger K, Blatter M, et al. Randomized multicenter trial documenting the efficacy and safety of a lactose-free and a lactose-containing formula for term infants. *J Am Diet Assoc.* 2000;100(2):212–217.

Nutritive Value of Milk and Alternative Sources

Nancy F. Krebs, M.D., M.S.

Milk and dairy products provide an important dietary source of several nutrients, including especially calcium. Due to broad-scale fortification, milk also is a major source of vitamin D in the U.S. diet. Relevant to the topic of the Consensus Conference, lactose intolerance, this paper will address the following areas: (1) the nutritional composition of selected milk and dairy products; (2) alternative food sources of nutrients found in milk and dairy products; and (3) nutrient contributions of dairy products to the U.S. diet.

Nutritional Composition of Dairy Products

As indicated in Table 1, a serving of low-fat milk provides approximately 300 mg calcium, or about 23% of the Adequate Intake (AI) for adolescents and 30% of the AI for adults.[1] The current Dietary Guidelines for Americans recommend that persons over 9 years of age consume three servings per day of dairy foods, which will provide all or a high percentage of the recommended calcium intake for all age groups.[2]

Table 1. Energy and Selected Nutrients in a Single Serving of Dairy Products

	Low-Fat (1%) Milk (240 g)	Yogurt, Low Fat, Plain (240 g)	Cheddar Cheese (45 g)
Energy (kcal)	101	154	181
Protein (g)	8.1	12.9	11.2
Fat (g)	2.3	3.8	14.9
Lactose (g)	12.5	8.4	0.10
Calcium (mg)	300	448	324
Vitamin D (IU)	115	2	10

Source: U.S. Department of Agriculture's Nutrient Database
Web site: nal.usda.gov/fnic/foodcomp/search

Closely related to calcium absorption and utilization, vitamin D is another nutrient provided by liquid milk products through broad-scale fortification. As shown in Table 1, one serving of vitamin D-fortified milk provides approximately half of the current AI for vitamin D.[1] With the recent recognition that many Americans of all ages, including those with a variety of disease conditions, have vitamin D insufficiency, some have recommended intakes beyond the current AI for this hormone-vitamin.[3] If the vitamin D AI is increased, fortified dairy products are likely to continue to make an important contribution. Other dairy products are not routinely fortified with vitamin D. For example, yogurt is not routinely fortified and fortified yogurt products range widely, providing 40–120 IU of vitamin D per serving.

Lactose, also known as “milk sugar,” varies widely in dairy products, as also may be seen in Table 1. Although yogurt contains lactose, this food may be better tolerated than milk by individuals with lactose intolerance because the bacteria in the yogurt partially digest some of the lactose into its constituent monosaccharides, glucose and galactose. Other essential nutrients that dairy products contribute to the diet include protein, B vitamins (especially riboflavin), vitamin A, phosphorus, magnesium, potassium, and zinc. Full-fat dairy products contain a high percentage of saturated fat. For example, for cheddar cheese, 74% of the calories are from fat and 64% of the fat is saturated fat. This illustrates the basis for emphasis on low-fat dairy products in dietary recommendations,[2,4] but the contribution of calcium from cheese (as a percentage) from the U.S. food supply has steadily increased over the past 40 years.[5]

Milk Alternatives in the Diet

For a wide range of reasons, including lactose intolerance, many people seek alternatives to milk and dairy products. Commercially available products have proliferated to meet this demand. The nutrient profiles of two popular examples, soy and rice drinks, are shown in Table 2. These products are often fortified with calcium and vitamin D, although the specific amounts vary with different products. When consumed by adults in the context of a mixed diet, these products can provide roughly equivalent amounts of these nutrients. Rice milk in particular, however, is very low in protein, and the quality of the protein is not high. Thus, for young children, who have relatively high protein needs and often consume milk as a major caloric contributor in their diet, rice drink provides a weak choice in comparison to either cow milk or soy drink.

Table 2. Fluid Milk Alternatives as Sources of Calcium

	Commercial Soy Milk (fortified), 240 g	**Commercial Rice Drink (fortified), 240 g**
Energy (kcal)	98.4	113
Protein (g)	6.9	0.67
Calcium (mg)	295*****	283
Vitamin D (IU)	118	101
Magnesium (mg)	38.4	26

***** Unfortified soy milk contains approximately 10 mg/240 ml.

Source: U.S. Department of Agriculture’s Nutrient Database
Web site: nal.usda.gov/fnic/foodcomp/search

Other alternative sources of calcium in the diet include canned salmon with the bones, greens (kale, turnip greens), and tofu processed with a calcium salt. Each of these examples provides approximately 100–200 mg of calcium per serving. Other calcium-fortified products, such as orange juice and breakfast cereals, can make substantial contributions to calcium intake.

Nutrient Contributions of Dairy Products in the U.S. Diet

According to data from the U.S. Department of Agriculture, dairy products provide approximately 70% of calcium in the U.S. food supply.[5] This percentage has gradually and modestly declined over the past 45 years, possibly reflecting the availability of more calcium- fortified products. Data from the National Health and Nutrition Examination Survey (NHANES), 2005–2006, indicate that calcium and other key nutrients from milk overall are close to recommended amounts, but they may fall short for some groups.[6] Calcium intakes do not generally exceed the AI but approach it for many age groups, especially for males. The exception appears to be adolescents, who have the highest AI (1,300 mg).[1] All groups' mean intakes were below the AI, with the overall average intake being 79% of the AI. Mean intakes were lowest in the two groups with highest rates of lactase deficiency, African Americans and Hispanics,[7] at 65% and 76% of the AI, respectively.[5]

In summary, dairy products, make a significant contribution to the calcium intake of the U.S. population overall. Dairy products that are fortified with vitamin D also provide a good dietary source for this nutrient. Groups with lactase deficiency tend to have lower dietary calcium intakes. Several alternative food sources, including fortified milk substitutes and other foods, provide comparable calcium intake per serving, but these will differ in the overall nutrient profile.

References

1. Institute of Medicine. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press; 2006.

2. U.S. Department of Health and Human Services and U.S. Department of Agriculture. *Dietary Guidelines for Americans, 2005*. 6th ed. Washington, DC: U.S. Government Printing Office; 2005.

3. Holick MF. Vitamin D deficiency. *New Engl J Med.* 2007;357(3):266–281.

4. Obarzanek E, Sacks FM, Vollmer WM, et al. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr.* 2001;74(1):80–89.

5. U.S. Department of Agriculture (USDA), Center for Nutrition Policy and Promotion. Home Economics Research Report, Number 58. Nutrient Content of the U.S. Food Supply, 2005. Washington, DC: USDA; 2008.

6. U.S. Department of Agriculture (USDA), Agricultural Research Service. Nutrient Intakes From Food: Mean Amounts Consumed per Individual, One Day, 2005–2006. Washington, DC: USDA; 2008.

7. Heyman MB. Lactose intolerance in infants, children, and adolescents. *Pediatrics.* 2006;118(3):1279–1286.

Cellular and Molecular Biology of Lactase

Eric Sibley, M.D., Ph.D.

Lactase Protein Structure and Function

The digestive enzyme lactase-phlorizin hydrolase, lactase, catalyzes the digestive hydrolysis of lactose, the predominant carbohydrate in milk. The lactose disaccharide consists of a glucose and a galactose molecule linked by a beta (1-4) glycosidic bond. Lactase enzymatic activity cleaves the beta (1-4) glycosidic bond in lactose molecules, thereby releasing the constituent monomers glucose and galactose for absorption by intestinal cells. Lactase is a brush border membrane protein produced by enterocytes, the absorptive epithelial cells of the small intestine. The human lactase protein is initially synthesized as a 210–220 kDa immature peptide.[1] The precursor peptide is then processed by glycosylation and cleavage, and finally inserted into the brush border membrane as a mature 160 kDa subunit homodimer. Lactase activity is essential for the survival of most newborn mammals, because it is the only intestinal enzyme capable of hydrolyzing lactose. Undigested lactose molecules cannot be absorbed intact by intestinal cells. In the absence of sufficient lactase hydrolysis, undigested lactose is fermented by bacteria in the distal ileum and colon to yield short-chain fatty acids, hydrogen, carbon dioxide, and methane. The fermentative products and undigested lactose molecules can result in symptoms of flatulence, diarrhea, and abdominal pain characteristic of lactose intolerance.

Lactase Gene Expression and Spatiotemporal Regulation

The human lactase gene, *Lct*, is located on the long arm of chromosome 2 at loci 2q21 and consists of 17 exons spanning approximately 55 kb.[2] The human lactase cDNA encodes a single polypeptide chain containing 1,972 amino acids. Lactase gene expression is cell specific with expression only in enterocytes, the absorptive epithelial cells of the small intestine. Transcriptional regulation of the lactase gene has been characterized in intestinal cell culture. The lactase promoter is activated in cell culture by cooperative interaction between intestine-specific transcription factors including Cdx-2,[3–7] GATA family members,[8–12] and HNF-1.[4,10,12]

Lactase gene expression is spatially restricted along both vertical and longitudinal axes in the small intestine. Along the vertical axis, immature enterocytes derived from stem cells in the crypts differentiate and begin to express the lactase gene as they migrate from the crypt to the villus tip. Along the longitudinal axis, lactase gene is expressed prenatally in the colon and small intestine. Postnatally, however, the mature spatial gradient is established with maximal lactase gene expression in the distal duodenum and jejunum, and significantly lower expression in the more proximal and distal segments of the intestine.[13]

Lactase gene expression also is temporally regulated during gut development and maturation. Lactase enzyme activity is maximal in the small intestine of pre-weaned mammals and subsequently declines during maturation. In most mammalian species, the maturational decline in lactase expression occurs at the time of weaning.[14] The age of onset of the maturational decline of lactase expression in humans is variable, ranging from the toddler years to young adulthood.[15,16] Postdecline, the level of lactase activity is 5–10% of childhood levels in most populations worldwide.[17] The temporal decline in lactase activity is due largely to a decline in lactase mRNA abundance in small intestinal enterocytes. Studies in humans and other mammals indicate that regulation of gene transcription is the primary mechanism mediating changes in lactase expression during gut development and maturation.[18,19] In support of a transcriptional regulatory mechanism, fragments of the lactase gene promoter are capable of mediating a post-weaning decline in reporter gene expression in transgenic mice.[20,21]

Persistence of Human Lactase Gene Expression

The maturational decline in lactase activity, adult-onset hypolactasia or lactase nonpersistence, renders most of the world's adult human population intolerant of excessive consumption of milk and other dairy products. In some adults, however, high levels of lactase activity persist in adulthood. This hereditary persistence of lactase is common primarily in people of northern European descent and is attributed to inheritance of an autosomal-dominant mutation that prevents the normal maturational decline in lactase expression.[15,16,22] Lactase persistence also is prevalent in select African ethnic pastoral populations.[16] Based on analysis of allelic human lactase mRNA transcript levels, it was initially determined that the hereditary lactase persistence/nonpersistence phenotype is controlled by a cis-acting DNA element on chromosome 2 in the general region of the lactase gene.[22] Subsequently, linkage disequilibrium and haplotype analysis in humans resulted in identification of several genetic single-nucleotide polymorphism (SNP) variants located ~14 kb upstream of the human lactase gene that are associated with lactase persistence/nonpersistence phenotypes.[23–26] The SNPs (G/C-14010, T/G-13915, C/T-13910, and C/G-13907) are located 5' to the lactase gene within intron 13 of the adjacent MCM6 gene.[27] The European C/T-13910 variant is a SNP, C to T. Complete correlation was reported between the lactase nonpersistence phenotype and homozygousity for the C variant. Similarly, complete correlation was reported between the lactase persistence phenotype and the presence of the T-variant allele.

There is interest in determining whether the DNA in the region of the -14 kb variants functions to regulate human lactase gene transcription. Transfection experiments have shown that the DNA region of the C/T-13910 lactase persistence/nonpersistence variant can interact with the Oct-1 transcription factor and function as a cis element capable of enhancing differential transcriptional activation of the lactase promoter in cell culture.[28–30] By contrast, however, the G-13915 polymorphism associated with lactase persistence has been reported to abolish, rather than enhance, Oct-1 binding.[25] Thus, while several genetic associations have been identified, specific molecular mechanisms for the persistence of lactase gene expression have yet to be fully defined.

References

1. Naim HY, Sterchi EE, Lentze MJ. Biosynthesis and maturation of lactase-phlorizin hydrolase in the human small intestinal epithelial cells. *Biochem J.* 1987;241:427-434.

2. Boll W, Wagner P, Mantei N. Structure of the chromosomal gene and cDNAs coding for lactase-phlorizin hydrolase in humans with adult-type hypolactasia or persistence of lactase. *Am J Hum Genet.* 1991;48:889–902.

3. Fang R, Santiago NA, Olds LC, Sibley E. The homeodomain protein Cdx2 regulates lactase gene promoter activity during enterocyte differentiation. *Gastroenterology.* 2000;118:115–127.

4. Mitchelmore C, Troelsen JT, Spodsberg N, Sjostrom H, Noren O. Interaction between the homeodomain proteins Cdx2 and HNF1 alpha mediates expression of the lactase-phlorizin hydrolase gene. *Biochem J.* 2000;346(Pt 2):529–535.

5. van Wering HM, Moyer L, Grand RJ, Krasinski SD. Novel interaction at the Cdx-2 binding sites of the lactase-phlorizin hydrolase promoter. *Biochem Biophys Res Commun.* 2002;299:587–593.

6. Troelsen JT, Mitchelmore C, Spodsberg N, Jensen AM, Noren O, Sjostrom H. Regulation of lactase-phlorizin hydrolase gene expression by the caudal-related homoeodomain protein Cdx-2. *Biochem J.* 1997;322(Pt 3):833–838.

7. Troelsen JT, Olsen J, Noren O, Sjostrom H. A novel intestinal trans-factor (NF-LPH1) interacts with the lactase-phlorizin hydrolase promoter and co-varies with the enzymatic activity. *J Biol Chem.* 1992;267:20407–20411.

8. Fang R, Olds LC, Santiago NA, Sibley E. GATA family transcription factors activate lactase gene promoter in intestinal Caco-2 cells. *Am J Physiol Gastrointest Liver Physiol.* 2001;280:G58–G67.

9. Fitzgerald K, Bazar L, Avigan MI. GATA-6 stimulates a cell line-specific activation element in the human lactase promoter. *Am J Physiol.* 1998;274(Pt 1):G314–G324.

10. Krasinski SD, Van Wering HM, Tannemaat MR, Grand RJ. Differential activation of intestinal gene promoters: functional interactions between GATA-5 and HNF-1 alpha. *Am J Physiol Gastrointest Liver Physiol.* 2001;281:G69–G84.

11. van Wering HM, Bosse T, Musters A, et al. Complex regulation of the lactase-phlorizin hydrolase promoter by GATA-4. *Am J Physiol Gastrointest Liver Physiol.* 2004;287:G899–G909.

12. van Wering HM, Huibregtse IL, van der Zwan SM, et al. Physical interaction between GATA-5 and hepatocyte nuclear factor-1 alpha results in synergistic activation of the human lactase-phlorizin hydrolase promoter. *J Biol Chem.* 2002;277:27659–27667.

13. Rings EH, Krasinski SD, van Beers EH, et al. Restriction of lactase gene expression along the proximal-to-distal axis of rat small intestine occurs during postnatal development. *Gastroenterology.* 1994;106:1223–1232.

14. Henning S, Rubin DC, Shulman RJ. Ontogeny of the intestinal mucosa. In: Johnson LR, ed. *Physiology of the Gastrointestinal Tract*. New York: Raven; 1992:571–610.

15. Flatz G. Genetics of lactose digestion in humans. *Adv Hum Genet.* 1987;16:1–77.

16. Sahi T. Genetics and epidemiology of adult-type hypolactasia. *Scand J Gastroenterol Suppl.* 1994;202:7–20.

17. Buller HA, Grand RJ. Lactose intolerance. *Annu Rev Med.* 1990;41:141–148.

18. Krasinski SD, Estrada G, Yeh KY, et al. Transcriptional regulation of intestinal hydrolase biosynthesis during postnatal development in rats. *Am J Physiol.* 1994;267(Pt 1):G584–G594.

19. Wang Y, Harvey CB, Hollox EJ, et al. The genetically programmed down-regulation of lactase in children. *Gastroenterology.* 1998;114:1230–1236.

20. Lee SY, Wang Z, Lin CK, et al. Regulation of intestine-specific spatiotemporal expression by the rat lactase promoter. *J Biol Chem.* 2002;277:13099–13105.

21. Troelsen JT, Mehlum A, Olsen J, et al. 1 kb of the lactase-phlorizin hydrolase promoter directs post-weaning decline and small intestinal-specific expression in transgenic mice. *FEBS Lett.* 1994;342:291–296.

22. Wang Y, Harvey CB, Pratt WS, et al. The lactase persistence/non-persistence polymorphism is controlled by a cis-acting element. *Hum Mol Genet.* 1995;4:657–662.

23. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Jarvela I. Identification of a variant associated with adult-type hypolactasia. *Nat Genet.* 2002;30:233–237.

24. Imtiaz F, Savilahti E, Sarnesto A, et al. The T/G 13915 variant upstream of the lactase gene (LCT) is the founder allele of lactase persistence in an urban Saudi population. *J Med Genet.* 2007;44:e89.

25. Ingram CJ, Elamin MF, Mulcare CA, et al. A novel polymorphism associated with lactose tolerance in Africa: multiple causes for lactase persistence? *Hum Genet.* 2007;120:779–788.

26. Tishkoff SA, Reed FA, Ranciaro A, et al. Convergent adaptation of human lactase persistence in Africa and Europe. *Nat Genet.* 2007;39:31-40.

27. Harvey CB, Wang Y, Darmoul D, Phillips A, Mantei N, Swallow DM. Characterisation of a human homologue of a yeast cell division cycle gene, MCM6, located adjacent to the 5' end of the lactase gene on chromosome 2q21. *FEBS Lett.* 1996;398:135–140.

28. Olds LC, Sibley E. Lactase persistence DNA variant enhances lactase promoter activity *in vitro*: functional role as a cis regulatory element. *Hum Mol Genet.* 2003;12:2333–2340.

29. Troelsen JT, Olsen J, Moller J, Sjostrom H. An upstream polymorphism associated with lactase persistence has increased enhancer activity. *Gastroenterology.* 2003;125:1686–1694.

30. Lewinsky RH, Jensen TG, Moller J, Stensballe A, Olsen J, Troelsen JT. T-13910 DNA variant associated with lactase persistence interacts with Oct-1 and stimulates lactase promoter activity *in vitro*. *Hum Mol Genet.* 2005;14:3945–3953.

What Is Lactose Intolerance and How To Measure It

Richard J. Grand, M.D.

Lactose intolerance is the term commonly used to describe symptoms experienced by people after drinking milk or ingesting milk products. These symptoms may include abdominal pain or cramps, abdominal distension, nausea, flatulence, and diarrhea. Symptoms may be mild, moderate, or severe, depending on a number of factors including the following:

- Quantity of ingested milk
- Fat content of the milk
- Rate of stomach emptying
- Rapidity with which the milk is transported through the intestine
- Individual sensitivity to abdominal discomfort
- Capacity of bacteria in the colon to digest lactose not absorbed in the small intestine
- Psychological impact of anticipation of symptoms in those who have had previous symptoms during milk intake.

Lactose intolerance occurs when there is an inadequate amount of the small intestinal enzyme, lactase, which is required for the digestion and absorption of dietary lactose.[1] As very little intact lactose is absorbed, lactose must be split by lactase into its constituent sugars—glucose and galactose—to facilitate absorption.[2] When lactase levels are too low to provide for appropriate digestion, lactose is not absorbed (this is known as *lactose malabsorption*), and the lactose in the small intestine and colon produces the symptoms described above.

Lactose malabsorption is established by one of the following:

(1) A test of lactose absorption (lactose absorption test)

(2) A test of lactose nonabsorption (lactose breath hydrogen test)

(3) Measurement of intestinal lactase performed using biopsy samples of the intestinal lining obtained from the third portion of the duodenum during upper gastrointestinal endoscopy.

The quantity of lactase present in the intestine is determined by genetic factors.[3] In virtually all humans, lactase activity is abundant in infancy and early childhood. Thereafter, in the majority of the world's population, lactase activity falls between the ages of 3 and 7 to a level that is approximately 10% of the childhood value and it

remains low through adulthood.[4] This is known as *lactase nonpersistence*. In the majority of people of Northern European ancestry, however, lactase levels remain in the childhood range throughout life. This is known as *lactase persistence*. Although in the United States, population-based studies of lactase activity have not been performed, available data reveal that lactase nonpersistence is likely to be prevalent among African American, Asian, Hispanic, and Native American adults (see Table 1).[5]

Table 1. Frequency of Lactose Intolerance in Adults in Various Populations

Location	% Lactose Intolerant Adults*
Asians, US	90–100
Ibo, Yoruba, Africa	90
Inuits, Greenland	85
Southern Italians	71
African Americans	65
Caucasians, US	21
British, UK	6
Danes	3

*Lactose nonpersistence is the preponderant phenotype. Data from Scrimshaw and Murray, 1988.[5]

Low intestinal lactase activity also may be found in premature infants up to 32 weeks' gestation and in a very rare disorder known as *congenital lactase deficiency.*[1] This condition has been reported in the United Kingdom and in Finland, but documented cases have not been described in the United States.

A genetic test has been established that has been used as a surrogate marker for lactase nonpersistence or persistence.[6,7] Polymorphisms in the lactase gene at -13,910 bases upstream of the transcriptional start site are most commonly assessed. People in or from Northern Europe (including Caucasians in the United States) with a CC genotype are likely to be lactase nonpersistent, while those with a TT genotype are likely to be lactase persistent. People with a TC genotype may be nonpersistent or persistent. An exception to these patterns occurs in many population groups in Africa who drink milk (and therefore are likely to be lactase persistent) and who have a CC genotype.[8] Thus, in the clinical setting, the genetic background of an individual with lactose-related symptoms must be considered when using genetic markers for diagnosis, and the results must be correlated with a functional test (either the lactose breath hydrogen or the lactose tolerance test).[9]

An alternative approach to the diagnosis of lactose intolerance is the short-term elimination of lactose-containing foods from the diet. As lactose restriction will lead to rapid resolution of symptoms, information will be available quickly. Generally, symptoms due to lactose ingestion will disappear within 1–2 days. Thus, no long-term sequelae are associated with this approach. When other tests are not accessible, brief lactose restriction is a safe and informative method by which to assess symptom responses to ingested lactose.

References

1. Montgomery RK, Grand RJ, Büller H. Lactose intolerance. May 2009. uptodate.com. Accessed November 30, 2009.

2. Troelsen JT. Adult-type hypolactasia and regulation of lactase expression. *Biochim Biophys Acta.* 2005;1723:19–32.

3. Grand RJ, Montgomery RK, Chitkara DK, Hirschhorn JN. Changing genes; losing lactase. *Gut*. 2003;52:617–619.

4. Newcomer AD, McGill DB. Distribution of disaccharidase activity in the small bowel of normal and lactase-deficient subjects. *Gastroenterology*. 1966;51:481–488.

5. Scrimshaw NS, Murray AB. The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. *Am J Clin Nutr.* 1988;48:1079–1159.

6. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Järvelä I. Identification of a variant associated with adult-type hypolactasia. *Nat Genet.* 2002;30:233–237.

7. Kuokkanen M, Enattah NS, Oksanen A, Savilahti E, Orpana A, Järvelä I. Transcriptional regulation of the lactase-phlorizin hydrolase gene by polymorphisms associated with adult-type hypolactasia. *Gut*. 2003;52:647–652.

8. Mulcare CA, Weale ME, Jones AL, et al. The T allele of a single-nucleotide polymorphism 13.9 kb upstream of the lactase gene (LCT) (C-13.9kbT) does not predict or cause the lactase-persistence phenotype in Africans. *Am J Hum Genet*. 2004;74:1102–1110.

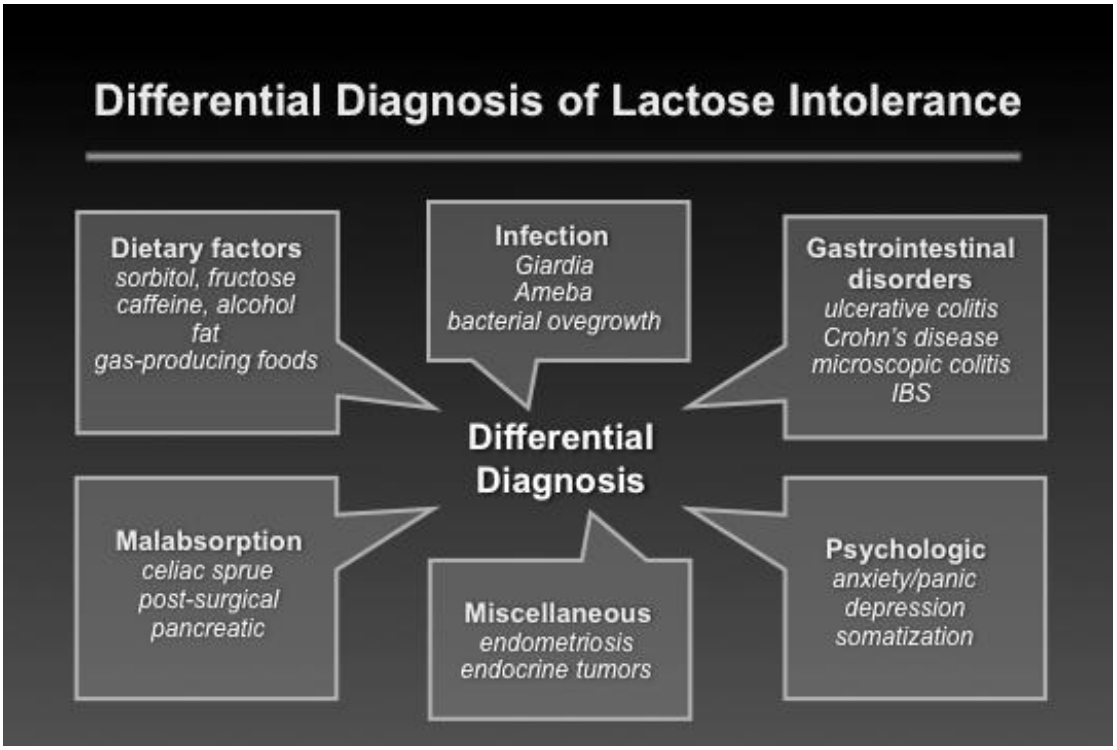
9. Newcomer AD, McGill DB, Thomas PJ, Hofmann AF. Prospective comparison of indirect methods for detecting lactose deficiency. *N Engl J Med.* 1975;293:1232–1236.

Clinical Presentation: But What If It Is Not Lactose Intolerance?

Lin Chang, M.D.

Lactose malabsorption typically causes gastrointestinal (GI) symptoms such as abdominal pain, bloating, flatulence, and diarrhea induced by dairy product consumption.[1] Although the diagnosis in clinical practice can be confirmed by a lactose hydrogen breath test, it is not routinely ordered and can be falsely negative if there is a predominance of methane-producing bacteria or the patient has been on antibiotics.[2] Instead, patients are frequently asked to assess symptoms while avoiding dairy products for a period of time followed by a lactose product challenge to determine if they are lactose intolerant. In patients where a consistent link between lactose products and symptoms does not exist, other conditions that cause similar symptoms need to be considered, particularly because the treatment approach would be different (see Figure 1).

Figure 1. Differential Diagnosis of Lactose Intolerance



There are several gastrointestinal disorders which can present with chronic or recurrent postprandial abdominal pain, diarrhea, and bloating. The most common of these disorders is irritable bowel syndrome (IBS), which has a significant worldwide prevalence and is estimated to affect 10–15% of the U.S. population.[3] There is currently

no reliable diagnostic biomarker for IBS, and therefore it is a symptom-based diagnosis. Diagnostic criteria for IBS, such as the Rome III criteria, were originally developed for research purposes but also are used in clinical practice.[3] The diagnosis of IBS is based on the presence of chronic or recurrent abdominal pain or discomfort associated with diarrhea and/or constipation. Bloating and urgency are common supportive symptoms of IBS. IBS is subgrouped into IBS with diarrhea, IBS with constipation, and IBS with mixed pattern. The IBS with diarrhea subtype should be considered as part of the differential diagnosis of lactose intolerance. Up to 65% of IBS patients report that their symptoms are increased with meals.[4] Evidence suggests that lactose malabsorption is more prevalent in IBS patients than healthy individuals. In addition, the clinical response to lactose malabsorption may be exaggerated in IBS patients compared to controls. Therefore, it is recommended that IBS patients be questioned about an association between symptoms and lactose ingestion. If questions about the presence of lactose malabsorption persist after a careful history and review of a food diary, performance of a lactose hydrogen breath test can be considered.[5]

Inflammatory bowel disorders such as ulcerative colitis, Crohn's disease, and microscopic colitis frequently present with abdominal pain and diarrhea. In patients with inflammatory bowel disease (IBD) with macroscopic inflammation (i.e., ulcerative colitis and Crohn's disease), bloody stools, unintentional weight loss, and anemia are often present and would argue against the symptoms being due to a noninflammatory condition such as lactose malabsorption. Diagnosis of IBD is based on clinical symptoms, endoscopic evidence of inflammation, and absence of infection in stool studies.[6] However, microscopic colitis (lymphocytic and collagenous colitis) can present with symptoms similar to lactose malabsorption, that is, nonbloody chronic intermittent diarrhea, but it typically presents in middle-age patients and is more common in women.[7]

Celiac disease is an immune-mediated enteropathic condition triggered in genetically susceptible individuals by the ingestion of gluten.[8] Currently, celiac disease presents in individuals between the ages of 10 and 40. Data demonstrate that up to 75% of patients with celiac disease present with symptoms suggestive of lactose malabsorption or IBS, including recurrent abdominal discomfort, bloating, or diarrhea, in the absence of alarm symptoms and signs.[9] In the United States, the prevalence is 1–4%. Diagnosis of celiac disease can be made with serologic screening and confirmation with small bowel biopsies. The mainstay of treatment is adherence to a gluten-free diet.

The differential diagnosis of lactose intolerance also includes intolerances to other foods such as fructose-containing products, sorbitol, and fatty foods. Fructose is absorbed across villous enterocytes by carrier-mediated facilitated diffusion, which seems to be of low capacity. The absorptive capacity of fructose in the small intestine is saturable. Failure to completely absorb fructose in the small intestine (i.e., fructose malabsorption) leads to the delivery of fructose to the colonic lumen together with water due to its osmotic effect. Luminal bacteria rapidly ferment fructose to hydrogen, carbon dioxide, and short-chain fatty acids. Thus if sufficient fructose reaches the colon, luminal distention may occur due to the osmotic load and rapid gas production, which potentially

leads to bloating, abdominal discomfort, and motility changes. Fructose consumption is rising with a >1,000% rise between 1970 and 1990, which may explain a greater recognition of fructose malabsorption. Previous studies have found that the majority of patients with unexplained GI symptoms have a positive fructose breath test.[10] A recent study evaluated the efficacy of a diet that restricts poorly absorbed, short-chain carbohydrates including fructose, called FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) in patients with IBS-like symptoms.[11] The low FODMAPs diet restricts foods including fructans, fructose, and foods in which free fructose greatly exceeds free glucose. This diet led to marked and sustained improvement in all gut symptoms in 74% of 62 patients with IBS and fructose malabsorption. However, this was a retrospective but controlled study and would need confirmation in larger studies.

In summary, the differential diagnosis of lactose intolerance includes GI disorders such as IBS, IBD, and celiac disease, other food intolerances, and endocrine disorders. A careful history including identifying a link of GI symptoms with dairy product intake can be helpful in determining if lactose intolerance is the cause of recurrent GI symptoms. A lactose hydrogen breath test can confirm its presence. However, in patients whose symptoms are not consistently linked to dairy products, consideration of other conditions that can be the primary cause of the symptoms or coexist with lactose intolerance is required and can affect the treatment approach.

References

1. Bayless TM, Rothfeld B, Massa C, Wise L, Paige D, Bedine MS. Lactose and milk intolerance: clinical implications. *N Engl J Med.* 1975;292:1156–1159.

2. Lomer MC, Parkes GC, Sanderson JD. Review article: lactose intolerance in clinical practice—myths and realities. *Aliment Pharmacol Ther.* 2008;27:93–103.

3. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology.* 2006;130:1480–1491.

4. Park MI, Camilleri M. Is there a role of food allergy in irritable bowel syndrome and functional dyspepsia? A systematic review. *Neurogastroenterol Motil.* 2006;18:595–607.

5. American Collge of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An Evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104(Suppl 1):S1–S35.

6. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2004;99:1371–1385.

7. Zins BJ, Sandborn WJ, Tremaine WJ. Collagenous and lymphocytic colitis: subject review and therapeutic alternatives. *Am J Gastroenterol*. 1995;90:1394–1400.

8. Fasano A, Berti I, Gerarduzzi T. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med.* 2003;163:286–292.

9. Zipser RD, Patel S, Yahya KZ, Baisch DW, Monarch E. Presentations of adult celiac disease in a nationwide patient support group. *Dig Dis Sci.* 2003;48:761–764.

10. Rao SS, Attaluri A, Anderson L, Stumbo P. Ability of the normal human small intestine to absorb fructose: evaluation by breath testing. *Clin Gastroenterol Hepatol.* 2007;5:959–963.

11. Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol.* 2008;6:765–771.

Population Genetics: Evolutionary History of Lactose Tolerance in Africa

Alessia Ranciaro, Ph.D., and Sarah A. Tishkoff, Ph.D.

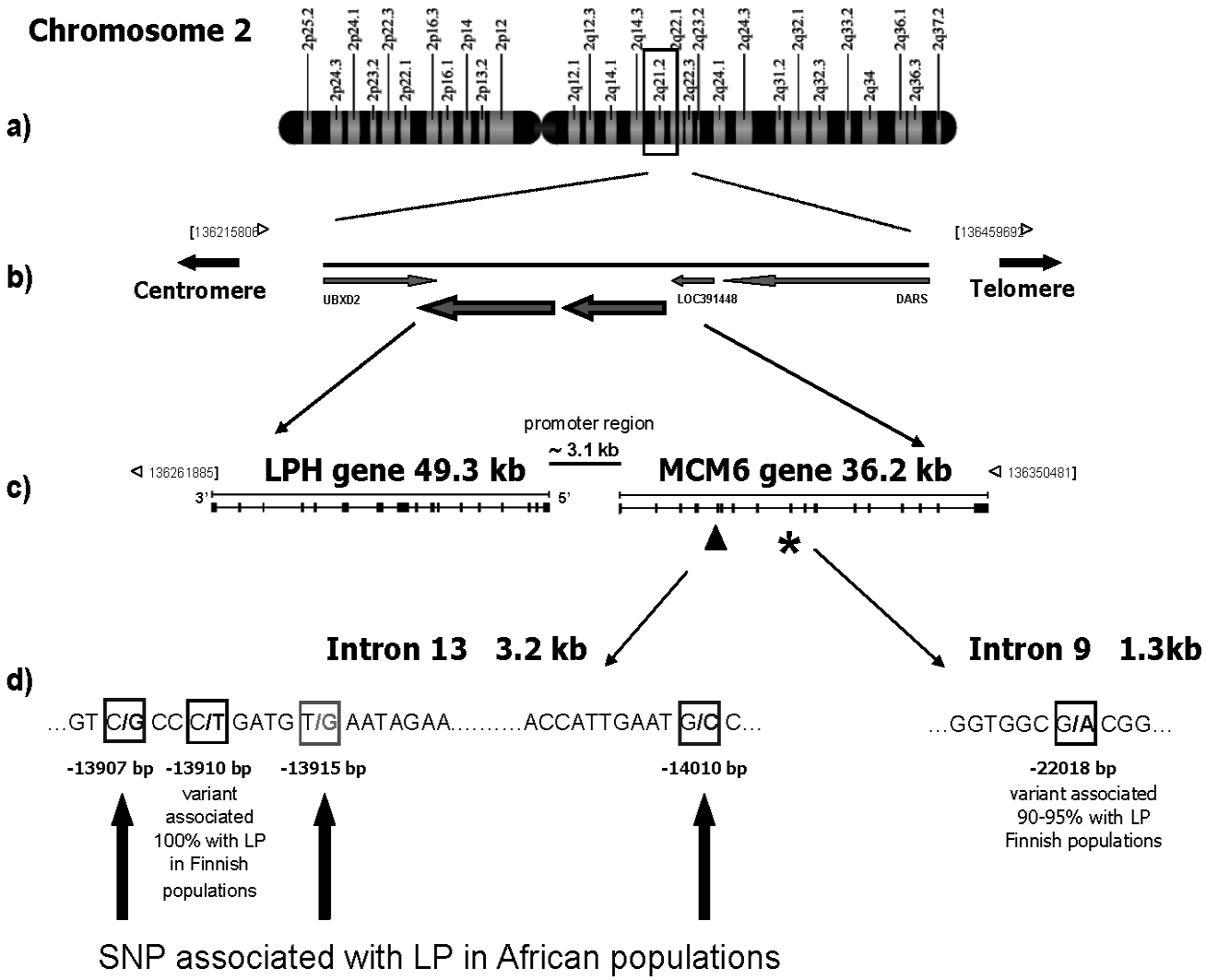
The digestion of lactose, the primary sugar present in milk, is catalyzed by the enzyme lactase-phlorizin hydrolase (LPH), lactase, expressed exclusively in the brush border cells of the small intestine. In most mammals, levels of the enzyme lactase decline rapidly after weaning and adults are not able to digest the sugar lactose present in milk. Individuals who are unable to digest lactose as adults are commonly referred to as "lactose intolerant," and the trait is referred to as "lactase nonpersistence" (LNP).[1,2] Individuals who can digest lactose are "lactose tolerant" and have the "lactase persistence" (LP) trait.[3,4] Digestion of fresh milk in individuals who are lactose intolerant can result in severe abdominal distress including abdominal pain, flatulence, and diarrhea.[5] In developing countries such as Africa, diarrhea resulting from milk consumption can result in severe negative health consequences. Milk products that are soured, or otherwise treated with bacteria that secrete lactase (e.g., *Lactobacillus acidophilus*), such as cheese and yogurt, are easier to digest in lactose-intolerant individuals because they contain relatively low levels of lactose.[6–8]

The geographic distribution of the LP trait in human populations has been shown to be correlated with the cultural trait of cattle herding and dairying. For example, the LP trait is at highest frequencies in northern European populations (>90% in Swedes and Danes), with decreasing frequencies across southern Europe and the Middle East (~50% in Spanish, French, and pastoralist Arabic populations), and is at low frequency in Native Americans and Pacific Islanders, as well as in most non-pastoralist sub-Saharan African and southeast Asian populations (~1% in Chinese, ~5%–20% in West African agriculturalists).[4] However, the LP trait is common among pastoralist populations from Africa who have a history of drinking fresh milk (~90% in Tutsi, ~50% in Fulani).[4] Based on the correlation between the prevalence of the LP trait and the cultural practice of cattle domestication and dairying, lactose tolerance is considered an example of gene-culture coadaptation in populations that consume milk.[9–11]
The reasons that adult milk consumption is adaptive are not clear. Selective forces could include the obvious nutritional benefits from milk such as protein, vitamin D, and calcium.[12] Calcium and vitamin D absorption could be important in northern latitude populations, which have less sunlight exposure and may be susceptible to rickets and osteomalacia.[13,14] However, in African populations, the selective advantage of adult milk consumption could be as a source of water in arid zones.[13] It also is possible that there are additional unidentified selective advantages of milk consumption.

Pedigree studies have indicated that the LP trait is inherited in an autosomal dominant manner. The LPH gene, which codes for the lactase enzyme, was mapped to the long arm of chromosome 2[15,16] more than two decades ago, but the genetic variants associated with the LP trait remained elusive. In 2002, Enattah et al. identified two new single-nucleotide polymorphisms (SNPs) associated with the LP trait in Europeans

located ~14 kb and ~22 kb upstream of the lactase gene (*LCT*) within introns 13 and 9 of the adjacent minichromosome maintenance 6 gene (*MCM6*)[17] (see Figure 1). These were (1) C/T_{-13910}, which was 100% associated with the LP trait in Finnish populations and 86%–98% associated with the LP trait in other European populations, and (2) G/A_{-22018}, which was greater than 95% associated with the LP trait in the Finnish population.[17] Further functional studies have shown that the T_{-13910} variant upregulates *LCT* gene expression[18–21] and that people who carry the T_{-13910} mutation have similar chromosomal backgrounds as far as 1 million base pairs away, indicating that this haplotype has been under strong selection within the last 5,000–10,000 years.[18–22]

Figure 1. SNP Associated With LP in African Populations



a. The box represents the region where the *LPH* and *MCM6* genes are located on chromosome 2.
b. Enlarged *MCM6* and *LPH* gene regions.
c. Structure and length of the *MCM6* and *LPH* genes. Solid boxes represent coding regions.
d. Location of LP-associated variants within introns 9 and 13 of the *MCM6* gene in African and European populations.

The T_{-13910} mutation is likely to be the causal variant for the LP trait in Europeans, but this mutation has not been observed in African populations with a high prevalence of the LP trait, such as the Dinka and Nuer from southern Sudan or the Maasai from Kenya and Tanzania,[23–26] although it has been observed at low frequency in several West and North African populations, including the Fulani, Mozabite, Arabic Baggara, and Bulala,[22,24,25,27,28] likely due to gene flow from outside of Africa. The absence of the T_{-13910} mutation in most African populations that have the LP trait suggests that this trait arose multiple times in ethnically diverse populations.

Recent and independent studies[26,27] have provided new insight into the genetic basis of the LP trait in non-European human populations. Three new variants associated with the LP trait were identified in intron 13 of *MCM6* near the T-13910 variant (Figure 1). These include the following: (1) C_{-14010} is at highest frequency in Tanzanian and Kenyan populations and at low frequency in some southern African Bantu-speaking (e.g., Xhosa, Ovimbundu, Nyaneka-Nkhumbi, Kuvale) and San populations.[25,26,28,29] The presence of the C-14010 variant in the southern African populations suggests that pastoralism in that region, which is thought to have originated within the past ~2,000 years, may have been introduced by eastern African pastoralists.[25,28] (2) G_{-13907} is present in northern Sudanese, northern Kenyan, and Ethiopian populations.[26,27] (3) G_{-13915} is most common in Middle Eastern populations but also is present in northern Sudanese and northern Kenyan populations, where it may have been introduced due to recent gene flow from the Middle East.[26,27]

The African and Middle Eastern variants associated with the LP trait originated on different chromosome backgrounds from that of the European T_{-13910} variant and exhibit a striking pattern of extended haplotype homozygosity, consistent with the independent origin and recent spread of these variants in the past 10,000 years due to the strong force of natural selection.[26] The independent origin of LP-associated variants in Africans and Europeans is an example of parallel evolution due to strong selective pressure resulting from shared cultural traits including animal domestication and adult milk consumption. However, the genetic variants associated with LP in Africa do not account for all of the phenotypic variation observed for this trait and are entirely missing from several populations that have high rates of LP, suggesting that additional genetic variants associated with the LP trait may exist in Africa.[26]

References

1. Dahlqvist A, et al. Human intestinal disaccharidases and hereditary disaccharide intolerance. The hydrolysis of sucrose, isomaltose, palatinose (isomaltulose), and a 1,6-alpha-oligosaccharide (isomalto-oligosaccharide) preparation. *J Clin Invest.* 1963;42:556–562.

2. Auricchio S, et al. Isolated intestinal lactase deficiency in the adult. *Lancet.* 1963;2:324–326.

3. Swallow DM, Poulter M, Hollox EJ. Intolerance to lactose and other dietary sugars. *Drug Metab Dispos.* 2001;29:513–516.

4. Swallow DM. Genetics of lactase persistence and lactose intolerance. *Ann Rev Genet.* 2003;37:97–219.

5. Swagerty DL Jr, Walling AD, Klein RM. Lactose intolerance. *Am Fam Physician.* 2002;65:1845–1850.

6. Onwulata CI, Rao DR, Vankineni P. Relative efficiency of yogurt, sweet acidophilus milk, hydrolyzed-lactose milk, and a commercial lactase tablet in alleviating lactose maldigestion. *Am J Clin Nutr.* 1989;49:1233–1237.

7. Adolfsson O, Meydani SN, Russell RM. Yogurt and gut function. *Am J Clin Nutr.* 2004;80:245–256.

8. Vanhove M. The Beja language today in Sudan: the state of the art in linguistics. In: *7th International Studies Conference 2006.* Bergen, Norway: University of Bergen.

9. Durham PL, Nanthakumar EJ, Snyder JM. Developmental regulation of surfactant-associated proteins in rabbit fetal lung *in vivo*. *Exp Lung Res.* 1992;18:775–793.

10. Simoons FJ. Primary adult lactose intolerance and the milking habit: a problem in biological and cultural interrelations. I. Review of the medical research. *Am J Dig Dis.* 1969;14:819–836.

11. Simoons FJ. Primary adult lactose intolerance and the milking habit: a problem in biologic and cultural interrelations. II. A culture historical hypothesis. *Am J Dig Dis.* 1970;15:695–710.

12. Adachi A, Kobayashi T. Identification of vitamin D3 and 7-dehydrocholesterol in cow's milk by gas chromatography-mass spectrometry and their quantitation by high-performance liquid chromatography. *J Nutr Sci Vitaminol (Tokyo)*. 1979;25:67–78.

13. Flatz G, Rotthauwe HW. Lactose nutrition and natural selection. *Lancet.* 1973;2(7820):76–77.

14. Thacher TD. Images in clinical medicine. Nutritional rickets. *N Engl J Med.* 1999;341:576.

15. Kruse TA, et al. The human lactase-phlorizin hydrolase gene is located on chromosome 2. *FEBS Lett.* 1988;240:123–126.

16. Harvey CB, et al. Lactase haplotype frequencies in Caucasians: association with the lactase persistence/non-persistence polymorphism. *Ann Hum Genet.* 1998;62:215–223.

17. Enattah NS, et al. Identification of a variant associated with adult-type hypolactasia. *Nat Genet.* 2002;30:233–237.

18. Olds LC, Sibley E. Lactase persistence DNA variant enhances lactase promoter activity *in vitro*: functional role as a cis regulatory element. *Hum Mol Genet.* 2003;12:2333–2340.

19. Troelsen JT, et al. An upstream polymorphism associated with lactase persistence has increased enhancer activity. *Gastroenterology.* 2003;125:1686–1694.

20. Troelsen JT. Adult-type hypolactasia and regulation of lactase expression. *Biochim Biophys Acta.* 2005;1723:19–32.

21. Lewinsky RH, et al. T-13910 DNA variant associated with lactase persistence interacts with Oct-1 and stimulates lactase promoter activity *in vitro*. *Hum Mol Genet.* 2005;14:3945–3953.

22. Bersaglieri T, et al. Genetic signatures of strong recent positive selection at the lactase gene. *Am J Hum Genet.* 2004;74:1111–1120.

23. Myles S, et al. Genetic evidence in support of a shared Eurasian-North African dairying origin. *Hum Genet.* 2005;117:34–42.

24. Mulcare CA, et al. The T allele of a single-nucleotide polymorphism 13.9 kb upstream of the lactase gene (LCT) (C-13.9kbT) does not predict or cause the lactase-persistence phenotype in Africans. *Am J Hum Genet.* 2004;74:1102–1110.

25. Coelho M, et al. Microsatellite variation and evolution of human lactase persistence. *Hum Genet.* 2005;117(4):329–339.

26. Tishkoff SA, et al. Convergent adaptation of human lactase persistence in Africa and Europe. *Nat Genet.* 2007;39:31–40.

27. Ingram CJ, et al. A novel polymorphism associated with lactose tolerance in Africa: multiple causes for lactase persistence? *Hum Genet.* 2007;120:779–788.

28. Ranciaro A, Tishkoff SA. Unpublished data.

29. Torniainen S, et al. Screening of variants for lactase persistence/non-persistence in populations from South Africa and Ghana. *BMC Genet.* 2009;10:31.

Lactose Intolerance and Ethnic Prevalence

Wilma J. Wooten, M.D., M.P.H.

A Barrier to Good Health

- Multiple food groups contribute to maintaining a healthy body and system functions.
- Less than 75% of African Americans meet the *2005 Dietary Guidelines for Americans,* which recommends three servings of dairy foods per day (Beydoun 2008; NHANES data).
- Because of its **nutrient-rich** package, consumption of dairy products can play a unique role in preventing many illnesses and disease states.
- Just over half (55%) of African Americans eat one or more servings of dairy foods a day.
- African American children consume only 0.8 to 1.0 servings of milk per day.
- By consuming the recommended three servings of low-fat dairy products (milk, yogurt, or cheese), a number of health benefits can be achieved.
- Lactose intolerance can be a barrier to consuming the recommended 3-A-Day servings.
- An estimated 75% of African Americans fail to meet daily calcium requirements because of lactose intolerance.
- In a study conducted by the National Medical Association, while only 24% of African Americans consider themselves to be lactose intolerant, the majority of African Americans (86%) get just more than half of the recommended daily amount of calcium.

What Is Lactose Intolerance?

Many terms are used when describing lactose intolerance. Here are the facts:

Lactose Maldigestion

- Occurs when digestion of lactose is reduced as a result of low activity of the enzyme lactase.

Lactase Nonpersistence

- The normal age-related decline in lactase activity is often used to refer to lactose maldigestion.

Lactose Intolerance

- Refers to gastrointestinal symptoms resulting from consuming too much lactose.
- These symptoms of lactose maldigestion are referred to as lactose intolerance.
- Inability to metabolize **lactose**, a sugar found in milk and other dairy products, because the required enzyme lactase is absent in the intestinal system or its

availability is lowered. Lactase breaks down milk sugar into two simpler forms of sugar called glucose and galactose, which are then absorbed into the bloodstream.

- While the symptoms may be the same, lactose intolerance should not be confused with cow's milk intolerance. They are not the same. Intolerance to cow's milk is an allergic reaction that is triggered by the immune system. Lactose intolerance is a problem caused by the digestive system.

Lactose Intolerance Symptoms

- Symptoms range from mild to severe.
- Symptoms include nausea, cramps, bloating, gas, and diarrhea.
- Symptoms begin about 30 minutes to 2 hours after eating or drinking foods containing lactose.
- Many factors determine severity of symptoms and include:
  - Amount of lactose a person can tolerate
  - Person's age
  - Ethnicity
  - Digestion rate

Prevalence of Lactose Intolerance

- Lactose intolerance is estimated to affect 25% of the American population.
- Group prevalence is as follows:
  - 15% (6% to 19%) – whites
  - 53% – Mexican Americans
  - 62% to 100% – Native Americans
  - 80% – African Americans
  - 90% – Asian Americans

Benefits of the Nutrient-Rich Package

- Vitamin D – enhances absorption of calcium and phosphorous
- Riboflavin B2 – facilitates metabolism
- Calcium – supports bone health, blood clotting, nerve transmission
- Magnesium – supports general metabolism
- Potassium – facilitates nerve conduction
- Vitamin A – deficiency results in blindness
- Phosphorus – facilitates absorption of glucose

What Can Providers Do?

- **KNOW** and understand the roles and sources of needed nutrients provided by dairy.
  - Follow the *2005 Dietary Guidelines for Americans*.
  - Know the Food Pyramid groups and their benefits.

- Follow guidelines from the DASH (Dietary Approaches To Stop Hypertension) Diet.

- **ASK** patients if they have lactose intolerance.
- **IDENTIFY those at risk.**
  - Review positive linkages between dairy products and key disease states.
  - Identify pregnant women, the elderly, hypertensives, diabetics, and other risk groups whose health may be even marginally improved by protecting against nutrient insufficiency.
- **ADVISE patients.**
  - Encourage patients to consider formal testing for lactose intolerance.
    - Many other foods cause similar lactose intolerance symptoms.
    - Self-diagnosis is more pronounced but may be inaccurate.
  - Provide guidance on gradual introduction of dairy into the diet.
- **EDUCATE.**
  - Disseminate dietary guidelines and DASH Diet information to African American patients to educate about the critical role of consuming at least three daily servings of milk, yogurt, or cheese and how this ensures a sufficiency of calcium, riboflavin, protein, potassium, and other nutrients.

What Can Consumers Do?

- Gradually introducing non- or low-fat dairy products into the diet has been found to be an effective method to reduce symptoms of lactose intolerance.
- Follow these tips:
  - Drink small portions of ***milk*** with food.
  - Eat ***yogurt*** with live and active cultures (can minimize lactose intolerance symptoms because it aids in the creation of a lactose enzyme that can aid in lactose digestion).
  - Consume ***hard cheese***, such as cheddar or Swiss.
- Choose alternatives within the milk food group, such as
  - Lactose-free milk or
  - Enzyme lactase (prior to the consumption of milk products).
- Knowing the appropriate serving size is important.
  - Milk – ½ glass is approximately 4 ounces.
  - Cheese – one serving is 1½ ounces.
  - Yogurt – ½ cup

The Truth About Lactose Intolerance

- Lactose intolerance is common, is easy to treat, and can be managed.
- Since dairy nutrients address important health concerns, addressing lactose intolerance is an investment in health.
- Symptoms can be controlled through simple dietary strategies.
- It is possible to consume dairy, even in the face of a history of maldigestion or lactose intolerance issues.

- Gradually increasing lactose in the diet is an effective strategy to manage lactose intolerance and meet optional dairy needs.
- Individuals who do not consume three daily servings of low-fat or nonfat dairy products may be depriving themselves of important nutrients such as calcium, vitamin D, and potassium, thus increasing their risk of certain chronic diseases such as hypertension, stroke, osteoporosis, obesity, diabetes, and colon cancer.
- An investment in the appropriate daily recommendations of dairy is an investment in one's health.

References

1. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med.* 1997;336:1117–1124.

2. Beydoun MA, Gary TL, Caballero H, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their associations with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008;87:1914–1925.

3. Byers KG, Savaiano DA. The myth of increased lactose intolerance in African-Americans. *J Am Coll Nutr.* 2005;24(6 Suppl):569S–573S.

4. Fulgoni V III, Nicholls J, Reed A, et al. Dairy consumption and related nutrient intake in African-American adults and children in the United States: continuing survey of food intakes by individuals 1994–1996, 1998, and National Health and Nutrition Examination Survey 1999–2000. *J Am Diet Assoc.* 2007;107(2):256–264.

5. Inman-Felton AE. Overview of lactose maldigestion (lactase nonpersistence). *J Am Diet Assoc.* 1999;98:481–489.

6. Jackson KA, Savaiano DA. Lactose maldigestion, calcium intake and osteoporosis in African-, Asian-, and Hispanic-Americans. *J Am Coll Nutr.* 2001;20(2 Suppl):198S-207S.

7. Lactose Intolerance. Washington, DC: National Digestive Diseases Information Clearinghouse; 1994. NIH Publication No. 94-2751.

8. Wooten W, Price W. The role of dairy and dairy nutrients in the diet of African-Americans. *J Nat Med Assoc.* 2004;96(12):20S–24S.

Aging: Lactose Intolerance and Calcium Absorption in the Elderly

Richard J. Wood, Ph.D.

Lactose is a naturally occurring disaccharide found in high amounts (0.5%) in milk. There is no appreciable absorption of intact lactose in the gut. Rather, lactose is first broken down into its constituent monosaccharides—glucose and galactose. The ability to digest lactose is due to the presence of the enzyme lactase (*lactase-phlorizin hydrolase*) in the brush border membrane of the enterocytes in the small intestine. Lactase is needed by the newborn and suckling infant to digest lactose in breast milk. However, lactase activity is usually lost as children age with marked increases in the prevalence of lactose malabsorption that can occur between 3 to 5 years of age[1,2] in populations with a high prevalence of lactose intolerance, whereas a more gradual increase in prevalence occurs in populations with lower prevalence rates.[3] This nonpersistence of lactase activity or adult-type *hypolactasia* is a common inherited condition. The prevalence of adult-type hypolactasia can vary considerably among different populations. For example, the prevalence of adult-type hypolactasia varies from 3% to 75% among Caucasian populations in Europe.[3] It is estimated that approximately 30% of the U.S. population has lactose maldigestion.[4]

Hypolactasia has been shown recently to be associated with single nucleotide polymorphisms in the lactase (LCT) gene found on the long arm of chromosome 2. A DNA variant, C/T_{-13910}, which is upstream of the LCT gene is associated with lactase nonpersistence.[5] A cytosine (C) to thymine (T) change at this nucleotide position is completely associated with lactase persistence. The CC genotype is associated with lactase nonpersistence, while the CT and TT genotypes are associated with lactase persistence. A second single nucleotide polymorphism involving a guanine and adenine change, G/A_{-22018}, also is associated with lactase nonpersistence. The GG genotype is associated with lactase nonpersistence, while the AA genotype is associated with lactase persistence. A strong majority of individuals with the GA heterozygous genotype show lactase persistence. This new genetic tool to identify hypolactasia offers a convenient method to more fully characterize the extent of lactose maldigestion in various populations.

Hypolactasia can cause symptomatic *lactose intolerance* in children and adults following lactose consumption in milk and milk products as a consequence of decreased lactose digestion in the small intestine and increased availability of lactose to the colon. Lactose in the colon becomes a substrate for bacterial metabolism that can lead to lactose intolerance. Lactose intolerance is characterized by gastrointestinal symptoms that can include bloating, abdominal pain, increased flatulence, and diarrhea. In most cases, tolerance for lactose is dose dependent and many subjects with demonstrated *lactose maldigestion*, commonly determined by a positive hydrogen breath test following a large 50 g oral lactose dose, can tolerate physiological doses of lactose found in a usual

serving of milk (12 g lactose) without adverse gastrointestinal symptoms.[6,7] Likewise, many individuals who claim to be *milk intolerant* and restrict their milk intake do not show a positive breath hydrogen test in response to oral ingestion of milk.[8] On the other hand, symptoms of lactose intolerance can vary considerably between individuals with lactose maldigestion and some experience gastrointestinal symptoms after consuming one or less glass of milk.[9]

Does Aging Influence the Prevalence of Lactose Maldigestion and Lactose Intolerance?

Although many studies have characterized the prevalence of lactose maldigestion and symptoms of lactose intolerance in various adult populations, there is surprisingly little information concerning this condition in the elderly, especially in the very old (>80 years). What little evidence is available indicates that the prevalence of lactose maldigestion may increase with age in adults, but that symptoms of lactose intolerance do not increase with age.

Given that milk is a rich source of dietary calcium and that recommended calcium intakes are increased in the elderly, the impact of lactase deficiency on symptoms of *lactose intolerance*, decreased calcium intake via *milk avoidance*, and possibly decreased *calcium absorption*, could have significant nutritional consequences on calcium balance and be a negative risk factor for osteoporosis. However, a review of the available published literature up to October 2009 revealed no study that had systematically investigated all of these conditions in a single population of elderly subjects. Moreover, among the few studies done with elderly subjects, the findings are inconsistent; this could be due to having too few older subjects in the study or coexisting gastrointestinal problems that make interpretation of the findings uncertain.

Suarez and Savaiano studied lactose digestion and symptoms of lactose intolerance in U.S. Asian American young adults (20–40 years old, mean age 31) and elderly persons (>65 years old, mean age 68) with a positive hydrogen breath test—that is, all subjects were lactose maldigesters—and found no difference in mean breath hydrogen production between the two age groups or in symptoms of *lactose intolerance* over an 8-hour period.[10] The administered lactose dose was 0.5 g lactose/kg body weight.

Goulding et al. assessed the prevalence of lactose maldigestion in 80 New Zealand women between age 40–79 (20 subjects per decade).[11] They found that overall, 32% of the women had evidence of lactose maldigestion based on a 50 g lactose breath hydrogen test. These investigators observed that the prevalence of *lactose maldigestion* increased with age from 15% in the 40- to 59-year-old group to 50% in the 60- to 79-year-old group. No difference in prevalence was noted between the 60–69 and 70–79 age groups, however. Calcium intake was generally high in the study subjects. Evidence of significantly lower milk and *calcium intake* between lactose digesters and maldigesters was only seen in the oldest group (70–79 years). Overall, few gastrointestinal symptoms were reported in the lactose maldigesters, and no age effect on *lactose intolerance* was noted, despite a twofold increase in the prevalence of lactose maldigestion in the older subjects.

Di Stefano and colleagues studied lactose digestion in 84 Italian male and female subjects (23–94 years old) following the administration of 400 mL semi-skim *milk* containing 20 g lactose.[12] Thirty-four of the subjects were >74 years old. Breath hydrogen samples were obtained over 4 hours. Symptoms of *lactose intolerance* were recorded over a 24-hour period following the lactose test. The prevalence of *lactose maldigestion* from milk was significantly higher (83%) in older subjects (>74 years old) than in subjects 65–74 years old (65%) and subjects <65 years old (58%). However, lactose intolerance among lactose maldigesters followed a different age pattern. The prevalence of *lactose intolerance* in the younger (<65 years old) group was 80%, which was significantly higher than both the middle elder (65–74 years old) group (50%) and the older elder (>74 years old) group (48%). No differences in *calcium intake* were seen between lactose absorbers and nonabsorbers in this study regardless of age.

Kerber et al. recently reported that older age was associated with an increase in the prevalence of lactose maldigestion in Austrian subjects, but only in those subjects who were heterozygous for the LCT genotype C/T_{-13910} for lactase persistence.[13] Hydrogen breath testing with a 50 g lactose dose and genotyping for two single nucleotide polymorphisms (C/T_{-13910} and G/A_{-22018}) were done in 120 outpatients who visited the physician's office for evaluation of symptoms of *irritable bowel syndrome* (IBS). In this group of patients with possible IBS, gastrointestinal symptoms after lactose ingestion were common in those with a positive hydrogen breath test (90% reporting gastrointestinal symptoms) and those with a negative breath test (32% reporting gastrointestinal symptoms). No age effects on *lactose intolerance* symptoms were reported. However, in heterozygotes for the C/T_{-13910} genotype, the prevalence of *lactose maldigestion* significantly increased from 15% in the group <31 years old to 33% in the group 31–65 years old. An apparent increase in the prevalence (50%) of a lactose maldigestion was seen in the oldest group >65 years old, but this difference was not statistically significant compared to the other groups, probably due to the small number of heterozygous subjects in the older age category (4/8). The association of lactose intolerance symptoms or lactose maldigestion with dietary milk and calcium intake was not reported in this study.

Does Lactose Maldigestion Influence Calcium Absorption in the Elderly?

Another important question concerning lactose maldigestion in the elderly is to what extent, if any, lactose malabsorption influences intestinal calcium absorption. This question is of particular interest in this population group because aging is associated with a decrease in calcium intake and intestinal calcium absorption efficiency.

However, a review of the literature indicates that although the question of lactose effects on calcium absorption has been the subject of many studies beginning in the 1970s to the present, it has not been adequately addressed in the elderly. Moreover, there is no convincing evidence that a *physiological* dose of lactose affects calcium absorption in nonelderly adults.

An early study in younger adults of the effects of lactose ingestion on ^{47}Ca absorption and retention in lactose digesters and maldigesters found that administration of a milk drink containing 39 g lactose or lactose-free milk containing 39 g glucose had discordant effects in lactose-tolerant and lactose-intolerant subjects.[14] Similar 4-hour ^{47}Ca absorption kinetic profiles were found in both groups after consuming the lactose-free milk, but the lactose digestion group had a higher serum ^{47}Ca absorption profile with lactose-containing milk drink, while the lactose maldigestion group had a lower calcium absorption profile. However, fecal ^{47}Ca excretion and whole body retention of ^{47}Ca after 1 week was *equivalent* in both groups regardless of lactose treatment, confounding interpretation of the serum kinetic profiles and suggesting that differences in the blood kinetics of ^{47}Ca after lactose-milk drinking may have been due to differences in gastric emptying rather than reflecting differences in intestinal calcium absorption efficiency.

Debongnie and colleagues studied small intestinal calcium absorption in lactose digesters and maldigesters (<65 years old) by an ileal perfusion absorption technique and found *no effect* of 12 g lactose in milk on calcium absorption.[15]

Tremaine et al. investigated the effects of lactose-containing or lactase-hydrolyzed milk on calcium absorption in adult subjects (24–58 years old) using a double calcium-isotope technique and a 6-hour serial blood collection protocol.[16] *No difference* in calcium absorption fraction was seen due to the presence of lactose in either lactose digesters or nondigesters.

Griessen et al. used a double calcium-isotope absorption test to determine the effects of lactose (23 g) and lactose-free milk in lactose digesters and nondigesters, 22–32 years old, over a 24-hour period.[17] *No effect* on calcium absorption was apparent due to the presence of lactose in the milk.

In a recent study, Obermayer-Pietsch and colleagues assessed calcium absorption using a 180-minute strontium absorption test in postmenopausal women (mean age 65) with either the LCT gene “CC” genotype, associated with hypolactasia, or the LCT “TT” genotype, not associated with hypolactasia.[18] In the presence of a 50 g dose of lactose in water, there was a 54% lower serum strontium AUC in the CC genotype hypolactasia group compared to the nonhypolactasia TT genotype group. Moreover, within the CC genotype group, calcium equivalent absorption was *56% lower* after lactose compared to water alone.

References

1. Chang MH, Hsu HY, Chen CJ, Lee CH, Hsu JY. Lactose malabsorption and small-intestinal lactase in normal Chinese children. *J Pediatr Gastroenterol Nutr*. 1987;6:369–372.

2. Nose O, Iida Y, Kai H, Harada T, Ogawa M, Yabuuchi H. Breath hydrogen test for detecting lactose malabsorption in infants and children. Prevalence of lactose malabsorption in Japanese children and adults. *Arch Dis Child.* 1979;54:436–440.

3. Sahi T. Genetics and epidemiology of adult-type hypolactasia. *Scand J Gastroenterol Suppl.* 1994;202:7–20.

4. Suarez FL, Adshead J, Furne JK, Levitt MD. Lactose maldigestion is not an impediment to the intake of 1500 mg calcium daily as dairy products. *Am J Clin Nutr.* 1998;68:1118–1122.

5. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Jarvela I. Identification of a variant associated with adult-type hypolactasia. *Nat Genet.* 2002;30:233–237.

6. Leis R, Tojo R, Pavon P, Douwes A. Prevalence of lactose malabsorption in Galicia. *J Pediatr Gastroenterol Nutr*. 1997;25:296–300.

7. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med.* 1995;333:1–4.

8. Rosado JL, Allen LH, Solomons NW. Milk consumption, symptom response, and lactose digestion in milk intolerance. *Am J Clin Nutr.* 1987;45:1457–1460.

9. Sahi T, Launiala K, Laitinen H. Hypolactasia in a fixed cohort of young Finnish adults. A follow-up study. *Scand J Gastroenterol.* 1983;18:865–870.

10. Suarez FL, Savaiano DA. Lactose digestion and tolerance in adult and elderly Asian-Americans. *Am J Clin Nutr.* 1994;59:1021–1024.

11. Goulding A, Taylor RW, Keil D, Gold E, Lewis-Barned NJ, Williams SM. Lactose malabsorption and rate of bone loss in older women. *Age Ageing*. 1999;28:175–180.

12. Di Stefano M, Veneto G, Malservisi S, Strocchi A, Corazza GR. Lactose malabsorption and intolerance in the elderly. *Scand J Gastroenterol.* 2001;36:1274–1278.

13. Kerber M, Oberkanins C, Kriegshauser G, et al. Hydrogen breath testing versus LCT genotyping for the diagnosis of lactose intolerance: a matter of age? *Clin Chim Acta*. 2007;383:91–96.

14. Kocian J, Skala I, Bakos K. Calcium absorption from milk and lactose-free milk in healthy subjects and patients with lactose intolerance. *Digestion.* 1973;9:317–324.

15. Debongnie JC, Newcomer AD, McGill DB, Phillips SF. Absorption of nutrients in lactase deficiency. *Dig Dis Sci.* 1979;24:225–231.

16. Tremaine WJ, Newcomer AD, Riggs BL, McGill DB. Calcium absorption from milk in lactase-deficient and lactase-sufficient adults. *Dig Dis Sci.* 1986;31:376–378.

17. Griessen M, Cochet B, Infante F, et al. Calcium absorption from milk in lactase-deficient subjects. *Am J Clin Nutr.* 1989;49:377–384.

18. Obermayer-Pietsch BM, Gugatschka M, Reitter S, et al. Adult-type hypolactasia and calcium availability: decreased calcium intake or impaired calcium absorption? *Osteoporos Int.* 2007;18:445–451.

Evidence-based Practice Center Presentation I: Methods of Systematic Review and the Prevalence of Lactose Intolerance and Differences by Race, Ethnicity, and Age

Timothy J. Wilt, M.D., M.P.H.; Aasma Shaukat, M.D., M.P.H.; Tatyana Shamliyan, M.D., M.S.; Brent C. Taylor, Ph.D., M.P.H.; Roderick MacDonald, M.S.; James Tacklind; Indulis Rutks; Sarah Jane Schwarzenberg, M.D.; Robert L. Kane, M.D.; Michael Levitt, M.D.

Introduction

Milk and milk products contain high concentrations of the disaccharide lactose. Intestinal absorption of lactose requires that the disaccharide be hydrolyzed to its component monosaccharides, both of which are rapidly transported across the small bowel mucosa. A brush border beta-galactosidase, lactase, carries out this hydrolysis. While infants virtually always have high concentrations of lactase, sometime after weaning a genetically programmed reduction in lactase synthesis results in very low lactase activity in some adult subjects, a situation known as lactase nonpersistence.

Lactase nonpersistence results in incomplete digestion of an ingested load of lactose; hence lactose is malabsorbed and reaches the colon. If sufficient lactose enters the colon, the subject may experience symptoms of abdominal pain, bloating, excess flatulence, and diarrhea, a condition known as lactose intolerance. Diseases of the small bowel mucosa (infection, celiac disease) may also be associated with low brush border lactase, with resultant lactose malabsorption and lactose intolerance.

The terminology involved in lactose absorption/intolerance is as follows:

a. *Lactase nonpersistence*—indicates that brush border lactase activity is only a small fraction of the infantile level, a condition documented by analysis of brush border biopsies. Recently, it has been shown that a genotype (C/C) of the lactase promoter gene is a predictor of lactase nonpersistence and can be used as indirect evidence of lactase nonpersistence.

b. *Lactose malabsorption* (LM)—indicates that a sizable fraction of a dosage of lactose is not absorbed in the small bowel and thus is delivered to the colon. Since such malabsorption is virtually always a result of low levels of lactase, there is a nearly one-to-one relationship of lactase nonpersistence (or deficiency) and LM. LM is objectively demonstrated via measurements of breath H_2 or blood glucose concentrations following ingestion of a lactose load.

c. *Lactose intolerance* (LI)—indicates that malabsorbed lactose produces symptoms (diarrhea, abdominal discomfort, flatulence, or bloating). It should be stressed that this symptomatic response to LM is linked to the quantity of lactose malabsorbed

(as well as other variables); that is, ingestion of limited quantities of lactose does not cause recognizable symptoms in lactose malabsorbers, while very large doses commonly induce appreciable LI symptoms. As a result, the prevalence of lactase nonpersistence or LM could far exceed the prevalence of LI symptoms in population groups ingesting modest quantities of lactose.

Methods

We searched several databases including MEDLINE® via PubMed® and via Ovid to find studies published in English since 1967 until April 2009. We updated this search for U.S. studies published up until October 2009, and we hand-searched additional articles referred to us by our Technical Expert Panel. We included observations that examined prevalence, symptoms, and outcomes of LI in different age, gender, racial, and ethnic groups. We excluded populations with other gastrointestinal disorders, including individuals diagnosed with irritable bowel syndrome, inflammatory or infectious bowel diseases, or milk allergies. We excluded children younger than 4 years.

Results

A total of 54 articles met inclusion criteria, including 15 articles from the United States. Studies did not directly assess LI in a blinded lactose challenge but instead assessed unblinded subjective LI symptoms, an inability to fully absorb lactose (LM), or lactase nonpersistence. The data available tended to be from highly selected populations and were likely not representative of the overall U.S. population. We report results according to the following conditions: LI, LM, or lactase nonpersistence. Within these conditions, we further describe findings according to assessment method and populations studied.

Lactose Intolerance Symptoms

Symptoms following blinded lactose challenge. We identified no studies that reported on the prevalence of LI based on our "gold-standard" definition; that is, gastrointestinal symptoms that are more prevalent and severe after ingestion of 50 grams of lactose (or less) as a single dose by a lactose malabsorbing subject that are not observed when the subject ingests an indistinguishable placebo.

Symptoms following nonblinded lactose challenge. We identified 21 studies that reported LI-related symptoms (abdominal pain, bloating, excess flatulence, and diarrhea) following a nonblinded lactose challenge. Few assessed U.S. populations. No studies were published in the last 30 years. There were four older U.S. convenience sample studies that reported results on different subpopulations.[1–4] One study of healthy Caucasian volunteers with no history of milk intolerance reported that symptoms were rare and confined primarily to those with biopsy-determined hypolactasia.[1] In another study on healthy adults, Hispanics were 43% more likely to report symptoms following a lactose challenge compared to white non-Hispanics.[2] Similarly, in healthy children,[3] the rate of symptoms was twice as high among Hispanic children (41% versus 20% in non-Hispanic). The fourth U.S. study included African American (n=69) and Caucasian

(n=30) children between the ages of 4 and 9. The overall frequency of symptoms following a challenge was quite low in young children, but the rate increased with age and was higher in African American children compared to Caucasian children.[4] Age up to adulthood was a consistent predictor of LI-related symptoms. Racial and ethnic variation was present, but the variation in symptoms reported following a challenge did not seem as extreme as the racial and ethnic variation seen in lactose malabsorption and prevalence of lactase nonpersistence.

Symptoms without lactose challenge. We identified seven studies reporting baseline self-reported symptoms in 6,161 people. There was only one U.S. population-based study.[5] This study included only self-reported LI with no additional confirmation of the diagnosis. Overall, U.S. estimated prevalence of self-reported LI was 12% from this study with estimates of 8% in European Americans, 10% in Hispanic Americans, and 20% in African Americans. The rest of the self-reported studies' results provided little evidence to address our research questions about population prevalence and the impact of age and ethnicity. Overall, the prevalence of self-reported symptoms was typically lower than the prevalence of symptoms following a lactose challenge.

Lactose Malabsorption

Determined by hydrogen breath test following lactose challenge. We identified 31 studies, evaluating participants from a wide range of ages and ethnicities that reported LM prevalence as defined by subjects with a positive hydrogen breath test. None of the U.S. studies were representative population-based studies. All U.S. studies focused on reporting results in populations of patients with gastrointestinal symptoms at baseline,[6–9] with the exception of one three-decade-old study of American Indians[10] and one convenience sample of adults from the Army, senior centers, nursing homes, and a university.[11]

Within the U.S. studies of patients with gastrointestinal symptoms at baseline, the prevalence of LM in Caucasian adult populations ranged from 6% to 24%.[7,8,11] Some data suggested high levels of LM among American Indians, but this effect was substantially attenuated among those with American Indian and Caucasian mixed ancestry.[10] One prior review showed that the prevalence of LM may be greater than 70% in African Americans, around 50% in Hispanic Americans, and even higher for Asian Americans.[12] Age is an important contributor to the rate of LM, since nearly every population group identified showed low rates of LM in the youngest age groups, particularly those less than 6 years of age.[13–19] In populations with high adult rates of LM, rates peaked between the ages of 10 and 16.

Lactase Nonpersisters (Adult-Type Hypolactasia)

Biopsy identification. We identified five studies that reported on the prevalence of lactase persistence as diagnosed by biopsy assays. These estimates ranged from 6% to 34% among Caucasians, to 75% among nonwhites; however, there was little to no correlation with symptoms of LI. It is difficult to generalize these findings to create population estimates or understand their clinical relevance.

Genetic test association. The most commonly reported genetic mutation for adult-type hypolactasia is the single nucleotide polymorphism (SNP) of the lactase (LCT) gene. The C allele is the globally most prevalent allele, while the less common T allele is dominantly associated with lactase persistence.[20] Nine studies were identified that reported genotype frequencies for LCT -13910C>T SNP mutation, indicating a genetic predisposition for hypolactasia, or lactose nonpersistence. None of these studies were of U.S. populations. There were no obvious differences in genotype by age group.[21,22] In North European studies, Caucasians had frequencies between 10% and 20% for the homozygous C/C genotype.[21–26]

Summary and Discussion

Most of the identified research assessed subjective symptoms in an unblinded fashion, or an inability of individuals to fully absorb lactose irrespective of symptoms or lactase nonpersistence. Available data tended to be from highly selected populations and were not likely to be representative of the overall U.S. population. The prevalence rates varied substantially, depending on whether rates were reported by self-report of symptoms, symptoms following a lactose challenge, or from clinical tests of lactose malabsorption or lactase nonpersistence. Within each of these groups, prevalence rates also varied widely, depending on the source of the study population (e.g., patients referred for lactose intolerance testing, the general population, or a convenience sample of study participants).

Therefore, reliable estimates of U.S. prevalence rates for LI are not currently available, although there is some evidence that the magnitude of LI will be very low in young children and remain low into adult ages for most populations of Northern European descent. For African American, Hispanic, Asian, and American Indian populations, the rates of LI will likely be higher in late childhood and adulthood.

References

1. Newcomer AD, McGill DB. Disaccharidase activity in the small intestine: prevalence of lactase deficiency in 100 healthy subjects. *Gastroenterology.* 1967;53(6):881-889.

2. Woteki CE, Weser E, Young EA. Lactose malabsorption in Mexican-American adults. *Am J Clin Nutr.* 1977;30(4):470–475.

3. Woteki CE, Weser E, Young EA. Lactose malabsorption in Mexican-American children. *Am J Clin Nutr.* 1976;29(1):19–24.

4. Garza C, Scrimshaw NS. Relationship of lactose intolerance to milk intolerance in young children. *Am J Clin Nutr.* 1976;29(2):192–196.

5. Nicklas TA, Qu H, Hughes SO, Wagner SE, Foushee HR, Shewchuk RM. Prevalence of self-reported lactose intolerance in a multi-ethnic sample of adults. *Nutr Today.* 2009;44(5):222–227.

6. Barr RG, Levine MD, Watkins JB. Recurrent abdominal pain of childhood due to lactose intolerance. *N Engl J Med.* 1979;300(26):1449–1452.

7. Newcomer AD, McGill DB. Irritable bowel syndrome. Role of lactase deficiency. *Mayo Clin Proc.* 1983;58(5):339–341.

8. Tolliver BA, Herrera JL, DiPalma JA. Evaluation of patients who meet clinical criteria for irritable bowel syndrome. *Am J Gastroenterol.* 1994;89(2):176–178.

9. Webster RB, DiPalma JA, Gremse DA. Lactose maldigestion and recurrent abdominal pain in children. *Dig Dis Sci.* 1995;40(7):1506–1510.

10. Johnson JD, Simoons FJ, Hurwitz R, et al. Lactose malabsorption among adult Indians of the Great Basin and American Southwest. *Am J Clin Nutr.* 1978;(3):381–387.

11. Rao DR, Bello H, Warren AP, Brown GE. Prevalence of lactose maldigestion. Influence and interaction of age, race, and sex. *Dig Dis Sci.* 1994;39(7):1519-1524.

12. Scrimshaw NS, Murray EB. The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. *Am J Clin Nutr.* 1988;48(4 Suppl):1079–1159.

13. Carroccio A, Montalto G, Cavera G, Notarbatolo A. Lactose intolerance and self-reported milk intolerance: relationship with lactose maldigestion and nutrient intake. Lactase Deficiency Study Group. *J Am Coll Nutr.* 1998;17(6):631–636.

14. Leis R, Tojo R, Pavón P, Douwes A. Prevalence of lactose malabsorption in Galicia. *J Pediatr Gastroenterol Nutr.* 1997;25(3):296–300.

15. Maggi R, Sayagues B, Fernandez A, et al. Lactose malabsorption and intolerance in Uruguayan population by breath hydrogen test (H2). *J Pediatr Gastroenterol Nutr.* 1987;6(3):373–376.

16. Schirru E, Corona V, Usai-Satta P, et al. Decline of lactase activity and c/t-13910 variant in Sardinian childhood. *J Pediatr Gastroenterol Nutr.* 2007;45(4):503–506.

17. Tadesse K, Yuen RC, Leung DT. Late-onset hypolactasia in Hong Kong school children. *Ann Trop Paediatr.* 1991;11(3):289–292.

18. Ting CW, Hwang B, Wu TC. Developmental changes of lactose malabsorption in normal Chinese children: a study using breath hydrogen test with a physiological dose of lactose. *J Pediatr Gastroenterol Nutr.* 1988;7(6):848–851.

19. Yang Y, He M, Cui H, Bian L, Wang Z. The prevalence of lactase deficiency and lactose intolerance in Chinese children of different ages. *Chin Med J (Engl).* 2000;113(12):1129–1132.

20. Swallow DM. Genetics of lactase persistence and lactose intolerance. *Annu Rev Genet.* 2003;37:197–219.

21. Anthoni S, Elg P, Haahtela T, Kolho KL. Should milk-specific IgE antibodies be measured in adults in primary care? *Scand J Prim Health Care.* 2008;26(4):197–202.

22. Almon R, Engfeldt P, Tysk C, Sjostrom M, Nilsson TK. Prevalence and trends in adult-type hypolactasia in different age cohorts in central Sweden diagnosed by genotyping for the adult-type hypolactasia-linked LCT -13910C > T mutation. *Scand J Gastroenterol.* 2007;42(2):165–170.

23. Enattah N, Pekkarinen T, Välimäki MJ, Löyttyniemi E, Järvelä I. Genetically defined adult-type hypolactasia and self-reported lactose intolerance as risk factors of osteoporosis in Finnish postmenopausal women. *Eur J Clin Nutr.* 2005;59(10):1105–1111.

24. Enattah N, Valimaki VV, Välimäki MJ, Löyttyniemi E, Sahi T, Järvelä I. Molecularly defined lactose malabsorption, peak bone mass and bone turnover rate in young Finnish men. *Calcif Tissue Int.* 2004;75(6):488–493.

25. Lehtimäki T, Hemminki J, Rontu R, et al. The effects of adult-type hypolactasia on body height growth and dietary calcium intake from childhood into young adulthood: a 21-year follow-up study—the Cardiovascular Risk in Young Finns Study. *Pediatrics.* 2006;118(4):1553–1559.

26. Rasinperä H, Savilahti E, Enattah NS, et al. A genetic test which can be used to diagnose adult-type hypolactasia in children. *Gut.* 2004;53(11):1571–1576.

Consequences of Excluding Dairy, Milk Avoiders, Calcium Requirements in Children

Connie M. Weaver, Ph.D.

Milk products, along with fruits and vegetables and whole grains, were identified by the 2005 Dietary Guidelines Advisory Committee for Americans as foods that needed to be increased in order to meet nutrient needs and for improved health.[1] The role of milk products in meeting three nutrients for various age groups is illustrated in Table 1. Most food guidance patterns recommend 3 cups of low-fat dairy products daily. The table contrasts the proportion of individuals meeting the dairy recommendations with those receiving less than one serving of dairy products as assessed from data from the 1999–2004 National Health and Nutrition Examination Survey (NHANES).[2] The best and most economical source of the limiting nutrients is dairy.[3] Supplements typically do not fill the gap of all these nutrients for those who do not consume recommended intakes of dairy products. Using NHANES 2001–2002 data, Gao et al. determined that it is impossible to meet calcium recommendations while meeting other nutrient recommendations with a dairy-free diet within the current U.S. dietary pattern.[4] Using the 1999–2004 NHANES data, Nicklas et al. determined that <3% of the U.S. population met potassium recommendations and 55% did not even meet their Estimated Average Requirements for magnesium.[2]

Table 1. Role of Milk Products in Food Patterns: % of Recommendation in Children

	Age Group			
	2–8 years		9–18 years	
	With Dairy	Without Dairy	With Dairy	Without Dairy
Calcium	146	54	97	32
Potassium	70	73	59	38
Magnesium	254	160	114	69

With = 2.5–3.5 servings/day
Without = <1 serving/day

Data taken from Nicklas et al., 2009.[2]

The consequences of excluding dairy in the diet is most associated with compromised bone health and are most severe in childhood during development of peak bone mass. Lifelong projection of bone mass is illustrated in Figure 1. Bone accretion is high during the first year of life, but cow's milk is not recommended before the age of 1. Infants rely on breast milk or formula and on average meet their nutrient needs. The pubertal growth spurt depicted in Figure 2 is a critical time for building peak bone mass to protect against fracture risk as a child and later in life when osteoporosis affects 10 million Americans.[6] Almost half of adult peak bone mass is acquired during adolescence.[7] Because approximately 95% of adult peak bone mass is acquired by the age of 16.2 years,[8] nutrition can only influence peak bone mass appreciably before the end of adolescence. Thereafter, any benefits are geared to minimizing loss of peak bone mass, a much lower benefit for investment strategy.

Figure 1. Bone Mass and Life Stage: Influence of Calcium Intake

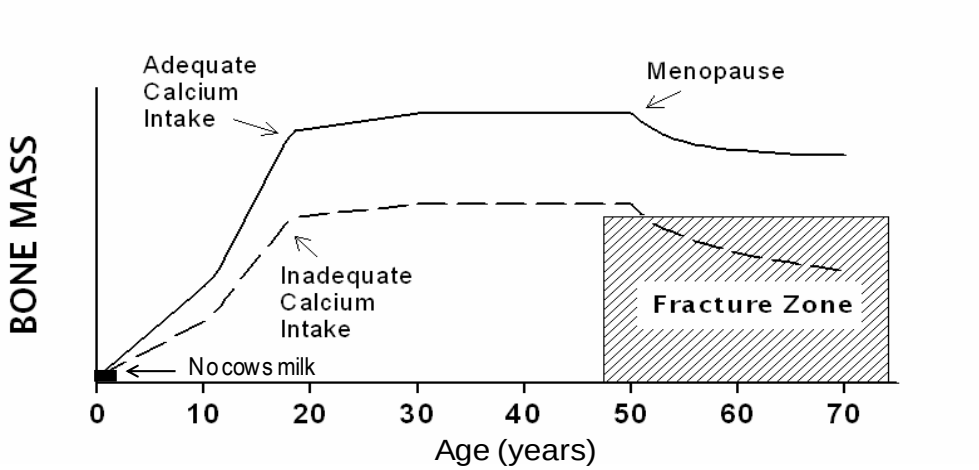
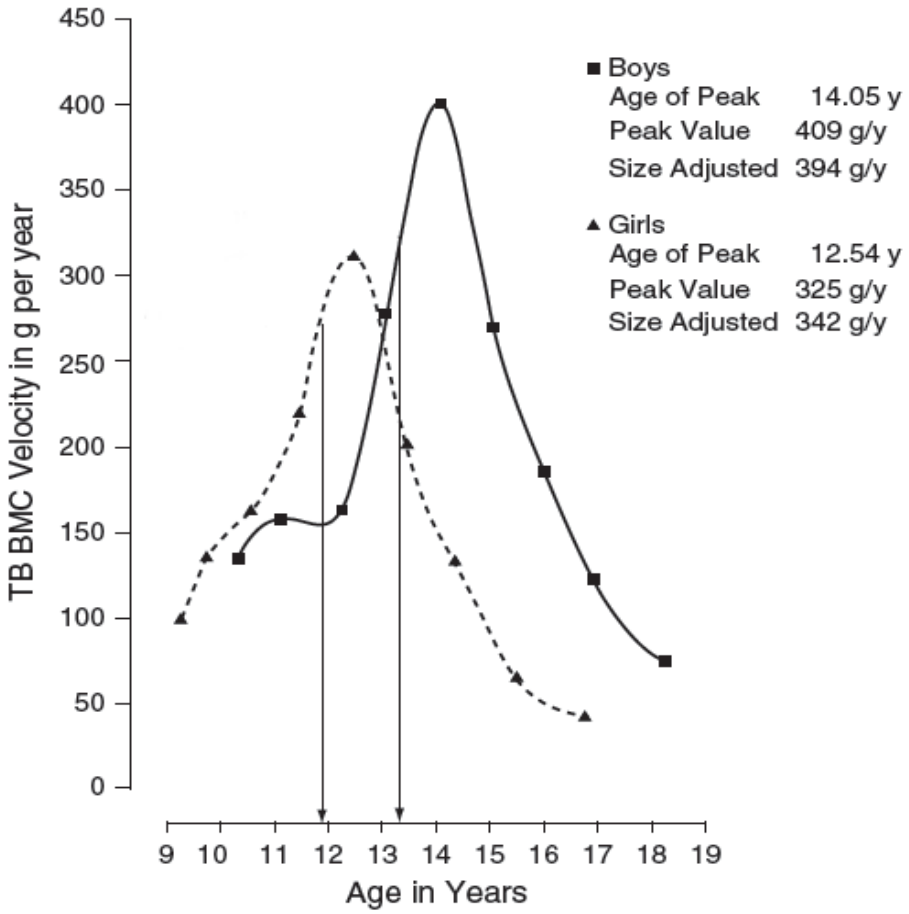


Figure 2. Total Body BMC Pubertal Growth Spurt

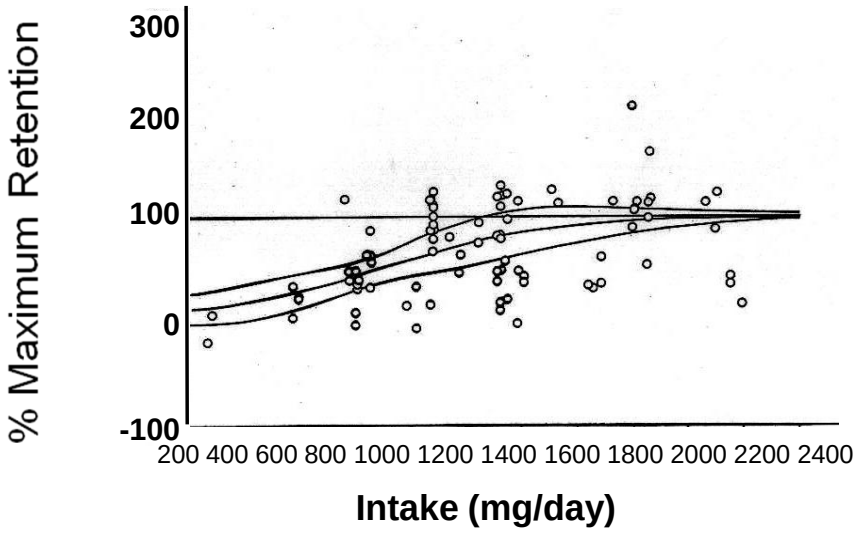


From Baily et al., 1999.[5]

Calcium intake recommendations were determined by the Institute of Medicine where possible as the calcium intake for attaining maximal calcium retention.[9] In adolescents, the data available for calcium balance were in white girls. From Figure 3, the 1997 adequate intake (AI) for calcium in children age 9–18 was determined to be 1,300 mg/d. Since then, calcium retention over a range of intakes has been determined for white boys[11,12] and black girls.[13] The calcium intakes for maximal skeletal accretion were not significantly different from the white girls. Calcium intake explained 12.3% of the variance in calcium retention in adolescent girls, and race explained 13.7%.[13] Recommendations for the key bone nutrients in children are given in Table 2. Recommendations for magnesium and phosphorus were based on the factorial method, which adjusts losses by growth and absorption efficiency.[9]

Figure 3. Maximal Calcium Retention as a Function of Intake

(Basis for Current Requirements)



From Jackman et al., 1997.[10]

Table 2. Dietary Reference Intakes for Bone-Related Nutrients in Children and Adolescents

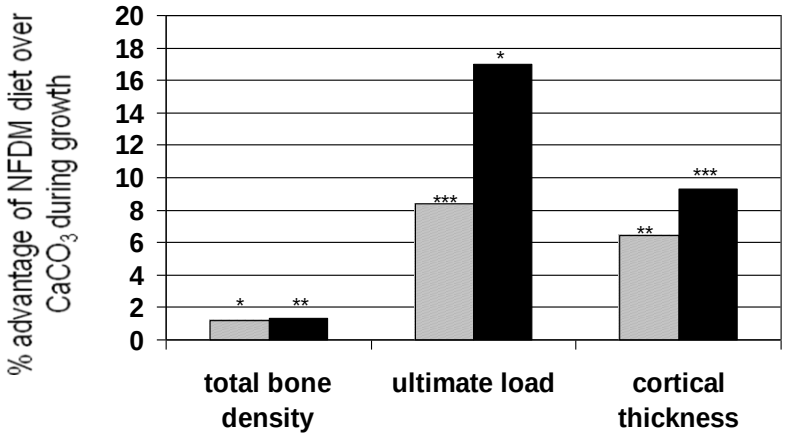
	Nutrient							
	Calcium (mg/day)		**Vitamin D (µg/day**		**Phosphorus (mg/day**		**Magnesium**	
Life Stage Group	**AI**	**UL**	**AI**	**UL**	**RDA**	**UL**	**RDA**	**UL**
(0–6 months)	210	ND	5	25			30[a]	ND
(7–12 months)	270	ND	5	25			75[a]	
(1–3 years)	500	2,500	5	50	380	3,000	80	65[b]
(4–8 years)	800	2,500	5	50	405	3,000	130	110[b]
9 through 18 years	1,300	2,500	5	50	1,055	4,000	240	350[b]
14 through 18 years	1,300	2,500	5	50	1,055	4,000		
(females)							360	350[b]
(males)							410	350[b]
Pregnancy ≤18 years	1,300	2,500	5	50	1,055	3,500	400	350[b]
Lactation ≤18 years	1,300	2,500	5	50	1,055	4,000	360	350[b]

[a]AI, Adequate Intake.
[b]Supplementary, not from food.

From Institute of Medicine, 1997.[9]

Benefits to growing bone by milk consumption appear to be more than merely providing required nutrients important to growing bone. In a growing rat model, when adequate dietary calcium was given as nonfat dry milk, bones were larger and stronger than when calcium was supplied as calcium carbonate.[14] Moreover, when rats were switched to the same low calcium diet during adulthood, rats fed nonfat dry milk during growth retained many of the advantages compared to rats fed calcium carbonate as shown in Figure 4. In humans, this phenomenon also appears to be true. A meta-analysis of trials of dairy products and dietary calcium on bone mineral content (BMC) in children showed significantly higher total body and lumbar spine BMC with higher intakes when the comparison group had low calcium intakes.[15] In a retrospective study of postmenopausal women in NHANES III, low milk intakes during childhood was associated with twice the risk of fracture.[16]

Figure 4. Percent increase in bone properties for femurs of young rats fed 0.4% calcium as nonfat dry milk (NFDM) diets over rats fed 0.4% calcium as CaCO3 for 10 weeks (slashed bars) and in rats switched to 0.2% calcium as CaCO3 after an additional 10 weeks (solid bars)



(n=50/group). * p<0.01, ** p<0.001, *** p<0.0001
From Weaver et al., 2009.[14]

Studies of milk avoiders compared to age-matched cohorts in the same population with geographical and cultural environment studies are the strongest type of observational studies as they are the least confounded by factors such as other dietary constituents, race, sunlight, and physical activity. Studies of this type show an advantage to milk drinking in both children and adults. Milk avoiders in New Zealand children had a fracture risk of 34.8% compared to 13.0% for matched cohorts.[17] In early pubertal girls in California and Indiana, perceived milk intolerance was inversely related to BMC of several bone sites (p=0.009 for the lumbar spine and trends for total hip, femoral neck, and total body).[18] In contrast, lactose maldigestion as measured by hydrogen breath analysis was not related to bone measures.

References

1. U.S. Department of Health and Human Services and U.S. Department of Agriculture. *Dietary Guideline for Americans, 2005.* 6th ed. Washington, DC: U.S. Government Printing Office; 2005.

2. Nicklas TA, O'Neil CE, Fulgoni VL. The role of dairy in meeting the recommendations for shortfall nutrients in the American Diet. *J Am Coll Nutr.* 2009;28(Suppl 1):73S–81S.

3. Fulgoni V III, Nichols J, Reed A, et al. Dietary consumption and related nutrient intake in African-American adults and children in the United States: continuing survey of food intakes by individuals 1994–1996, 1998, and the National Health and Nutrition Examination Survey 1999–2000. *J Am Diet Assoc.* 2007;107(2):256-264.

4. Gao X, Wilde PE, Lichtenstein AH, Tucker KL. Meeting adequate intake for dietary calcium without dairy foods in adolescents aged 9 to 18 years (National Health and Nutrition Examination Survey 2001–2002). *J Am Diet Assoc.* 2006;106(11):1759–1765.

5. Baily DA, McKay HA, Mirwald RL, et al. A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: The University of Saskatchewan Bone Mineral Accrual Study. *J Bone Miner Res.* 1999;14(10):1672–1679.

6. National Osteoporosis Foundation. Osteoporosis Fast Facts. nof.org/osteoporosis/diseasefacts.htm. Accessed October 26, 2009.

7. Heaney RP, Abrams S, Dawson-Hughes B, et al. Peak bone mass. *Osteoporosis Int.* 2000;11(12):985, 1009.

8. Teegarden D, Proulx WR, Martin BR, et al. Peak bone mass in young women. *J Bone Miner Res.* 1995;10(5):711–715.

9. Institute of Medicine. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington DC: National Academies Press; 1997.

10. Jackman LA, Millane SS, Martin BR, et al. Calcium retention in relation to calcium intake and postmenarcheal age in adolescent females. *Am J Clin Nutr.* 1997;66(2):327–333.

11. Braun M, Martin BR, Kern M, et al. Calcium retention in adolescent boys on a range of controlled calcium intakes. *Am J Clin Nutr.* 2006;84(2):414–418.

12. Hill K, Braun MM, Kern M, et al. Predictors of calcium retention in adolescent boys. *J Clin Endocrin Metab.* 2008;93(12):4743–4748.

13. Braun M, Palacios C, Wigertz K, et al. Racial differences in skeletal calcium retention in adolescent girls on a range of controlled calcium intakes. *Am J Clin Nutr.* 2007;85(6):1657–1663.

14. Weaver CM, Janle E, Martin B, et al. Dairy versus calcium carbonate in promoting peak bone mass and bone maintenance during subsequent calcium deficiency. *J Bone Miner Res.* 2009;24(8):1411–1419.

15. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: results of a meta-analysis. *Bone.* 2008;43(2):312–321.

16. Kalkwarf HJ, Khoury JC, Lamphear BP. Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in U.S. women. *Am J Clin Nutr.* 2003;77(1):257–265.

17. Goulding A, Rockell JE, Black RE, Grant AM, Jones IE, Williams SM. Children who avoid drinking cow's milk are at increased risk for prepubertal bone fractures. *J Am Diet Assoc.* 2004;104(2):250–253.

18. Matlik L, Savaiano D, McCabe G, VanLoan M, Blue CL, Boushey CJ. Perceived milk intolerance is related to bone mineral content in 10- to 13-year-old female adolescents. *Pediatrics.* 2007;120(3):e669–e677.

Consequences of Excluding Dairy or of Avoiding Milk in Adults

Robert P. Heaney, M.D., FACP, FACN

A preliminary question to be addressed is: Are individuals with lactose intolerance (perceived or real) milk avoiders? Common sense would suggest that they are, and the body of scientific evidence backs that up.[1–9] Fluid milk intake is certainly low in patients with lactose intolerance, and total dietary calcium intake is reported to be reduced by 33% to more than 80%. This is just as true for adults as it is for children.[10] Calcium tracer studies have shown that individuals with lactose maldigestion are nevertheless able to absorb calcium normally. Hence, so far as is known, the principal consequence of lactose intolerance is low dairy intake. Thus this brief review will focus on the latter, since its consequences will be the same for individuals with lactose intolerance as for those who avoid milk for any other reasons.

It must be acknowledged that, prior to the domestication of milk-producing animals, dairy was not a part of the human diet. It is sometimes argued that modern humans are the only species that drink the milk of another animal, but we are also the only species to wear the skins of other animals and the only species to cook our food. These are all indications of human adaptability, not of inappropriate behavior. With the paleolithic diet, it was relatively easy to get all of the micronutrients one required, simply as a byproduct of getting the calories needed to fuel daily energy expenditures. That is not easily possible with modern diets, which tend to be energy-rich and micronutrient-poor. It is exceedingly difficult (if not altogether impossible) to obtain a balanced diet from readily available food sources without including dairy.

The first, and perhaps the most obvious, nutrient concerned is calcium. Diets containing three servings of dairy foods per day typically meet the relevant calcium intake requirements, whereas diets deficient in dairy are not only deficient in calcium but in multiple other nutrients as well. Several years ago Barger-Lux and I[11] evaluated the diets of two large cohorts of women, rating them on whether they contained at least two-thirds of the recommended intake level for nine key nutrients. We found that individuals with inadequate calcium intakes were typically deficient in four of the other nine nutrients in addition to calcium. Thus, calcium intake was a marker of diet quality with high intakes (principally from dairy) indicating total diet adequacy, and low calcium intakes, polynutrient deficiency. This finding has been amply confirmed in other studies.[12]

The importance of ensuring an adequate calcium intake in its own right has been enshrined in several National Institutes of Health Consensus Development Conference reports,[13–15] as well as in the Surgeon General's Report on Bone Health and Osteoporosis.[16] Hence, I believe we can take it as a given that low calcium intake is harmful. Not only do individuals with lactose maldigestion have lower dairy intakes, they also have lower values for bone mineral density,[1–4,7,17] and higher risk for fracture,[1,2,18] thus establishing at least a skeletal consequence of dairy avoidance.

But it is an oversimplification to focus exclusively on single nutrients, even calcium. Nutrients are not drugs, and they do not act in a vacuum. Rather, like the instruments in a symphony orchestra, they produce their effects in concert with one another. A striking example of this mutual dependence is seen in the interaction of calcium and protein in the diet. Until recently, high protein intakes were considered to be potentially harmful for bone because of their effect on urinary calcium excretion. Increased calciuria was clearly demonstrated for protein and for pure amino acids, whether taken orally or intravenously.[19,20] However, when protein was fed as a food, strangely there was no effect on calcium balance.[21,22] More recently, it has become clear that calcium and protein, rather than antagonists, are actually synergistic in their skeletal effects.[23,24] In postmenopausal women with low protein intakes, increasing calcium intake can slow bone loss, but not much more. By contrast, with high protein intakes, added calcium leads to actual bone gain. This is an important consideration in our context because individuals with low dairy intakes are missing not only the calcium but also a rich source of dietary protein, which is as necessary for bone rebuilding as is the calcium that is the more obvious component of bony material.

But it does not stop there. Although potassium is abundant in the food chain and can be accessed in a number of different ways, in actual practice the single most important source of potassium in contemporary diets is dairy. The Scientific Committee of the Dietary Guidelines for Americans, in their 2005 deliberations, raised the recommended intake of dairy to three servings per day because it was the only way they could find to approach the then new potassium intake recommendations.[25] High potassium intakes are good not only for the whole body, but potassium itself has been associated positively with bone density as well.[26,27] This is also the case for magnesium,[26] which is another nutrient in short supply in the American diet and is reasonably abundant in dairy foods.

Is it easily possible to get all of these nutrients if one is a dairy avoider? Possible, but not easy. For example, soy beverages, which are marketed as substitutes for cow milk, are not dairy equivalent. The calcium added to these beverages to bring them up to the standard of dairy milk is less well absorbed than milk calcium,[28] and frequently is not even ingested, as it settles to the bottom of the carton as a difficult-to-suspend sludge.[29] Other calcium-fortified foods can help the body meet the calcium requirement, but they tend to lack the other nutrients present in milk. Calcium-fortified orange juice, which is a good food in its own right, simply does not provide the full suite of nutrients one would get from a dairy food. However, in some cases, calcium supplements do appear to offset the effects of low dairy consumption on bone mineral density.[5]

While the focus of this session is predominantly on skeletal effects, it should be stressed that inadequate dairy intake has multiple other consequences as well, including increased risk of metabolic syndrome, hypertension, preeclampsia, obesity, and certain forms of cancer, particularly colon cancer.[30–34] Thus milk avoidance is, for most adults, a risky behavior.

References

1. Obermayer-Pietschy BM, Bonelli CM, Walter DE, et al. Genetic disposition for adult lactose intolerance and relation to diet, bone density, and bone fractures. *J Bone Miner Res.* 2004;19(1):42–47.

2. Honkanen R, Kröger H, Alhava E, Turpeinen P, Tuppurainen M, Saarikoski S. Lactose intolerance associated with fractures of weight-bearing bones in Finnish women aged 38–57 years. *Bone.* 1997;21(6):473–477.

3. Honkanen R, Pulkkinen P, Järvinen R, et al. Does lactose intolerance predispose to low bone density? A population-based study of perimenopausal Finnish women. *Bone.* 1996;19:23–28.

4. Segal E, Dvorkin L, Lavy A, et al. Bone density in axial and appendicular skeleton in patients with lactose intolerance: influence of calcium intake and vitamin D status. *J Am Coll Nutr.* 2003;22(3):201–207.

5. Enattah N, Pekkarinen T, Välimäki MJ, Löyttyniemi E, Järvelä I. Genetically defined adult-type hypolactasia and self-reported lactose intolerance as risk factors of osteoporosis in Finnish postmenopausal women. *Eur J Clin Nutr.* 2005;59(10):1105–1111.

6. Lehtimäki T, Hemminki J, Rontu R, et al. The effects of adult-type hypolactasia on body height growth and dietary calcium intake from childhood into young adulthood: a 21-year follow-up study—The Cardiovascular Risk in Young Finns Study. *Pediatrics.* 2006;118(4):1553–1559.

7. Corazza GR, Benati G, Di Sario A, et al. Lactose intolerance and bone mass in postmenopausal Italian women. *Br J Nutr.* 1995;73(3):479–487.

8. Laaksonen MM, Mikkilä V, Räsänen L, et al. Genetic lactase non-persistence, consumption of milk products and intakes of milk nutrients in Finns from childhood to young adulthood. *Br J Nutr.* 2009;102(1):8–17.

9. Kull M, Kallihorm R, Lember M. Impact of molecularly defined hypolactasia, self-perceived milk intolerance and milk consumption on bone mineral density in a population sample in Northern Europe. *Scand J Gastroenterol.* 2009;44(4):415–421.

10. Goulding A, Rockell JE, Black RE, Grant AM, Jones IE, Williams SM. Children who avoid drinking cow's milk are at increased risk for prepubertal bone fractures. *J Am Diet Assoc.* 2004;104:250–253.

11. Barger-Lux MJ, Heaney RP, Packard PT, Lappe JM, Recker RR. Nutritional correlates of low calcium intake. *Clin Applied Nutr.* 1992;2(4):39–44.

12. Nicklas TA, O'Neil, CE, Fulgoni VL. The role of dairy in meeting the recommendations for shortfall nutrients in the American diet. *J Am Coll Nutr.* 2009;28(1):73S–81S.

13. Consensus Development Conference: prophylaxis and treatment of osteoporosis. *Am J Med.* 1991;90:107–110.

14. Consensus Development Conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med.* 1993;94:646–650.

15. NIH Consensus Development Panel on Optimal Calcium Intake. *J Am Med Assoc.* 1994;272(24)1942–1948.

16. U.S. Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General.* Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General; 2004.

17. Laaksonen MM, Impivaara O, Sievänen H, et al. Associations of genetic lactase non-persistence and sex with bone loss in young adulthood. *Bone.* 2009;44(5):1003–1009.

18. Kudlacek S, Freudenthaler O, Weissböeck H, Schneider B, Willvonseder R. Lactose intolerance: a risk factor for reduced bone mineral density and vertebral fractures? *J Gastroenterol.* 2002;37(12):1014–1019.

19. Margen S, Chu J-Y, Kaufmann NA, Calloway DH. Studies in calcium metabolism. I. The calciuretic effect of dietary protein. *Am J Clin Nutr.* 1974;27(6):584–589.

20. Bengoa JM, Sitrin MD, Wood RJ, Rosenberg IH. Amino acid-induced hypercalciuria in patients on total parenteral nutrition. *Am J Clin Nutr.* 1983;38(2):264–269.

21. Spencer H, Kramer L, DeBartolo M, Norris C, Osis D. Further studies of the effect of a high protein diet as meat on calcium metabolism. *Am J Clin Nutr.* 1983;37:924–929.

22. Roughead ZK, Johnson LK, Lykken GI, Hunt JR. Controlled high meat diets do not affect calcium retention or indices of bone status in healthy postmenopausal women. *J Nutr.* 2003;133:1020–1026.

23. Dawson-Hughes B, Harris SS. Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. *Am J Clin Nutr.* 2002;75:773–779.

24. Heaney RP. Effects of protein on the calcium economy. In: Burckhardt P, Heaney RP, Dawson-Hughes B, eds. *Nutritional Aspects of Osteoporosis 2006*. Amsterdam: Elsevier, Inc.; 2007:191–197.

25. U.S. Department of Health and Human Services and U.S. Department of Agriculture. Dietary Guidelines for Americans 2005 Advisory Committee Report. health.gov/dietaryguidelines/dga2005/document/html/executivesummary.htm. Accessed November 20, 2009.

26. Lanham-New SA. The balance of bone health: tipping the scales in favor of potassium-rich, bicarbonate-rich foods. *J Nutr.* 2008;138(1):172S–177S.

27. Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC Jr. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med.* 1994;330:1776–1781.

28. Heaney RP, Dowell MS, Rafferty K, Bierman J. Bioavailability of the calcium in fortified soy imitation milk, with some observations on method. *Am J Clin Nutr.* 2000;71:1166–1169.

29. Heaney RP, Rafferty K, Bierman J. Not all calcium-fortified beverages are equal. *Nutr Today*. 2005;40(1):39–44.

30. Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. *J Am Med Assoc.* 2002;287:2081–2089.

31. Heaney RP, Rafferty K. The preponderance of the evidence: an example from the issue of calcium intake and body composition. *Nutr Rev.* 2008;67(1):32–39.

32. Bucher HC, Guyatt GH, Cook RJ, et al. Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia. *J Am Med Assoc.* 1996;275:1113–1117.

33. Wu K, Willett WC, Fuchs CS, Colditz GA, Giovannucci EL. Calcium intake and risk of colon cancer in women and men. *J Natl Cancer Inst.* 2002;94(6):437–446.

34. Cho E, Smith-Warner SA, Spiegelman D, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst.* 2004;96(13):1015–1022.

Evidence-based Practice Center Presentation II: The Bone Health Outcomes of Dairy-Exclusion Diets

Timothy J. Wilt, M.D., M.P.H.; Aasma Shaukat, M.D., M.P.H.; Tatyana Shamliyan, M.D., M.S.; Brent C. Taylor, Ph.D., M.P.H.; Roderick MacDonald, M.S.; James Tacklind; Indulis Rutks; Sarah Jane Schwarzenberg, M.D.; Robert L. Kane, M.D.; Michael Levitt, M.D.

Objectives

We reviewed evidence to determine bone health after dairy-exclusion diets.

Data Sources

We searched multiple electronic databases for original studies published in English from 1967–October 2009.

Methods

Fractures, bone mineral content (BMC), and bone mineral density (BMD) were compared in categories of lactose intake. We included studies that compared outcomes among populations reporting, or randomized, to consume diets very low in or free from lactose. We included the following populations: general, vegans, lactase nonpersisters, diagnosed or self-identified lactose intolerant (LI), or lactose malabsorber. Dietary recall may be unreliable, and our search identified few studies meeting these criteria. Therefore, we included studies that examined the association between individuals classified as LI, lactose malabsorbers, or lactase deficient and health outcomes even if they did not specifically state the amount of lactose/dairy consumed because evidence suggested that these populations were likely to consume diets low in lactose. We excluded the studies of patients with milk allergies, irritable bowel syndrome, chronic diarrhea, gastroenteritis, or other diagnosed gastrointestinal diseases.

Results

We identified 52 observational studies of 218,837 subjects who reported the association between lactose intake and bone health and nine randomized controlled clinical trials that provided causal effects of lactose intake on bone health. African American women were enrolled in one study.[1] The absence of specific documentation of the amount of lactose or dairy calcium consumed over long periods of time hampered synthesis of evidence in populations that are presumed to have low dairy intake.

Vegan children consumed 47% and vegan women 30% of the recommended dietary calcium intake. Among those with LI, children consumed 45% and women 37% of recommended dietary calcium. Among those with lactose malabsorption (LM), adults

consumed 44% and women consumed 50% of the recommended dietary calcium. Daily calcium intake was 32% of recommended values in women with LM and LI. Women with CC genetic polymorphism consumed 48% of recommended dairy calcium from all sources and 34% from milk. Men with CC genetic polymorphism consumed 58% of recommended dairy calcium from all sources and 1.3% from milk. Children with CC genetic polymorphism consumed 80% of recommended dietary calcium. Adults with CC genotype reported reduced milk intake.[2–5] The association was more consistent for women.[6,7] The association may diminish with aging.[8,9] Among children who avoided milk, those diagnosed with LI had much greater odds of milk-related symptoms.[10]

Observational studies showed that low milk consumers had fractures more frequently than populations with higher milk consumption. We considered the level of evidence low due to inconsistencies in the magnitude of the association and adjustments for confounding factors.[10–22] Two industry-sponsored studies reported that children who avoid milk intake for more than 4 months had increased risk of bone fractures.[10,11]

Evidence from nine studies of 111,485 adult women suggested an increase in risk of fracture in association with low dairy intake; however, only five reported a significant association.[12–20] Well-designed observational studies of men did not find a significant association between any osteoporotic or hip fracture and low milk intake.[21,22] One large cohort reported that vegans had increased relative risk of fractures compared to the general population.

The association between a single nucleotide polymorphism of the lactase (LCT) gene at chromosome 2q21-22 (associated with lactase deficiency and reduced lactose intake) and fractures in elderly adults was examined in five publications[3,6,7,23,24] with inconsistent increase in fractures in postmenopausal women.[6,7,23] One population-based study of 601 Finnish elderly adults found that those with CC genotype had more than a three-fold increase in crude odds of hip fracture and nearly a two-fold increase in crude odds of wrist fracture when compared to TT genotype.[3]

One study reported that children who avoided drinking cow's milk because of perceived milk intolerance did not have higher rates of fracture compared to milk avoiders who did not report symptoms of intolerance.[23] Finnish postmenopausal women with lactose intolerance did not have greater risk of any vertebral or nonvertebral fracture when compared to healthy women.[23] Austrian men and women with self-reported symptoms of LI during the hydrogen breath test had a 96% increase in crude odds of any fracture (odds ratio 1.96, 95% confidence interval 1.11; 3.48).[25] Estonian men and women with self-reported milk intolerance had increased crude odds of osteoporotic fracture.[5]

Low-level evidence indicates that adults with lactose-free or low lactose diets had osteopenia more often than controls.[26–28] Four studies demonstrated that children from Europe,[29] Asia,[30] or New Zealand[10,31] with lactose-free or low lactose diets had reduced BMC and BMD.[10,29–31]

A moderate level of evidence from randomized trials suggested that increased lactose intake resulted in improved BMC of the lumbar spine and femoral neck in prepubertal children with low-baseline milk intake (less than 50% of recommended calcium intake). Lactose effects were causal and direct, but the effect size varied across the studies and lowered the level of evidence. Dairy intervention with 1,794 or 1,067 mg of calcium per day compared to 400–879 mg of calcium per day for 12 months resulted in a significant increase in total body BMC in boys and girls from Hong Kong.[32] One randomized controlled trial that included prepubertal children with very low-baseline milk intake reported significant increases in total body BMC after dairy administration that provided 1,200 mg of calcium per day.[33] The effect, however, was not significant at 18 months of follow-up.[33] Lumbar spine BMC was increased in three randomized controlled trials,[32–34] while two trials did not report significant changes.[35,36] Children from Hong Kong with very low-baseline calcium intake had the greatest increase in lumbar spine BMC.[32] Dairy intervention increased lumbar spine BMC in girls[34] but not in boys.[35] The improvement in BMD was less evident.

Conclusions

Observational studies of different quality provided low-level evidence that childhood milk avoidance may be associated with increased risk of bone fractures. Selected adult populations with CC genotype, symptoms of milk intolerance, or diagnosed LM and reduced lactose intake may have increased odds of bone fracture. One large cohort reported that vegan vegetarians had increased relative risk of fractures. The effects of lactose-free or low lactose diet were more evident in women. Increasing lactose intake in children and adults with lactose-free or low lactose diets may increase BMC and BMD. The magnitude and significance varied across the studies, depending on the populations, definitions of exposure, time of follow-up, and types of bone measured.

References

1. Buchowski MS, Semenya J, Johnson AO. Dietary calcium intake in lactose maldigesting intolerant and tolerant African-American women. *J Am Coll Nutr.* 2002;21(1):47–54.

2. Lehtimaki T, Hemminki J, Rontu R, et al. The effects of adult-type hypolactasia on body height growth and dietary calcium intake from childhood into young adulthood: a 21-year follow-up study—the Cardiovascular Risk in Young Finns Study. *Pediatrics.* 2006;118(4):1553–1559.

3. Enattah NS, Sulkava R, Halonen P, Kontula K, Jarvela I. Genetic variant of lactase-persistent C/T-13910 is associated with bone fractures in very old age. *J Am Geriatr Soc.* 2005;53(1):79–82.

4. Gugatschka M, Dobnig H, Fahrleitner-Pammer A, et al. Molecularly-defined lactose malabsorption, milk consumption and anthropometric differences in adult males. *QJM.* 2005;98(12):857–863.

5. Kull M, Kallikorm R, Lember M. Impact of molecularly defined hypolactasia, self-perceived milk intolerance and milk consumption on bone mineral density in a population sample in northern Europe. *Scand J Gastroenterol.* 2009;44(4):415–421.

6. Obermayer-Pietsch BM, Bonelli CM, Walter DE, et al. Genetic predisposition for adult lactose intolerance and relation to diet, bone density, and bone fractures. *J Bone Miner Res.* 2004;19(1):42–47.

7. Obermayer-Pietsch BM, Gugatschka M, Reitter S, et al. Adult-type hypolactasia and calcium availability: decreased calcium intake or impaired calcium absorption? *Osteoporos Int.* 2007;18(4):445–451.

8. Goulding A, Taylor RW, Keil D, Gold E, Lewis-Barned NJ, Williams SM. Lactose malabsorption and rate of bone loss in older women. *Age Ageing.* 1999;28(2):175-180.

9. Horowitz M, Wishart J, Mundy L, Nordin BE. Lactose and calcium absorption in postmenopausal osteoporosis. *Arch Intern Med.* 1987;147(3):534–536.

10. Black RE, Williams SM, Jones IE, Goulding A. Children who avoid drinking cow milk have low dietary calcium intakes and poor bone health. *Am J Clin Nutr.* 2002;76(3):675–680.

11. Goulding A, Rockell JE, Black RE, Grant AM, Jones IE, Williams SM. Children who avoid drinking cow's milk are at increased risk for prepubertal bone fractures. *J Am Diet Assoc.* 2004;104(2):250–253.

12. Kelsey JL, Browner WS, Seeley DG, Nevitt MC, Cummings SR. Risk factors for fractures of the distal forearm and proximal humerus. The Study of Osteoporotic Fractures Research Group. *Am J Epidemiol.* 1992;135(5):477–489.

13. Nieves JW, Grisso JA, Kelsey JL. A case-control study of hip fracture: evaluation of selected dietary variables and teenage physical activity. *Osteoporos Int.* 1992;2(3):122–127.

14. Wyshak G, Frisch RE, Albright TE, Albright NL, Schiff I, Witschi J. Nonalcoholic carbonated beverage consumption and bone fractures among women former college athletes. *J Orthop Res.* 1989;7(1):91–99.

15. Tavani A, Negri E, La Vecchia C. Calcium, dairy products, and the risk of hip fracture in women in northern Italy. *Epidemiology.* 1995;6(5):554–557.

16. Johnell O, Gullberg B, Kanis JA, et al. Risk factors for hip fracture in European women: the MEDOS Study. Mediterranean Osteoporosis Study. *J Bone Miner Res.* 1995;10(11):1802–1815.

17. Feskanich D, Willett WC, Stampfer MJ, Colditz GA. Milk, dietary calcium, and bone fractures in women: a 12-year prospective study. *Am J Public Health.* 1997;87(6):992–997.

18. Turner LW, Wang MQ, Fu Q. Risk factors for hip fracture among southern older women. *South Med J.* 1998;91(6):533–540.

19. Johansson H, Oden A, Johnell O, et al. Optimization of BMD measurements to identify high risk groups for treatment—a test analysis. *J Bone Miner Res.* 2004;19(6):906–913.

20. Kalkwarf HJ, Khoury JC, Lanphear BP. Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in US women. *Am J Clin Nutr.* 2003;77(1):257–265.

21. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int.* 2005;16(7):799–804.

22. Fujiwara S, Kasagi F, Yamada M, Kodama K. Risk factors for hip fracture in a Japanese cohort. *J Bone Miner Res.* 1997;12(7):998–1004.

23. Enattah N, Pekkarinen T, Valimaki MJ, Loyttyniemi E, Jarvela I. Genetically defined adult-type hypolactasia and self-reported lactose intolerance as risk factors of osteoporosis in Finnish postmenopausal women. *Eur J Clin Nutr.* 2005;59(10):1105 1111.

24. Gugatschka M, Hoeller A, Fahrleitner-Pammer A, et al. Calcium supply, bone mineral density and genetically defined lactose maldigestion in a cohort of elderly men. *J Endocrinol Invest.* 2007;30(1):46–51.

25. Kudlacek S, Freudenthaler O, Weissboeck H, Schneider B, Willvonseder R. Lactose intolerance: a risk factor for reduced bone mineral density and vertebral fractures? *J Gastroenterol.* 2002;37(12):1014–1019.

26. Chiu JF, Lan SJ, Yang CY, et al. Long-term vegetarian diet and bone mineral density in postmenopausal Taiwanese women. *Calcif Tissue Int.* 1997;60(3):245 249.

27. Di Stefano M, Veneto G, Malservisi S, et al. Lactose malabsorption and intolerance and peak bone mass. *Gastroenterology.* 2002;122(7):1793–1799.

28. Birge SJ, Jr, Keutmann HT, Cuatrecasas P, Whedon GD. Osteoporosis, intestinal lactase deficiency and low dietary calcium intake. *N Engl J Med.* 1967;276(8):445 448.

29. Parsons TJ, van Dusseldorp M, van der Vliet M, van de Werken K, Schaafsma G, van Staveren WA. Reduced bone mass in Dutch adolescents fed a macrobiotic diet in early life. *J Bone Miner Res.* 1997;12(9):1486–1494.

30. Du XQ, Greenfield H, Fraser DR, Ge KY, Liu ZH, He W. Milk consumption and bone mineral content in Chinese adolescent girls. *Bone.* 2002;30(3):521–528.

31. Rockell JE, Williams SM, Taylor RW, Grant AM, Jones IE, Goulding A. Two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. *Osteoporos Int.* 2005;16(9):1016–1023.

32. Lau EM, Lynn H, Chan YH, Lau W, Woo J. Benefits of milk powder supplementation on bone accretion in Chinese children. *Osteoporos Int.* 2004;15(8):654–658.

33. Gibbons MJ, Gilchrist NL, Frampton C, et al. The effects of a high calcium dairy food on bone health in pre-pubertal children in New Zealand. *Asia Pac J Clin Nutr.* 2004;13(4):341–347.

34. Bonjour JP, Carrie AL, Ferrari S, et al. Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind, placebo-controlled trial. *J Clin Invest.* 1997;99(6):1287–1294.

35. Chevalley T, Bonjour JP, Ferrari S, Hans D, Rizzoli R. Skeletal site selectivity in the effects of calcium supplementation on areal bone mineral density gain: a randomized, double-blind, placebo-controlled trial in prepubertal boys. *J Clin Endocrinol Metab.* 2005;90(6):3342–3349.

36. Cheng S, Lyytikainen A, Kroger H, et al. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10- to 12-y-old girls: a 2-y randomized trial. *Am J Clin Nutr.* 2005;82(5):1115–1126.

Adaptation to Lactose Intolerance

Andrew Szilagyi, M.D., FACN

Adaptation to lactose intolerance means symptomatic reduction by regular ingestion of lactose-containing foods without the use of lactose digestive enzymes. This may allow increased quantities to be consumed and is restricted to lactase-nonpersistent (LNP) persons (maldigesters).[1–3]

In the first clinical study, a 50% reduction of symptoms (mainly bloat and gas) was achieved accompanied by reduced hydrogen responses that mimicked phenotypic lactase-persistent (LP) persons.[2] Using lactulose as an adapter to lactose, a 50% reduction of overall symptoms also was attained (itemization not done) but without a phenotypic LP hydrogen response.[4] Subsequent studies showed that at physiological doses (low dose) LP and LNP persons could not distinguish symptoms with lactose or placebo.[5–7] It is estimated that about 6–9 g of single-dose lactose is still digestible in LNP.[8,9] A daily intake of about 15–20 g was suggested to be necessary for adaptation to be instigated.[10]

The mechanism(s) of this process has been attributed to several, probably interrelated, variables.

1. *Subjective effects*: Learning experience may be acquired with continued consumption.[11] Many persons with LNP overstate symptoms,[12] and many LP persons also believe themselves to be intolerant, although with less severe symptoms.[10]

2. *Altered intestinal transit and substrate delivery:* Pregnant LNP persons improve symptoms throughout pregnancy and may worsen after delivery.[13,14] As a model, symptomatic improvement was achieved in men undergoing lactose challenge tests after Imodium pretreatment. This drug prolongs intestinal transit time and also increases absorption of fluids and electrolytes, possibly mimicking progesterone.[15]

3. *Direct induction of intestinal lactase*: This occurs in small animals[16,17] but not in man.[18] Also in the above example of a progesterone effect, there is no evidence of *in vitro* lactase induction in Caco-2 cells.[19]

4. *Failure of lactase induction*: This leads to bypass of intestinal digestion and effects on colon bacteria, predominantly in LNP. Although it is postulated that LP persons consuming high doses of lactose may derive such benefits,[20] to date there are no data to support this view over a short time period.[21,22]

Selective bacterial promotion is supported by the following evidence: (1) *In vitro*, lactose consumption is reconstituted by lactobacilli and bifidobacteria.[23,24] **(**2) An *in vitro* prebiotic index of lactose of 5.75 (ratio of increased lactic-acid-producing bacteria to

decreased clostridia and bacteroides) is described.[25] (3) Induction of bifidobacteria in a colonic model is reported.[26] (4) Short-term human induction of lactobacilli[27] and bifidobacteria[11,27] is noted. Ito and Kimura also found reductions in bacteroides and clostridia.[27]

Measurement of breath hydrogen and fecal bacterial beta-galactosidase activity constitutes a physiological test of the lactose adaptive process. The concept was described more than a decade and a half ago. It was shown *in vitro* that decreased hydrogen was due to reduction in hydrogen production and was accompanied by increased bacterial lactase in the stool after lactose rechallenge.[2,28] Based on such, time to symptomatic adaptation ranges from 16 days to months (months based on observational studies, average 2 to 4 weeks in laboratory studies). Upon discontinuation, lingering effects occur but again the timing is not clear. Although beta-galactosidase returns to baseline in 48 hours,[2] the effect on reduction of hydrogen and symptoms is less well defined.

Early colonic events are not clear either. Fecal beta-galactosidase increased two- to three-fold after 2–3 weeks.[2–4] However, bacterial expansion occurs after 6 days.[27] Alternatively, Tannock et al. showed in a 3-week trial that early response to oligosaccharides may be associated with enhanced bacterial metabolism without colony expansion.[29] Merely consuming lactic-acid-producing bacteria does not improve symptoms of lactose intolerance or hydrogen response.[30] Selectivity for oligofructose metabolism by bifidobacteria was shown to be inversely dependent on differential rates and substrate chain length.[31] Similar differential metabolic advantages for galacto-oligosaccharides (and hence possibly lactose) also may exist.[32]

Possible Epidemiologic Relevance of Adaptation

Differential interaction between lactose and LP/LNP status, with a prebiotic effect in LNP and less so or none in LP, might influence certain disease risks under natural conditions. An inverse relationship between risks of “Western” diseases and national population distribution of LP/LNP status and dairy food consumption was described.[33] In particular, colorectal cancer data at the patient level exhibited an unusual association with dairy foods (protective) versus the epidemiological data (suggesting increased risk). Crude analysis suggested that protection occurred both in high dairy-consuming, high LP populations and low dairy-consuming, high LNP populations.[34] While putative “protectors” in dairy foods are attributed to calcium and/or conjugated linoleic acid, demonstration of a prebiotic effect of lactose predominantly in LNP populations forces examination of the bacterial role in protection. Other diseases may be similarly affected.

Summary and Conclusions

Multiple studies have shown that at physiological doses of lactose, symptom issues are subjective. Since prebiotic effects may alter some disease risks in LNP, further evaluation should be placed on determining such possibilities.

References

1. Scrimshaw NS, Murray EB. The acceptability of milk and milk products in populations with high prevalence of lactose intolerance. *Am J Clin Nutr.* 1988;48(4 Suppl):1079–1159.

2. Hertzler SR, Savaiano DA. Colonic adaptation to daily lactose feeding in lactose maldigesters reduces lactose intolerance. *Am J Clin Nutr.*1996;64:232–236.

3. Pribila BA, Hertzler SR, Martin BR, et al. Improved lactose digestion and intolerance among African-American adolescent girls fed a dairy-rich diet. *J Am Diet Assoc.* 2000;100:524–528.

4. Szilagyi A, Rivard J, Fokeeff K. Improved parameters of lactose maldigestion using lactulose. *Dig Dis Sci.* 2001;46:1509–1519.

5. Vesa TH, Korpela RA, Sahi T. Tolerance to small amounts of lactose in lactose maldigesters. *Am J Clin Nutr.* 1996;64:197–201.

6. Suarez FL, Savaiano DA, Levitt MD. A comparison after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med.* 1995;333:1–4.

7. Suarez FL, Savaiano DA, Adrisi P, Levitt MD. Tolerance to the daily ingestion of two cups of milk by individuals claiming lactose intolerance. *Am J Clin Nutr.* 1997;65:1502–1506.

8. Oku T, Nakamura S, Ichinose M. Maximum permissive dose of lactose and lactitol for transitory diarrhea, and utilizable capacity for lactose in Japanese female adults. *J Nutr Sci Vitaminol.* 2005;51:51–57.

9. Hertzler SR, Huynh, Savaiano DA. How much lactose is low lactose? *J Am Diet Assoc.* 1996;96:243–246.

10. Szilagyi A, Malolepszy P, Yesovitch S, et al. Inverse dose effect of pretest dietary lactose on hydrogen results and symptoms in lactase nonpersistent subjects. *Dig Dis Sci.* 2005;50:2178–2182.

11. Briet F, Pochart P, Marteau P, et al. Improved clinical tolerance to chronic lactose ingestion in subjects with lactose intolerance: a placebo effect? *Gut.* 1997;41:632-635.

12. Savaiano DA, Boushey CJ, McCabe GP. Lactose intolerance symptoms assessed by meta-analysis: a grain of truth that leads to exaggeration. *J Nutr.* 2006;136:1107-1113.

13. Villar J, Kestler E, Castillo P, et al. Improved lactose digestion during pregnancy: a case of physiologic adaptation? *Obstet Gynecol.* 1988;71:697–700.

14. Szilagyi A, Salamon R, Martin M, et al. Lactose handling by women with lactose malabsorption is improved during pregnancy. *Clin Invest Med.* 1996;19:416–426.

15. Szilagyi A, Salomon R, Seidman E. Influence of loperimide on lactose handling and oral-caecal transit time. *Aliment Pharmacol Ther.* 1996;10:765–770.

16. Yeh KY, Yeh M, Holt PR. Thyroxine and cortisone cooperate to modulate postnatal intestinal enzyme differentiation in the rat. *Am J Physiol.* 1991;260:G371–G378.

17. Peuhkuri K, Hukkanen M, Beale R, et al. Age and continuous lactose challenge modify lactase protein expression and enzyme activity in gut epithelium in the rat. *Am J Physiol Pharmacol.* 1997;48:719–729.

18. Gilat T, Russo S, Gelman-Malachi E, Aldor TA. Lactase in man: a non-adaptable enzyme. *Gastroenterology.* 1972;62:1125–1127.

19. Salomon R, Levy E, Levesque D, et al. Caco-2 cell disaccharidase activities are unaffected by gestational hormones. *Can J Physiol Pharmacol.* 1996;74:1126–1131.

20. Bond JH, Levitt MD. Quantitative measurement of lactose absorption. *Gastroenterology.* 1976;70:1058–1062.

21. Szilagyi A, Shrier I, Heilpern D, et al. Differential impact of lactose/lactase phenotype on colonic microflora. (Abstract). *Microb Ecol.* 2009;57:562–588.

22. Farnworth ER, Chouinard YP, Jacques H, et al. The effect of drinking milk containing conjugated linoleic acid on fecal microbiological profile, enzymatic activity, and fecal characteristics in humans. *Nutr J.* 2007;6:15. Published online 2007 July 9; doi:10.1186/1475-2891-6-15.

23. Jiang T, Savaiano DA. *In vitro* lactose fermentation by human colonic bacteria is modified by *Lactobacillus acidophilus* supplementation. *J Nutr.* 1997;1237:1489–1495.

24. Jiang T, Savaiano DA. Modification of colonic fermentation by bifidobacteria and pH *in vitro*. Impact on lactose metabolism, short-chain fatty acid, and lactate production. *Dig Dis Sci.* 1997;42:2370–2377.

25. Luz Sanz M, Gibson GR, Rastall RA. Influence of disaccharide structure on prebiotic activity *in vitro*. *J Agric Food Chem.* 2005;53:5192–5199.

26. Makivuokko HA, Saarinen MT, Ouwehand AC, Rautonen NE. Effects of lactose on colon microbial community structure and function in a four-stage semi-continuous culture system. *Biosci Biotechno Biochem.* 2006;70:2056–2063.

27. Ito M, Kimura M. Influence of lactose on faecal microflora in lactose maldigesters. *Microb Ecol Health Dis.*1993;6:73–76.

28. Hertzler SR, Savaiano DA, Levitt, MD. Fecal hydrogen production and consumption measurements. Response to daily lactose ingestion by lactose maldigesters. *Dig Dis Sci.*1997;42:348–353.

29. Tannock GW, Munro K, Bibiloni R, et al. Impact of consumption of oligosaccharide-containing biscuits on fecal microbiota of humans. *Appl Environment Microbiol.* 2004;70:2129–2136.

30. Malolepszy P, Shrier I, Szilagyi A. Adaptation to lactose intolerance may not be achieved by long term ingestion of a multi-species containing probiotic: an extended preliminary study. *Intern J Probio Prebio.* 2006;1:113–120.

31. Falony G, Calmeyn T, Leroy F, et al. Coculture fermentations of *Bifidobacterium* species and *Bacteroides thetaiotaomicron* reveal a mechanistic insight into the prebiotic effect of inulin-type fructans. *Appl Environ Microbiol.* 2009;75:2312–2319.

32. Macfarlane GT, Steed H, Macfarlane S. Bacterial metabolism and health-related effects of galacto-oligosaccharides and other prebiotics. *J Appl Microbiol.* 2008;104:305–344.

33. Shrier I, Szilagyi A, Correa JA. Impact of lactose-containing foods and the genetics of lactase on diseases: an analytical review of population data. *Nutr Cancer.* 2008;60:292–300.

34. Szilagyi A, Nathwani U, Vinokuroff C, et al. The effect of lactose maldigestion on the relationship between dairy food intake and colorectal cancer: a systematic review. *Nutr Cancer.* 2006;55:141–150.

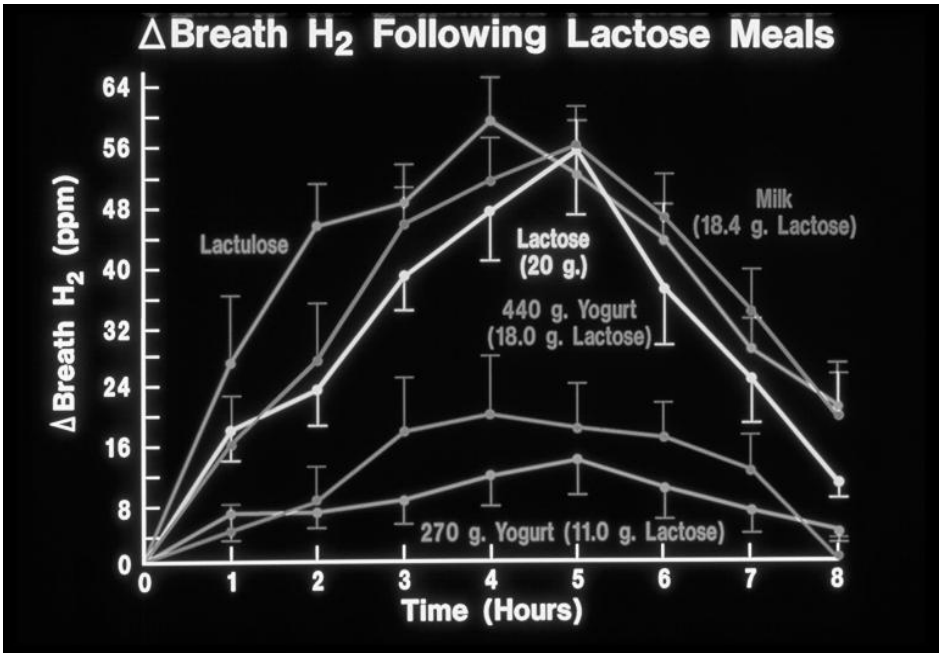
Dosing, Symptoms, and Tolerable Doses of Lactose

Dennis A. Savaiano, Ph.D.

What amount of lactose will cause symptoms in individuals who are lactase nonpersistent? The following factors (and likely additional ones not yet considered) will influence the relationship between dose of lactose and symptoms:

1. **Meal feeding and lactose tolerance:** The most practical approach for improving lactose tolerance is to consume milk with meals. Consuming lactose-containing foods as part of a meal has been shown to increase the time to peak breath hydrogen, decrease overall hydrogen production, and dramatically decrease symptoms of intolerance (by several-fold) in lactose maldigesters.[1,2] Other gastrointestinal transit-related factors that have been studied include altering the energy content, viscosity, temperature, and fat content of milk. These factors appear to have a much smaller or negligible effect on lactose tolerance.[3–5]

2. **Food source of lactose:** The lactose content of dairy foods varies significantly. Milk contains approximately 12 g of lactose in a typical 8-ounce serving. Hard cheeses contain little or no lactose, as the water-soluble whey is removed from the curds prior to final cheese production. Soft cheeses and ice creams typically contain intermediate levels of lactose per serving. In addition, the high solids content of ice creams and ice milks tends to modestly blunt the breath hydrogen and symptom response.[6] Yogurts are well tolerated by lactose maldigesters, primarily due the presence of high levels of microbial beta-galactosidase in the yogurt culture.



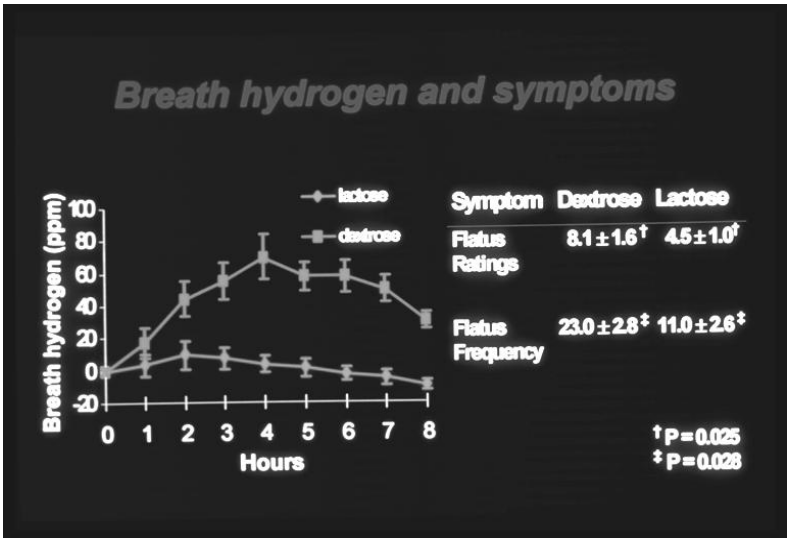
This activity is functional *in vivo* during intestinal digestion.[7] This effect is lost if the yogurt is heat killed or if minimal yogurt bacteria are included in the product, such as is the case with typical frozen yogurts.[8,9]

3. **Body size (GI capacity):** This likely influences tolerance simply by dilution and transit. Some studies have controlled this variable, feeding lactose on a kg body weight basis, while others have ignored it.

4. **Timing of the doses:** Lactose intolerance appears to be an acute effect due to a single dose of lactose as it transits through the intestine. If a total of approximately 25 g lactose is consumed as two separate doses of 12 g each at breakfast and dinner, symptoms are minimal.[10] Lactose maldigesters tolerate even a large amount of lactose (34 g or more) on a daily basis if the total dose is subdivided into smaller doses (i.e., 12 g or less) throughout the day.[10,11] Thus, lactose consumed at breakfast does not appear to contribute to potential symptoms from lactose consumed at lunch or dinner.

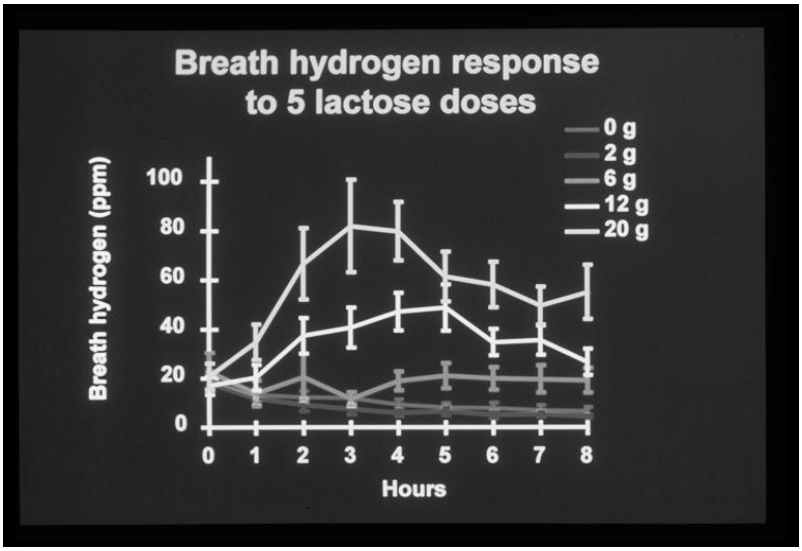
5. **Residual mammalian lactase:** Residual lactase in the small bowel (perhaps based on genetic variation and multiple phenotypes) likely is an additional factor that influences tolerance. Bond and Levitt,[12] using an intestinal intubation technique, demonstrated that lactose maldigesters may absorb anywhere from 42–75% of a 12.5 g lactose dose. The effect of variation in residual lactase on tolerance has not been elucidated.

6. **Colon adaptation:** Based on past history of lactose consumption, colon adaptation is likely a major factor in the variability in tolerance among nonpersistent individuals. Regular consumption of lactose has been shown to improve tolerance dramatically through adaptation of large intestinal metabolism.[13]



The effect is likely due to both microbial adaptation and selection. Tolerance is significantly improved and breath hydrogen is dramatically reduced in adapted individuals, while fecal beta-galactosidase is elevated six-fold. The enhancement of hydrogen utilization by the adapted colonic flora has been shown *in vitro.*[14]

7. **Dose-response:** Any study of dose-response to lactose must attempt to take into account as many of the above variables as is feasible along with appropriate blinding. Between 80% and 100% of lactose maldigesters will experience intolerance symptoms when a 50 g dose of lactose (equivalent to 1 liter of milk) is fed. However, there is significant evidence indicating that a blinded dose of lactose of 12 g or less (the equivalent to 1 cup of milk) is well tolerated among nonpersistent individuals.[15,16] The combination of the relatively small amount of lactose, coupled with residual lactase activity, likely results in minimal symptom responses at these low doses. Hertzler et al.,[15] using breath hydrogen analysis, determined that a 12 g dose of lactose was well tolerated with a small increase in abdominal discomfort.



Lactose Dose (g)	Flatus Frequency	Flatus Ratings	Abdominal Pain Ratings
0	4.0 + 1.3	3.4 + 1.0	1.7 + 0.8
2	4.3 + 1.8	3.8 + 1.4	1.7 + 0.9
6	5.1 + 0.6	1.9 + 0.9	1.2 + 0.5
12	4.6 + 1.1	3.5 + 1.3	3.4 + 0.8
20	9.0 + 2.6	6.6 + 1.8	5.3 + 1.8

Complete tolerance to doses of lactose up to 7 g has been confirmed by Vesa et al.[19] Furthermore, a double-masked study by Suarez et al.[16] found that even subjects who claimed to be severely lactose intolerant did not report more symptoms when 8 fluid ounces per day o*f regular versus 100% lactose-hydrolyzed milk was fed for 7 days. Larger, but still physiologic*, loads of lactose (e.g., 15–25 g) generally cause symptoms in about 50% of lactose maldigesters.[15,18]

References

1. Solomons NW, Guerrero A-M, Torun B. Dietary manipulation of postprandial colonic lactose fermentation: I. Effect of solid foods in a meal. *Am J Clin Nutr.* 1985;41:199–208.

2. Martini MC, Savaiano DA. Reduced intolerance symptoms from lactose consumed during a meal. *Am J Clin Nutr.* 1988;47:57–60.

3. Welsh JD, Hall WH. Gastric emptying of lactose and milk in subjects with lactose malabsorption. *Am J Dig Dis.* 1977;22:1060–1063.

4. Vesa TH, Marteau PR, Briet FB, Flourie B, Briend A, Rambaud J-C. Effects of milk viscosity on gastric emptying and lactose intolerance in lactose maldigesters. *Am J Clin Nutr.* 1997;66:123–126.

5. Vesa TH, Marteau PR, Briet FB, Boutron-Rualt M-C, Rambaud J-C. Raising milk energy content retards gastric emptying of lactose in lactose-intolerant humans with little effect on lactose digestion. *J Nutr.* 1997;127:2316–2320.

6. Scrimshaw NS, Murray EB. The acceptability of milk and milk products in populations with a high prevelance of lactose intolerance. *Am J Clin Nutr.* 1988;48:1083–1159.

7. Kolars, JC, Levitt MD, Aouji M, Savaiano DA. Yogurt: an autodigesting source of lactose. *New Engl J Med.* 1984;310:1–4.

8. Martini MC, Smith DE, Savaiano, DA. Lactose digestion from flavored and frozen yogurts, ice milk, and ice cream by lactase-deficient persons. *Am J Clin Nutr.* 1987;46:636–640.

9. Savaiano DA, AbouElAnouar A, Smith DE, Levitt, MD. Lactose malabsorption from yogurt, pasteurized yogurt, sweet acidophilus milk, and cultured milk in lactase-deficient individuals. *Am J Clin Nutr.* 1984;40:1219–1223.

10. Suarez FL, Savaiano DA, Arbisi P, Levitt, MD. Tolerance to the daily ingestion of two cups of milk by individuals claiming lactose intolerance. *Am J Clin Nutr.* 1997;65:1502–1506.

11. Suarez FL, Adshead J, Furne JK, Levitt MD. Lactose maldigestion is not an impediment to the intake of 1500 mg calcium daily as dairy products. *Am J Clin Nutr.* 1998;68:1118–1122.

12. Bond JH, Levitt MD. Quantitative measurements of lactose absorption. G*astroenterology.* 1976;70:1058–1062.

13. Hertzler SR, Savaiano DA. Colonic adaptation to daily lactose feeding in lactose maldigesters reduces lactose intolerance. *Am J Clin Nutr.* 1996;64:232–236.

14. Hertzler SR, Savaiano DA, Levitt MD. Fecal hydrogen production and consumption measurements: response to daily lactose ingestion by lactose maldigesters. *Dig Dis Sci.* 1997;42:348–353.

15. Hertzler SR, Huynh BL, Savaiano DA. How much lactose is low lactose? *J Am Diet Assoc.* 1996;96:243–246.

16. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *New Eng J Med.* 1995;333:1–4.

17. Vesa TH, Korpela RA, Sahi T. Tolerance to small amounts of lactose in lactose maldigesters. *Am J Clin Nutr.* 1996;64:197–201.

18. Savaiano DA, Hertzler SR, Jackson KA, Suarez FL. Nutrient consideration in lactose intolerance. In: *Nutrition in the Prevention of Disease.* Coulston AM, Rock CL, Monsen, ER, eds. Academic Press; 2001:563–575.

Evidence-based Practice Center Presentation III: The Tolerable Amount of Lactose Intake in Subjects With Lactose Intolerance

Timothy J. Wilt, M.D., M.P.H.; Aasma Shaukat, M.D., M.P.H.; Tatyana Shamliyan, M.D., M.S.; Brent C. Taylor, Ph.D., M.P.H.; Roderick MacDonald, M.S.; James Tacklind; Indulis Rutks; Sarah Jane Schwarzenberg, M.D.; Robert L. Kane, M.D.; Michael Levitt, M.D.

Objective

The objective was to determine the amount of lactose tolerable in subjects with lactose intolerance (LI).

Data Sources

The data sources were multiple electronic databases for blinded randomized controlled trials published in English from 1967–October 2009.

Methods

We extracted study, patient, intervention, and outcomes data from eligible studies. We quantified the type and severity of gastrointestinal symptoms and the amount and type of lactose causing patient-reported symptoms. We assessed the percentage reporting these outcomes as well as scores reported on symptom questionnaires. Because there was strong evidence of a placebo response, we limited inclusion to blinded randomized controlled trials. We attempted to categorize findings according to age, ethnicity, and patient-reported baseline LI severity.

Results

Twenty-eight randomized crossover trials were included. Half included lactose-digesting controls. The vast majority of studies were small (<30 subjects) with trial populations ranging between 6 and 150 subjects. Women constituted 55% of the subjects, and the mean age was 37 (20 studies reporting). Seven trials included children or adolescents, and four were exclusively children or adolescents. Among the 20 studies reporting race or ethnicity, 33% of the subjects were white, 30% Hispanic, 20% black, and 10% Asian. Studies did not report outcomes stratified by these baseline factors. In 11 studies, abdominal symptoms compatible with malabsorption of lactose prior to study entry were not required for participation. Lactose malabsorption (LM) was diagnosed following lactose tolerance tests by the hydrogen breath test in 13 of the studies,[1–13] and blood glucose test in 11 studies.[14–24] Diagnosis based on urinary galactose concentration was reported in one study,[25] and biochemical method of diagnosis was not reported in three trials.[26–28] Half of the trials included lactose-digesting controls.[3–6,9,13,15,18–22,26,28]

While subjects were routinely tested for LM, only a few studies then tested the intolerant subjects in blinded fashion with increasing doses of lactose administered throughout the day to determine the daily tolerable dosage of lactose. Most studies utilized a single dose of lactose and a lactose-free control administered in water or milk without food, frequently in not adequately blinded fashion (i.e., the taste of low-lactose milk differs from milk).

Interpreting and summarizing published data on the tolerable dosages of lactose in diagnosed LI subjects is confounded by a variety of patient, intervention, and outcome factors: (1) Most studies identified the study population based on the subjects' failure to absorb lactose (e.g., positive breath H_2 test) rather than the demonstration that the subjects were LI (symptomatic response to a dose of lactose in blinded, controlled experiments). Thus, the data summarized in this report largely reflect the dosage of lactose tolerated by subjects initially demonstrated to be lactose malabsorbers not LI. (2) Among various publications, there are major differences in how lactose was administered, for example, as a single dose versus multiple doses over the span of a day or the administration of lactose as an aqueous solution or milk without other food versus administration with other nutrients. Tolerance for lactose presumably is increased when taken in divided dosages and/or ingested with other nutrients. (3) The symptomatic response to lactose was variably reported as simply present or absent or as severity of symptoms graded by the subject on a numerical scale. In most studies, no data were provided as to the clinical relevance of the symptom scores. Thus, this summary necessarily reports on the significance of differences following ingestion of lactose versus a control and cannot provide data on information such as whether the severity of symptoms would have precluded the dietary ingestion of the test dose of lactose. (4) The routine ingestion of lactose seemingly increases tolerance to this sugar. The vast majority of the literature provides no data on pretest lactose consumption. (5) No study compared the frequency or severity of the symptomatic response to lactose based on the age, sex, or ethnicity of the lactose-malabsorbing subjects. Thus, it is not possible to determine whether differences exist in the quantity of lactose tolerated by various subgroups of lactose-malabsorbing subjects. The following charts summarize available data on the quantity of lactose tolerated by lactose-malabsorbing subjects, when lactose/milk was administered with (Figure1) or without (Figure 2) other nutrients.

Conclusion

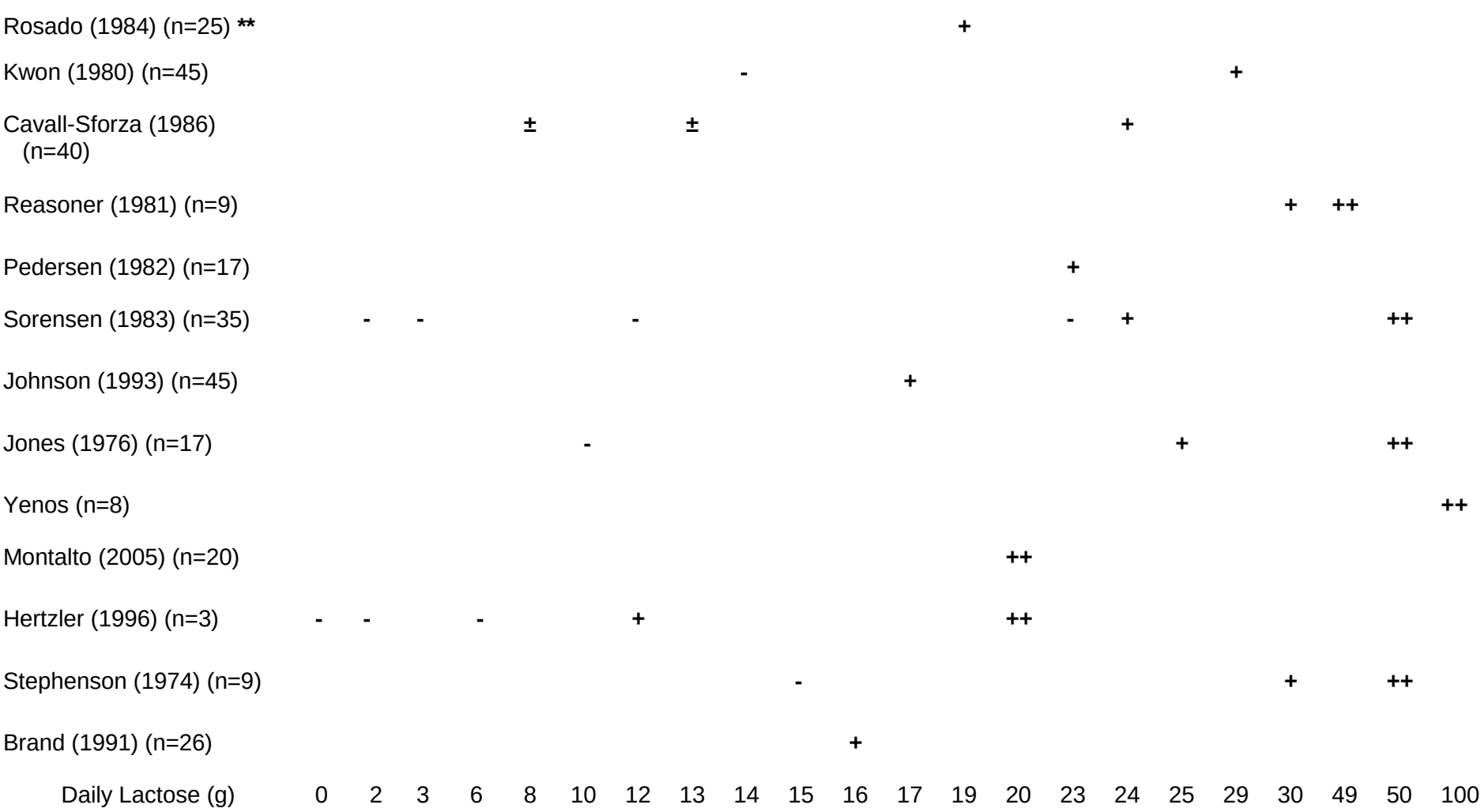
Evidence suggests that lactose may be better tolerated when ingested with other nutrients versus administration of an aqueous solution of lactose or milk as a single test dose without other nutrients. When taken with other nutrients, symptoms appear to be minimal with daily lactose dosages of less than 20 g (1.7 cups of milk), while many subjects experience severe symptoms with dosages of 50 g. In contrast, when lactose/milk is administered as a single test dose without other nutrients, dosages of 12 g may be symptomatic.

Figure 1. Symptomatic Response* of Adult Lactose Malabsorbers to Lactose Ingested With Nutrients Other Than Milk

PUBLICATION	0	3	6	7	9	12	15	18	22	30	34	42	49	50	56	63	70
Cheng (1979) (n=15)**														++			
Suarez (1998) (n=31)											+						
Vesa (1997) (n=30)								-									
Jones (1976) (n=16)				-			-			++							
Rorick (1979) (n=23)						-											
Suarez (1997) (n=19)									-								
Suarez (1995) (n=21)						-											
Newcomer (1978) (n=59)	-	-	-		-	-		-						++			
Hertzler (1996) (n=18)												-	-		-	-	-

***** Symptoms indicated by: - no or trivial symptoms, + minor symptoms, ++ severe symptoms.
****** n indicates number of lactose-malabsorbing subjects studied.

Figure 2. Symptomatic Response* of Adult Lactose Malabsorbers to Lactose Ingested Without Nutrients Other Than Milk



***** Symptoms indicated by: - no or trivial symptoms, + minor symptoms, ++ severe symptoms.
** n indicates number of lactose-malabsorbing subjects studied.

References

1. Montalto M, Nucera G, Santoro L, et al. Effect of exogenous beta-galactosidase in patients with lactose malabsorption and intolerance: a crossover double-blind placebo-controlled study. *Eur J Clin Nutr.* 2005;59(4):489–493.

2. Gremse DA, Greer AS, Vacik J, DiPalma JA. Abdominal pain associated with lactose ingestion in children with lactose intolerance. *Clin Pediatr (Phila).* 2003;42(4):341–345.

3. Suarez FL, Adshead J, Furne JK, Levitt MD. Lactose maldigestion is not an impediment to the intake of 1500 mg calcium daily as dairy products. *Am J Clin Nutr.* 1998;68(5):1118–1122.

4. Suarez FL, Savaiano D, Arbisi P, Levitt MD. Tolerance to the daily ingestion of two cups of milk by individuals claiming lactose intolerance. *Am J Clin Nutr.* 1997;65(5):1502–1506.

5. Vesa TH, Korpela RA, Sahi T. Tolerance to small amounts of lactose in lactose maldigesters. *Am J Clin Nutr.* 1996;64(2):197–201.

6. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med.* 1995;333(1):1–4.

7. Johnson AO, Semenya JG, Buchowski MS, Enwonwu CO, Scrimshaw NS. Correlation of lactose maldigestion, lactose intolerance, and milk intolerance. *Am J Clin Nutr.* 1993;57(3):399–401.

8. Brand JC, Holt S. Relative effectiveness of milks with reduced amounts of lactose in alleviating milk intolerance. *Am J Clin Nutr.* 1991;54(1):148–151.

9. Rorick MH, Scrimshaw NS. Comparative tolerance of elderly from differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks: a double-blind study. *J Gerontol.* 1979;34:191–196.

10. Lin MY, Yen CL, Chen SH. Management of lactose maldigestion by consuming milk containing lactobacilli. *Dig Dis Sci.* 1998;43(1):133–137.

11. Hertzler SR, Savaiano DA. Colonic adaptation to daily lactose feeding in lactose maldigesters reduces lactose intolerance. *Am J Clin Nutr.* 1996;64(2):232–236.

12. Hertzler SR, Huynh BC, Savaiano DA. How much lactose is low lactose? *J Am Diet Assoc.* 1996;96(3):243–246.

13. Newcomer AD, McGill DB, Thomas PJ, Hofmann AF. Tolerance to lactose among lactase-deficient American Indians. *Gastroenterology.* 1978;74(1):44–46.

14. Xenos K, Kyroudis S, Anagnostidis A, Papastathopoulos P. Treatment of lactose intolerance with exogenous beta-D-galactosidase in pellet form. *Eur J Drug Metab Pharmacokinet*. 1998;23(2):350–355.

15. Cavalli-Sforza LT, Strata A. Double-blind study on the tolerance of four types of milk in lactose malabsorbers and absorbers. *Hum Nutr Clin Nutr.* 1987;41(1):19–30.

16. Nielsen OH, Schiøtz PO, Rasmussen SN, Krasilnikoff PA. Calcium absorption and acceptance of low-lactose milk among children with primary lactase deficiency. *J Pediatr Gastroenterol Nutr.* 1984;3(2):219–223.

17. Rask Pedersen E, Jensen BH, Jensen HJ, Keldsbo IL, Hylander Møller E, Nørby Rasmussen S. Lactose malabsorption and tolerance of lactose-hydrolyzed milk. A double-blind controlled crossover study. *Scand J Gastroenterol.* 1982;17(7):861-864.

18. Reasoner J, Maculan TP, Rand AG, Thayer WR Jr. Clinical studies with low-lactose milk. *Am J Clin Nutr.* 1981;34(1):54–60.

19. Haverberg L, Kwon PH, Scrimshaw NS. Comparative tolerance of adolescents of differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks. I. Initial experience with a double-blind procedure. *Am J Clin Nutr.* 1980;33:17–21.

20. Kwon PH Jr, Rorick MH, Scrimshaw NS. Comparative tolerance of adolescents of differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks. II. Improvement of a double-blind test. *Am J Clin Nutr.* 1980;33(1):22–26.

21. Cheng AH, Brunser O, Espinoza J, et al. Long-term acceptance of low-lactose milk. *Am J Clin Nutr.* 1979;32(10):1989–1993.

22. Lisker R, Aguilar L. Double blind study of milk lactose intolerance. *Gastroenterology.* 1978;74(6):1283–1285.

23. Jones DV, Latham MC, Kosikowski FV, Woodward G. Symptom response to lactose-reduced milk in lactose-intolerant adults. *Am J Clin Nutr.* 1976;29(6):633-638.

24. Stephenson LS, Latham MC. Lactose intolerance and milk consumption: the relation of tolerance to symptoms. *Am J Clin Nutr.* 1974;27(3):296–303.

25. Vesa TH, Lember M, Korpela R. Milk fat does not affect the symptoms of lactose intolerance. *Eur J Clin Nutr.* 1997;51(9):633–636.

26. Rosado JL, Solomons NW, Lisker R, Bourges H. Enzyme replacement therapy for primary adult lactase deficiency. Effective reduction of lactose malabsorption and milk intolerance by direct addition of beta-galactosidase to milk at mealtime. *Gastroenterology.* 1984;87(5):1072–1082.

27. Lybeck Sørensen K, Vergara Meersohn M, Sonne J, Larsen L, Edelsten D, Gudmand-Høyer E. A new type of low-lactose milk. Tolerance by lactose malabsorbers and evaluation of protein nutritional value. *Scand J Gastroenterol.* 1983;18(8):1063–1068.

28. Paige DM, Bayless TM, Huang SS, Wexler R. Lactose hydrolyzed milk. *Am J Clin Nutr.* 1975;28(8):818–822.

Prebiotics and Lactose Intolerance

David S. Newburg, Ph.D.

Infant mammals generally contain the enzyme lactase in the duodenum and proximal jejunum, which is essential to digestion and utilization of the lactose from milk. Lactase expression declines after weaning and ends before adulthood. Lactase expression in most humans also follows this pattern, except in those descended from specific populations that have a history of dairy use throughout adulthood, notably those with northern European ancestry.[1] Continued expression of lactase is a dominant trait; thus genetic lactose intolerance is considered autosomal recessive.[2] However, the genotype of this lactase gene on chromosome 2 does not fully explain the phenotype of lactose intolerance. In animals, environmental factors can modulate the expression of the phenotype: Lactase expression has been induced by dietary lactose or the hormone cortisol; lactase expression has been reduced by thyroxine.[3–7] In contrast, lactase may not be inducible in lactose-intolerant humans,[8] despite the observation that many lactose maldigesters can tolerate small amounts of lactose in the diet and some tolerate a large bolus of dietary lactose.[9–11] Moreover, introduction of milk products into the diets of children within populations whose adults are lactose malabsorbers results in a decreased incidence of lactose intolerance over time.[12,13] These observations have led to the suggestion that adaptation by colonic microbiota may help spare genetically intolerant individuals from phenotypic expression of lactose maldigestion.[14]

Dietary glycans that are indigestible by mammals but stimulate specific changes in the microbiota and confer health benefits to the mammal are known as prebiotics. In lactose-intolerant individuals, lactose might be considered a prebiotic, as dietary lactose would be an indigestible dietary carbohydrate that could influence the microbiota in a way that could allow the microbiota to consume lactose and thereby spare the individual from symptoms of overt lactose intolerance.[15] Four testable postulates of this hypothesis are as follows:

- Lactose is not absorbed in lactose-intolerant individuals. (Demonstrated by a lack of blood glucose or galactose elevation following oral lactose.[16])

- Lactose is fermented by the microbiota. (The production of hydrogen gas follows oral lactose,[17,18] and antibiotics inhibit this response;[19] feces enriched in *Lactobacillus acidophilus* rapidly remove lactose from the medium.[20])

- Lactose favors growth of specific microbes of the microbiota. (Increased fecal beta-galactosidase follows prolonged ingestion of lactose by maldigesters.[21])

- Lactose benefits lactose malabsorbers similar to other indigestible carbohydrates (prebiotics). (Daily lactose feeding of maldigesters reduces lactose intolerance.[22])

This last point warrants careful consideration, as many types of prebiotics, including lactulose, inulin, fructo-oligosaccharides, galacto-oligosaccharides, pectins, resistant starch (limit dextrans), hemicelluloses, gums, and others are composed of many different sugars with specific linkages, giving them distinct properties. In some studies, lactulose and lactose have similar effects in protecting the recipient, presumably due to their similarities, as both are disaccharides terminating with galactose.[22] In other reports, a single dose of fructo-oligosaccharides and lactulose causes more symptoms in lactose maldigesters than in lactose digesters.[23] These disparate results may be due to different responses to acute administration rather than chronic administration, but also may be due to differences in prebiotic activity due to differences in the component sugars and linkages of these prebiotics. Human milk oligosaccharides, another class of prebiotic, contain lactose at their reducing ends,[24] and the chemical relatedness between lactose and the oligosaccharides may result in synergies for initiation, succession, and maintenance of the microbiota. The relationship between prebiotic-induced differences in microbiota and lactose intolerance remains a promising area of research.

References

1. Scrimshaw NS, Murray EB. The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. *Am J Clin Nutr.* 1988;48(4 Suppl):1079–1159.

2. Lloyd MI. The regulation of lactase expression in adult life. In: Auricchio S, Samenza G, eds. *Common Food Intolerances 2: Milk in Human Nutrition and Adult-Type Hypolactasia.* Basel: Karger; 1993:24–131.

3. Freund JN, et al. Levels and factors of control of small intestinal lactase expression in the laboratory rat. In: Auricchio S, Samenza G, eds. *Common Food Intolerances 2: Milk in Human Nutrition and Adult-Type Hypolactasia.* Basel: Karger; 1993:132-145.

4. Koldovsky O, Sunshine P. Effect of cortisone on the developmental pattern of the neutral and the acid beta-galactosidase of the small intestine of the rat. *Biochem J.* 1970;117(3):467–471.

5. Malo C, Ménard D. Opposite effects of one and three injections of cortisone or thyroxine on intestinal lactase activity in suckling mice. *Experientia.* 1979;35(4):493–494.

6. Raul F, Noriega R, Nsi-Emvo E, Doffoel M, Grenier JF. Lactase activity is under hormonal control in the intestine of adult rat. *Gut.* 1983;24(7):648–652.

7. Sahi T. Dietary lactose and the aetiology of human small-intestinal hypolactasia. *Gut.* 1978;19(11):1074–1086.

8. Gilat T, Russo S, Gelman-Malachi E, Aldor TA. Lactase in man: a nonadaptable enzyme. *Gastroenterology.* 1972;62(6):1125–1127.

9. Suarez FL, Savaiano D, Arbisi P, Levitt MD. Tolerance to the daily ingestion of two cups of milk by individuals claiming lactose intolerance. *Am J Clin Nutr. 1*997;65(5): 1502–1506.

10. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med.* 1995;333(1):1–4.

11. Vesa TH, Korpela RA, Sahi T. Tolerance to small amounts of lactose in lactose maldigesters. *Am J Clin Nutr.* 1996;64(2):197–201.

12. Habte D, Sterky G, Hjalmarsson B. Lactose malabsorption in Ethiopian children. *Acta Paediatr Scand.* 1973;62(6):649–654.

13. Sadre M, Karbasi K. Lactose intolerance in Iran. *Am J Clin Nutr.* 1979;32(9):1948-1954.

14. Villar J, Kestler E, Castillo P, Juarez A, Menendez R, Solomons NW. Improved lactose digestion during pregnancy: a case of physiologic adaptation? *Obstet Gynecol.* 1988;71(5):697–700.

15. Szilagyi A. Review article: lactose—a potential prebiotic. *Aliment Pharmacol Ther.* 2002;16(9):1591–1602.

16. Newcomer AD, McGill DB, Thomas PJ, Hofmann AF. Prospective comparison of indirect methods for detecting lactase deficiency. *N Engl J Med.* 1975;293(24):1232–1236.

17. Metz G, Gassull MA, Leeds AR, Blendis LM, Jenkins DJ. A simple method of measuring breath hydrogen in carbohydrate malabsorption by end-expiratory sampling. *Clin Sci Mol Med.* 1976;50:237–240.

18. van der Klei-van Moorsel JM, Douwes AC, van Oeveren JP. New principle for estimation of hydrogen in expired air. *Eur J Pediatr.* 1984;141(4):221–224.

19. Bond JH, Jr, Levitt MD. Use of pulmonary hydrogen (H 2) measurements to quantitate carbohydrate absorption. Study of partially gastrectomized patients. *J Clin Invest.* 1972;51(5):1219–1225.

20. Jiang T, Savaiano DA. *In vitro* lactose fermentation by human colonic bacteria is modified by *Lactobacillus acidophilus* supplementation. *J Nutr.* 1997;127(8):1489-1495.

21. Hertzler SR, Savaiano DA. Colonic adaptation to daily lactose feeding in lactose maldigesters reduces lactose intolerance. *Am J Clin Nutr.* 1996;64(2):232–236.

22. Szilagyi A, Rivard J, Fokeeff K. Improved parameters of lactose maldigestion using lactulose. *Dig Dis Sci.* 2001;46(7):1509–1519.

23. Teuri U, Vapaatalo H, Korpela R. Fructooligosaccharides and lactulose cause more symptoms in lactose maldigesters and subjects with pseudohypolactasia than in control lactose digesters. *Am J Clin Nutr.* 1999;69(5):973–979.

24. Newburg DS, Neubauer SH. Carbohydrates in milk: analysis, quantities, and significance. In: Jensen RG, ed. *Handbook of Milk Composition*. Orlando, FL: Academic Press; 1995:273–349.

Strategies for Managing Individuals With Diagnosed Lactose Intolerance: Probiotics

Mary Ellen Sanders, Ph.D.

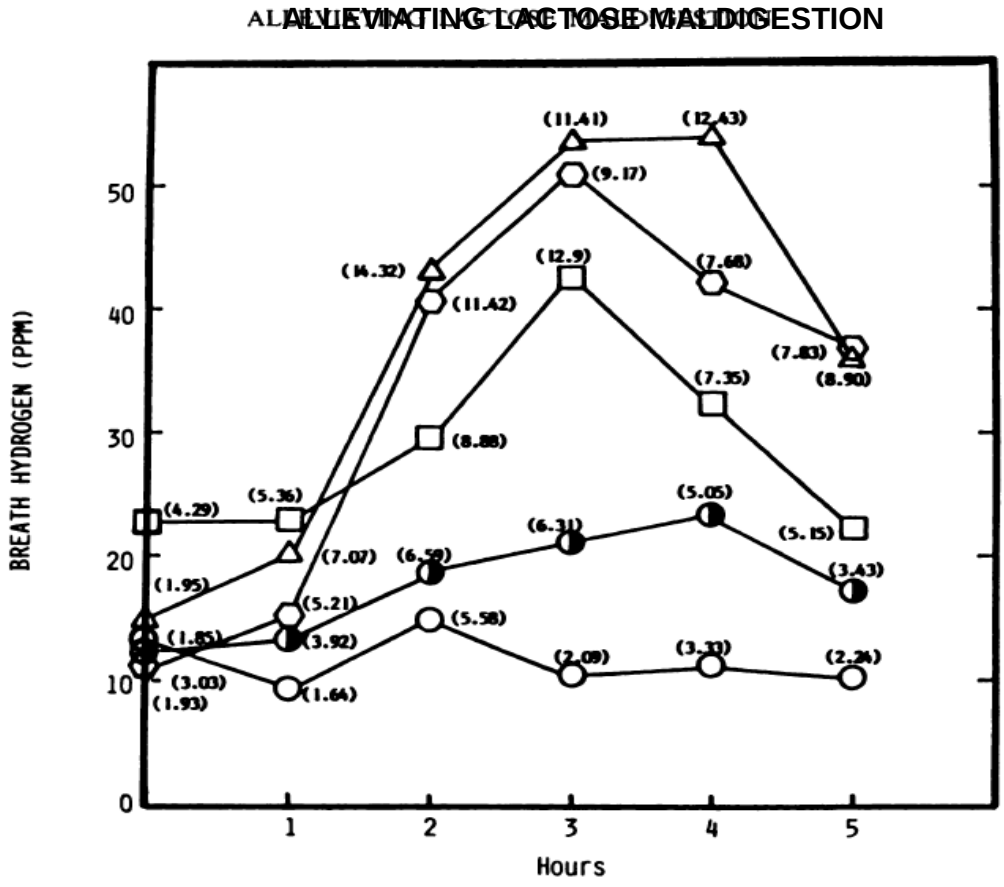
Probiotics are live microorganisms, which when administered in adequate amounts, confer a health benefit on the host.[1] Although probiotics include strains of *E. coli*, *Saccharomyces cerevisiae*, *Bacillus*, *Propionibacterium*, *Streptococcus thermophilus* (ST), and *Lactococcus*, the majority of probiotic strains hail from the *Lactobacillus* and *Bifidobacterium* genera. The usefulness of probiotics in providing dietary support for management of symptoms of lactose maldigestion has been studied for decades, with the preponderance of studies published in the 1980s and 1990s on ST and *Lactobacillus bulgaricus* (LB), *Bifidobacterium* strains, and other lactobacilli. Much of this research focuses on improved digestibility of yogurt (which contains the two starter culture bacteria, ST and LB) compared to milk, or to yogurt with heat-killed bacteria.[2] In general, the conclusions of this body of research are (1) some probiotics, given at adequate doses, can reduce symptoms associated with lactose maldigestion; (2) this ability is strain- and dose-specific,[3] although effects seem to be species specific for ST and LB; (3) mechanisms of this probiotic-mediated effect may include release of microbial lactase in the small intestine and/or alteration of fermentation patterns of the colonic microbiota; and (4) live bacteria are more effective than heat-killed. It is noteworthy that a lack of correlation of lactase levels (as assessed by *in vitro* methods) of the probiotic being tested and the ability to reduce breath hydrogen is observed,[4] suggesting the limitation of this assay for predicting probiotic effectiveness. The level of lactase delivered *in an available form* to the intestine is more important than how much lactase is produced by any particular strain.

The literature suggests that, in general, ST and LB strains are better than *Bifidobacterium* and other typical “probiotic” *Lactobacillus* strains at delivering lactase to the small intestine,[5] although the more traditional probiotic bacteria may act in the colon and be effective in providing symptom relief.[6] Figure 1 demonstrates that yogurt, with ST and LB, is more effective at reducing breath hydrogen excretion than several other products tested. This is thought to be largely due to their relatively high production of beta-galactosidase, and to bile-induced permeability of their cell walls, leading to release of the enzyme and *in situ* hydrolysis of lactose.[5] Table 1 shows the correlation between reduction in breath hydrogen excretion and symptom reduction.[5] LB and ST have a somewhat unique position in the probiotic schema in that they are largely unable to survive passage through the gastrointestinal tract. But it is precisely this physiological trait that seems to make them uniquely suited to effectively deliver lactase to the small intestine. In a test of the ability of lactose-maldigesting children to tolerate milk containing equal numbers of ST+LB or *L. acidophilus* NCFM (added as dried culture), the milk with ST+LB reduced both breath hydrogen excretion and intestinal symptoms, whereas the NCFM-supplemented milk only reduced symptoms.[7] These results suggest that ST+LB may be superior in this role, and that a fundamental difference exists in mode of action of these types of microbes. Furthermore, this sometimes-observed

decoupling of subjective symptom reporting and breath hydrogen excretion is an area in need of additional study.

Depending on the mechanism employed by a specific probiotic, one would hypothesize different timeframes for relief of lactose maldigestion symptoms that may have important practical implications. If the mechanism involves release of microbial lactase in the small intestine resulting in *in situ* lactase digestion, relief might be expected to be experienced only with simultaneous consumption of probiotic and lactose; if the mechanism is alteration of intestinal microbe populations or functions, one would expect a more sustained benefit, and one that would enable consumption of lactose temporally disconnected from consumption of the probiotic.

Figure 1. Temporal Changes in the Breath Hydrogen Levels of Subjects Consuming Various Milk Products[5]



All products contained 18 g lactose per serving except hydrolyzed-lactose milk, which contained 5 g lactose per serving. ○, yogurt; ◑, hydrolyzed-lactose milk; □, whole milk plus lactase tablet; ◘, sweet acidophilus milk; △, whole milk; n=10 healthy adult subjects.

Table 1. Number of Subjects Reporting Symptoms and Mean Peak Breath Hydrogen Levels After Consumption of Various Milk Products[5]

Products	Number of Subjects Reporting Symptoms*			Mean Peak Breath H_2†
	Flatulence	Diarrhea	Cramps	
				ppm
Whole milk	8	5	3	51.1 ± 9.2
Acidophilus milk	6	3	4	53.9 ± 11.4
Lactase tablets with milk	3	3	1	42.5 ± 12.9
Hydrolyzed-lactose milk	0	1	1	21.0 ± 6.3
Yogurt	0	0	0	10.4 ± 2.1

*None of the control subjects reported symptoms. Correlations between mean peak breath H2 and number of subjects reporting flatulence, diarrhea, and cramps were 0.80, 0.79, and 0.63, respectively;† *x* ± SEM at third hour; n=10.

Research indicates that certain probiotics may alleviate symptoms of lactose maldigestion. The degree of benefit may depend on the degree of lactase insufficiency, the characteristics of the person's colonic microbiota, and the characteristics and dose of the probiotic. Yogurt (or products with an equivalent lactose load) with live LB and ST (the presence of the National Yogurt Association "LAC Seal" provides a good indication for consumers that a yogurt contains adequate levels of live cultures) can generally be better tolerated by lactose maldigesters than products without these live bacteria. To what extent these bacteria delivered in the forms of dried, dietary supplements are effective is less rigorously demonstrated.

The presence of mixed results in the body of research in this field points to the difficulty in aggregating research on different strains, doses, populations, endpoints (biomarker vs. symptom), and delivery formats. There is a need for additional human studies that are properly blinded to improve confidence in symptom assessments, that follow changes in gut microbiota populations and activities using modern techniques, and that determine the impact of the probiotic delivery system (e.g., fermented milk products vs. dried bacteria) on probiotic functionality. In addition, microbiological issues related to bacterial and enzyme survival should be researched. Culture conditions affecting beta-galactosidase production are important to define. The dependence of a physiological effective state of the microbe on media, growth phase, and storage conditions also should be determined.

In the end, symptoms of lactose maldigestion are a result of disadvantageous colonic bacterial fermentation, and the ability to interfere with symptom development is a function of either depriving colonic bacteria lactose as a substrate or achieving colonic microbiota that do not ferment lactose to a problematic degree. Probiotics may be able to impact both of these factors, resulting in improved lactose tolerance.

References

1. Sanders M. How do we know when something called “probiotic” is really a probiotic? A guideline for consumers and healthcare professionals. *Functional Food Rev.* 2009;1:3–12.

2. de Vrese M, Stegelmann A, Richter B, Fenselau S, Laue C, Schrezenmeir J. Probiotics—compensation for lactase insufficiency. *Am J Clin Nutr*. 2001;73:421S-429S.

3. Lin MY, Savaiano D, Harlander S. Influence of nonfermented dairy products containing bacterial starter cultures on lactose maldigestion in humans. *J Dairy Sci.* 1991;74:87–95.

4. Kotz CM, Furne JK, Savaiano DA, Levitt MD. Factors affecting the ability of a high beta-galactosidase yogurt to enhance lactose absorption. *J Dairy Sci.* 1994;77:3538–3544.

5. Onwulata CI, Rao DR, Vankineni P. Relative efficiency of yogurt, sweet acidophilus milk, hydrolyzed-lactose milk, and a commercial lactase tablet in alleviating lactose maldigestion. *Am J Clin Nutr.* 1989;49:1233–1237.

6. Jiang T, Mustapha A, Savaiano DA. Improvement of lactose digestion in humans by ingestion of unfermented milk containing *Bifidobacterium longum*. *J Dairy Sci.* 1996;79:750–757.

7. Montes RG, Bayless TM, Saavedra JM, Perman JA. Effect of milks inoculated with *Lactobacillus acidophilus* or a yogurt starter culture in lactose-maldigesting children. *J Dairy Sci.* 1995;78:1657–1664.

Treatment Recommendations in Adults With Diagnosed Lactose Intolerance

Jeanette N. Keith, M.D.

Misperceptions of lactose tolerance are pervasive among healthcare professionals and in the community.[1,2] These misperceptions have led to arbitrary medical advice being given to patients with diagnosed lactose intolerance, magnifying misinformation and perpetuating myths.[3] To be effective in treating individuals with diagnosed lactose intolerance, it is important that patients understand that lactose maldigestion is an intraluminal event that occurs when excess lactose reaches the colon and is digested by colonic bacteria.[4] This process results in the production of hydrogen, methane gas, and acids. While lactose maldigestion is often asymptomatic, lactose intolerance describes the clinical syndrome associated with symptomatic ingestion. When determining the best strategy to treat an individual diagnosed with lactose intolerance, it is essential to know what test was performed and how much lactose was used as part of the test. Supraphysiologic levels of lactose used during breath hydrogen testing may not reflect tolerance to the amount of lactose found in a typical serving of dairy foods. The optimal test for the diagnosis of lactose intolerance remains debated.[5]

To manage individuals with diagnosed lactose intolerance effectively, first, we **inquire** about perceptions of tolerance. It is our practice to inquire about the onset and frequency of symptoms in an effort to distinguish between real and perceived lactose intolerance in the individual with lactose maldigestion. Second, we **identify** the specific symptoms associated with lactose consumption because different forms of dairy foods contain varying quantities of lactose per serving.[6] Factors that influence tolerance include the degree of fermentation specific to the dairy product, fat and protein content of the diet, gastric emptying, intestinal transit time, lactase enzyme activity level, percent lactose present, and colonic bacterial adaptation.[7] Other factors that affect tolerance include visceral sensitivity to foods[8] and the presence of coexisting gastrointestinal disorders such as irritable bowel syndrome and inflammatory bowel disease.[9]

Third, we **inform** patients about the process of lactose digestion and the health benefits of a diet rich in calcium and vitamin D using scientifically sound, Evidence-based data. Multiple studies document the effectiveness of the dairy-rich DASH (Dietary Approaches To Stop Hypertension) eating plan in treating hypertension, diabetes, obesity, and other chronic diseases. The eating plan was well tolerated by African American participants. Therefore, this is an eating plan suggested for lactose-intolerant individuals, particularly in minority populations.[10]

Fourth, we **implement** specific dietary strategies that have been shown to improve tolerance to dairy foods. There is high acceptance of dairy foods in lactose-intolerant populations when symptoms are minimized.[11] In practice, we explain that just as it takes about 21 days to learn a new behavior, adaptation of the gut to a lactose-containing diet generally requires 3 weeks of consistent dietary change to achieve full tolerance.[12] One

key suggestion for improving tolerance is to recommend consuming small quantities of dairy foods (e.g., 2–4 ounces) with a meal two to three times a day followed by gradual increases in dairy volume to the maximum level of tolerance.[13] Another suggestion to improve tolerance is to add a variety of dairy foods with different amounts of lactose to the diet. For example, yogurt and aged cheeses contain less lactose than fluid milk. In a study by Suarez et al., lactose maldigestion was not an impediment to the intake of 1,500 mg of calcium from dairy products when fluid milk intake was combined with cheese and yogurt consumption.[14] Other tips for tolerance include the addition of low-lactose milk powder as a nutritional supplement,[15] the use of lactase enzymes,[16] consumption of lactose-reduced products,[17] the use of probiotics,[18] the consumption of low-lactose-containing foods such as yogurt or aged cheeses,[19] and fermented products such as kefir.[20] Some studies also report increased tolerance to flavored milk as opposed to unflavored milk.[21] Nondairy beverages such as soy-based drinks are options for treatment but vary in their nutritional content and acceptability when compared to dairy foods.[22] Dairy avoidance for the treatment of lactose intolerance is not an optimal suggestion in clinical practice as it may contribute to essential nutrient deficiencies that are associated with diet-preventable chronic diseases. The nutrient package of dairy allows one to meet the daily dietary requirements for multiple nutrients, notably calcium, potassium, and magnesium.[23]

Understanding the health benefits of a calcium-rich diet and the process of lactose digestion is the foundation for treatment strategies in the management of lactose intolerance. The most effective dietary intervention for lactose intolerance is the one personalized to meet the needs of the individual affected by symptomatic lactose ingestion. It is important that recommendations be based on sound clinical evidence to avoid magnifying misinformation, perpetuating myths, and contributing to potential essential nutrient deficiencies.

References

1. Lomer MC, Parkes GC, Sanderson JD. Review article: lactose intolerance in clinical practice—myths and realities. *Aliment Pharmacol Ther*. 2008;27:93–103.

2. Harrington LK, Marberry JF. A re-appraisal of lactose intolerance. *Int J Clin Pract.* 2008;62:1541–1546.

3. McBean LD, Miller GD. Allaying fears and fallacies about lactose intolerance. *J Am Diet Assoc.* 1998;98:671–676.

4. Dykibra J,Gaskin DJ, Jasminka Z, Illich JZ. Lactose maldigestion revisited: diagnosis, prevalence in ethnic minorities, and dietary recommendations to overcome it. *Am J Lifestyle Med.* 2009;3:212–218.

5. Argnani F, Di Camillo M, Marinaro V, et al. Hydrogen breath test for the diagnosis of lactose intolerance, is the routine sugar load the best one? *World J Gastroenterol.* 2008;14(40):6204–6207.

6. McCray S. Lactose intolerance: considerations for the clinician. *Pract Gastroenterol.* 2003;27:21–39.

7. Vesa TH, Marteau P, Korpela R. Lactose intolerance. *J Am Coll Nutr*. 2000; 19(2 Suppl)165S–175S.

8. Di Stefano M, Mazzocchi S, Tana P, Moroni F, Corazza GR. Visceral hypersensitivity and intolerance symptoms in lactose malabsorption. *Neurogastroenterol Motil*. 2007;19(11):887–895.

9. Vernia P, Di Camillo M, Marinaro V. Lactose malabsorption, irritable bowel syndrome and self-reported milk intolerance. *Dig Liver Dis.* 2001;33:234–239.

10. Windhauser MM, Evans MA, McCollough ML, et al. Dietary adherence in the Dietary Approaches To Stop Hypertension trial. *J Am Diet Assoc*. 1999;99:S76-S83.

11. Scrimshaw NS, Murray EB. The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. *Am J Clin Nutr.* 1988;48(4 Suppl):1079–1159.

12. Pribila BA, Hertzler SR, Martin BR, Weaver CM, Savaiano DA. Improved lactose digestion and intolerance among African-American adolescent girls fed a dairy-rich diet. *J Am Diet Assoc*. 2000;100(5):524-528.

13. Jarvis JK, Miller GD. Overcoming the barrier of lactose intolerance to reduce health disparities. *J Natl Med Assoc*. 2002;94:55–66.

14. Suarez FL, Adshead J, Furne JK, Levitt MD. Lactose maldigestion is not an impediment to the intake of 1500 mg calcium daily as dairy products. *Am J Clin Nutr*. 1998;68:1118–1122.

15. Kwok T, Woo J, Kwan M. Does low lactose milk powder improve the nutritional intake and nutritional status of frail older Chinese people living in nursing homes? *J Nutr Health Aging*. 2001;5:17–21.

16. Montalto M, Curigliano V, Santoro L, et al. Management and treatment of lactose malabsorption. *World J Gastroenterol.* 2006;14:187–191.

17. Suarez FL, Savaiano DA, Levitt M. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med*. 1995;333:1–4.

18. de Vrese M, Stegelman A, Richter B, Fenselau S, Laue C, Schrezenmeir J. Probiotics–compensation for lactase insuffiency. *Am J Clin Nutr*. 2001;73:421S-429S.

19. Vesa TH, Marteau P, Zidi S, Briet F, Pochart P, Rambaud JC. Digestion and tolerance of lactose from yoghurt and different semi-solid fermented dairy products containing *Lactobacillus acidophilus* and bifidobacteria in lactose maldigesters—is bacterial lactase important? *Eur J Clin Nutr*. 1996;50:730–733.

20. Hertzler SR, Clancy SM. Kefir improves lactose digestion and tolerance in adults with lactose digestion. *J Am Diet Assoc*. 2003;103:582–587.

21. Welsh JD, Hall WH. Gastric emptying of lactose and milk in subjects with lactose malabsorption. *Am J Dig Dis*. 1977;22:1060–1063.

22. Gupta R, Gupta S. Dietary management of lactose intolerance—lactase treated milk versus soya milk. *Indian J Med Sci.* 1993;47:1–7.

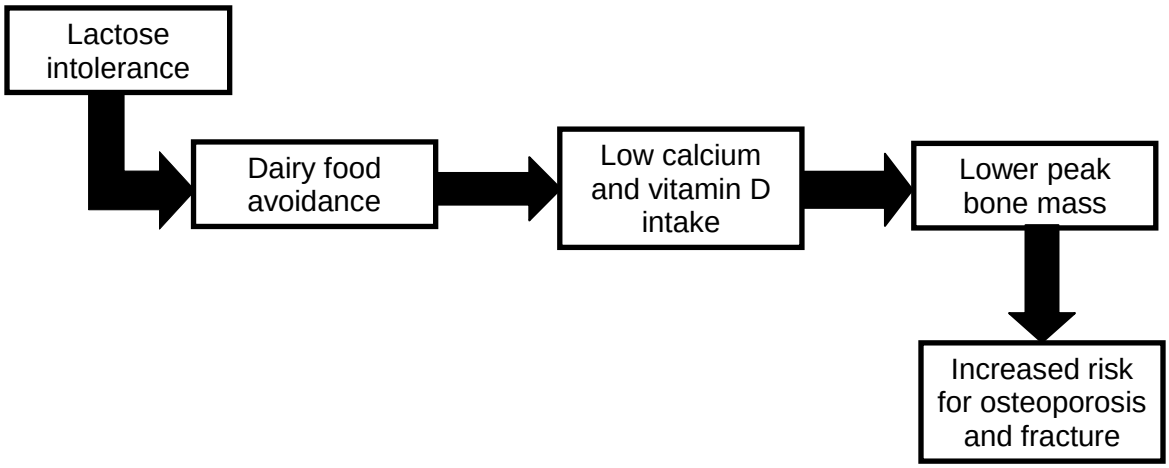
23. Nicklas TA, O'Neil CE, Fulgoni VL III. The role of dairy in meeting the recommendations for shortfall nutrients in the American diet. *J Am Coll Nutr.* 2009;28(Suppl 1):73S–81S.

Treatment Recommendations in Children

Catherine M. Gordon, M.D., M.Sc.

Lactose intolerance (LI) has been shown to have potential adverse effects on multiple health endpoints,[1–5] and bone health is the most common outcome that has been studied across the age spectrum.[1,6–11] LI leads to potential osteoporosis and fractures via the mechanisms illustrated in Figure 1.[10] Other potential adverse effects include hypertension and changes in weight and body composition, which may lead to insulin resistance syndromes and type 2 diabetes.[12–14] Health disparities also have been noted, with a potential overestimation of LI among minority populations.[4,15]

Figure 1. Model for LI Resulting in Osteoporosis and Fractures[10]



A few studies have examined bone health in individuals with LI. One study examined both bone mineral density (BMD) and fracture, and found that the rate of vertebral fractures was higher in those with documented LI.[6] Another study examined BMD by dual-energy x-ray absorptiometry (DXA) in 29 subjects with LI, 26 subjects with lactose malabsorption with symptoms of LI, and 49 healthy controls.[7] Both lumbar spine and femoral neck BMD by DXA were found to be lower among those with documented LI ($p<0.01$). Decreasing BMD also was inversely correlated with severity of LI symptoms.[7] A final study examined the association between perceived milk intolerance (PMI) and lactose maldigestion, dietary calcium intake, and bone mineral content in adolescent girls. Forty-seven out of 246 girls identified themselves to be milk intolerant. Forty completed breath hydrogen testing, and only 18 of the 40 had true lactose maldigestion. Among the 10- to 13-year-old girls studied, spinal bone mineral content (BMC) was significantly lower in those with PMI. These data suggest that PMI, starting as early as age 10, leads to self-imposed dairy restriction that may manifest as a lower spinal BMC in adolescent girls.

In 2007, the American Academy of Pediatrics (AAP) published a report outlining dietary strategies for infants, children, and adolescents with LI.[1] A review by McBean and Miller also provided guidance and sought to allay fears about LI.[5] General dietary management strategies are included in Table 1.[2] Knowledge about both the calcium and lactose content of food can be helpful in formulating a dietary plan for a child (Table 2).[1] Reflecting the importance of vitamin D to efficient calcium absorption and multiple health endpoints, the AAP now recommends vitamin D supplementation, 400 IU daily, to all infants, children, and teenagers.[16]

Table 1. Dietary Management Strategies That Allow Lactose Maldigestors To Successfully Incorporate Dairy Food Into Their Diets[2]

1. Consume small amounts of lactose-containing foods.
2. Chronic/repeated intake of lactose-containing foods allows colonic bacteria to adapt and more efficiently metabolize lactose.
3. Co-ingest lactose-containing foods with a meal.
4. Consider the form of the lactose-containing food. Hard cheeses, chocolate, higher fat milks, and ice cream are well tolerated.
5. Eat live culture yogurt.
6. Utilize commercially available lactose digestive aids.
7. Modify behaviors and perceptions from past experiences to learn that dairy/lactose-containing foods can be easily incorporated into the diet.
8. Consider the consumption of calcium-fortified foods.

Table 2. Lactose and Calcium Content of Common Foods[1]

Dairy Products	Calcium Content (mg)	Lactose Content (g)
Yogurt, plain, low fat, 1 cup	448	8.4
Milk, whole (3.25% fat), 1 cup	276	12.8
Milk, reduced fat, 1 cup	285	12.2
Ice cream, vanilla, ½ cup	92	4.9
Cheddar cheese, 1 ounce	204	0.07
Swiss cheese, 1 ounce	224	0.02
Cottage cheese, creamed (small curd), 1 cup	135	1.4

Calcium homeostasis is affected by protein intake, vitamin D status, salt intake, and genetic factors.[8] After the first year of life, the recommended adequate intake of calcium ranges from 500–1,300 mg of elemental calcium.[17] If calcium supplements are recommended, no more than 500 mg should be given per dose. Calcium citrate, carbonate, and glubionate are common preparations prescribed to pediatric patients.[17] There are foods that inhibit calcium absorption including consumption of iron, zinc, and magnesium; oxalic acid (found in spinach, rhubarb, beet leaves, chard, and chocolate); and phytic acid (found in the germ and bran of grains, as well as in legumes). Both caffeine and sodium intake can increase urinary calcium excretion.[17] Lastly, providers need to be mindful of calcium-drug interactions, such as L-thyroxine replacement therapy, anticonvulsants, H2 blockers and proton-pump inhibitors, bisphosphonates, antibiotics (e.g., quinolones, tetracycline), and glucocorticoids.

In summary, LI is a common disorder that has been linked with lower dietary calcium intake potentially leading to a low BMD and increased fracture risk. Treatment of LI is centered on dietary approaches to optimize protein, calcium, and vitamin D intake without ingesting excessive amounts of lactose. Current LI literature is particularly sparse in the area of longitudinal effects of LI on bone metabolism and other health parameters.

References

1. Heyman MB. Lactose intolerance in infants, children, and adolescents. *Pediatrics*. 2006;118:1279–1286.

2. Jackson KA, Savaiano DA. Lactose maldigestion, calcium intake and osteoporosis in African-, Asian-, and Hispanic-Americans. *J Am Coll Nutr*. 2001;20:198S–207S.

3. Lomer MCE, Parkes GC, Sanderson JD. Review article: lactose intolerance in clinical practice—myths and realities. *Aliment Pharmacol Ther*. 2008;27:93–103.

4. Jarvis JK, Miller GD. Overcoming the barrier of lactose intolerance to reduce health disparities*. J Natl Med Assoc.* 2002;94:55–66.

5. McBean LD, Miller GD. Allaying fears and fallacies about lactose intolerance. *J Am Diet Assoc.* 1998;98:671–676.

6. Kudlacek S, Freudenthaler O, Weissboeck H, Schneider B, Willvonseder R. Lactose intolerance: a risk factor for reduced bone mineral density and vertebral fractures? *J Gastroenterol*. 2002;37:1014–1019

7. Di Stefano M, Veneto G, Malservisi S, Cecchetti L, Minguzzi L, Strocchi A. Lactose malabsorption and intolerance and peak bone mass. *Gastroenterology*. 2002;122:1793–1799.

8. Heaney RP. Dairy and bone health. *J Am Coll Nutr.* 2009;28(Suppl 1):82S–90S.

9. Matlik L, Savaiano D, McCabe G, VanLoan M, Blue CL, Boushey CJ. Perceived milk intolerance is related to bone mineral content in 10- to 13-year-old female adolescents. *Pediatrics*. 2007;120:e669–e677.

10. Stallings VA. Calcium and bone health in children: a review. *Am J Ther*. 1997;4(7–8):259–273.

11. Tremaine WJ, Newcomer AD, Riggs BL, McGill DB. Calcium absorption from milk in lactase-deficient and lactase-sufficient adults. *Dig Dis Sci*. 1986;31:376–378.

12. Trembly A, Gilbert J. Milk products, insulin resistance syndrome and type 2 diabetes. *J Am Coll Nutr.* 2009;28:91S–102S.

13. Kris-Etherton PM, Grieger JA, Hilpert KF, West SG. Milk products, dietary patterns and blood pressure management. *J Am Coll Nutr.* 2009;28:103S–119S.

14. van Loan M. The role of dairy foods and dietary calcium in weight management. *J Am Coll Nutr.* 2009;28:120S–129S.

15. Sahi T. Genetics and epidemiology of adult-type hypolactasia. *Scand J Gastroenterol Suppl*. 1994;202:7–20.

16. Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding, American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. 2008;122:1142–1152.

17. Straub DA. Calcium supplementation in clinical practice: a review of forms, doses, and indications. *Nutr Clin Pract.* 2007;22:286–296.

Evidence-based Practice Center Presentation IV: Effective Strategies for the Management of Individuals with Diagnosed Lactose Intolerance

Timothy J. Wilt, M.D., M.P.H.; Aasma Shaukat, M.D., M.P.H.; Tatyana Shamliyan, M.D., M.S.; Brent C. Taylor, Ph.D., M.P.H.; Roderick MacDonald, M.S.; James Tacklind; Indulis Rutks; Sarah Jane Schwarzenberg, M.D.; Robert L. Kane, M.D.; Michael Levitt, M.D.

Introduction

Treatment for lactose intolerance consists of a lactose-restricted diet or the use of milk in which the lactose has been prehydrolyzed via treatment with lactase supplements. Lactase supplements taken at the time of milk ingestion also are commercially available.

Objective

The objective of this study was to assess the efficacy of the following strategies in management of symptoms of lactose intolerance.

Methods

We searched MEDLINE®, the Cochrane Library, and other databases to find studies published in English from 1967 until October 2009. We included randomized double-blind controlled trials of probiotics, enzyme replacement therapies with lactase from nonhuman sources, administration of lactose-reduced milk, and regimes of increases in dietary lactose load. We evaluated the efficacy of therapeutic agents and strategies in alleviating symptoms among individuals with diagnosed lactose malabsorption. Individuals diagnosed with irritable bowel syndrome, inflammatory or infectious bowel diseases, or milk allergies were excluded. We also excluded children younger than age 4. We judged level of evidence using modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.

Results

A total of 37 unique randomized studies (26 on lactase/lactose hydrolyzed milk supplements or lactose-reduced milk, 8 on probiotics, 2 on incremental lactose dose for colonic adaptation, and 1 on other agents) met inclusion criteria.

Lactase/Lactose Hydrolyzed Milk

Among 26 articles representing 28 unique trials, studies enrolled between 6 and 150 subjects. Women constituted 56% of the subjects (n=23 studies). The mean age of subjects was 37 years (n=19 studies). Six trials included children or adolescents.[1–6]

One trial enrolled elderly subjects.[7] Within the 19 studies reporting race or ethnicity, 40% of the subjects were white, 30% Hispanic, 20% black, and 9% Asian.[1–17] Subjects in 18 studies reported abdominal symptoms compatible with malabsorption of lactose prior to study entry.[1–3,8–11,14–16,18–25] All but one study reported on lactose-reduced or hydrolyzed milk by adding a lactase enzyme such as beta-galactosidase to the milk.

There was moderate evidence of improvement in symptoms from moderate and severe to mild or none, or an absolute reduction of at least 50% in abdominal pain/ cramping[1,2,10,14,24] and diarrhea[22] with use of lactose-reduced solution/milk, with lactose content of 0–2 grams (g), compared to a lactose dose of 12 g or more. Overall symptom score was reduced by 60% with lactose-reduced milk containing 7.5 g lactose compared to a similar amount of milk with 30 g lactose,[25] and by 13% with low-lactose skim milk with 0.8–6.5 g lactose compared to skim milk with 6.1–49 g lactose. Mean and total symptom scores also were reduced, from 3.7 to 0.36 with 70% hydrolyzed milk compared to placebo with 20 g lactose[18] and from a score of 46 for skim milk with 11.3 g lactose to a score of 17 with low-lactose milk with 3.2 g lactose.[14] Similar reductions were seen in summed scores for abdominal pain from 43 with milk containing 25 g lactose to 1 with lactose hydrolyzed milk containing 1.25 g lactose, and a mean score for abdominal pain from 7.5 with milk containing 12 g lactose to 4.1 with milk containing lactase,[1] both in children. In adults, one study showed a reduction in abdominal pain from moderate to none or mild with low-lactose milk containing 2.9 g lactose compared to skim milk containing 28.5 g lactose.[24] The proportion of subjects reporting symptoms was reduced by 18% with lactose-free milk containing 0 g lactose compared to lactose-reduced milk with 0.5 g lactose and a 50% reduction in those reporting at least one moderate to severe symptom for abdominal pain with low-lactose milk containing 1.6 g lactose compared to skim milk with 11.3 g lactose.[14] Compared to placebo, use of lactase supplements such as Lactogest, Dairy Ease, or Lactaid in doses of two to four capsules/tablets when taken with 400 ml of 2% milk containing 20 g lactose reduced overall symptom scores, mostly due to reduction in scores for flatulence,[22] but did not reduce symptoms when administered with a 50 g lactose dose.

Prebiotics and Probiotics

Trials enrolled between 9 and 28 subjects. Among the five studies reporting gender, women constituted 34% of the subjects.[26–30] Two studies enrolled only male subjects.[29,30] Subjects were typically young to middle-aged adults, and only one study enrolled subjects older than age 60. Five trials assessed probiotic test products, prepared by adding strains of *Lactobacillus acidophilus*, *L. bulgaricus,* or *Bifidobacterium longum* to milk prior to consumption.[26,27,31–33] Four studies evaluated yogurt products.[28–30,32] Lactose malabsorption was diagnosed by the hydrogen breath test in all studies. Only one study noted that the enrolled subjects reported symptoms compatible with malabsorption of lactose prior to study entry.[33] Overall symptom score was reduced from 12.5 with 2% milk containing 20 g lactose to 2.8 with the same milk formulation but with added *Lactobacillus* at 10^9 cfu/ml[31] and from fairly strong to mild with 400 ml of Bulgofilus milk compared to control, both with 18 g lactose. Reductions in other symptoms were either not reported, not significantly different, or likely of lower

clinical significance. The inclusion criteria were variable; the type, source, and concentration of yogurt and probiotics studied were variable; and no two studies studied the same agent.

Other Strategies

We found one cross-over study evaluating 10 days of incremental doses of lactose versus dextrose for colonic adaptation among 20 subjects with lactose malabsorption diagnosed on hydrogen breath tests.[34] Most subjects had only mild symptoms even at high doses of lactose consumption. Flatulence, but not abdominal pain and diarrhea, was reduced. A second study evaluated colonic adaptation to lactose by comparing symptoms among 46 adults with lactose malabsorption who were fed either 34 g lactose or sucrose in a double-blind fashion for 13 days.[35] The overall clinical score and individual mean scores for pain, flatulence, bloating, and borborygmi (stomach rumbling) showed similar improvement in the lactose and sucrose groups. One additional study found that rifaximin and lactose-free diets resulted in similar reductions in abdominal pain, diarrhea, bloating, and distension compared to baseline.[36]

Conclusions

We found moderate evidence to support reduction in overall symptoms and abdominal pain and diarrhea with consumption of lactose-reduced milk (to content of 0–2 g). For most other strategies, evidence of symptomatic improvement generally was based on a few small, short-term studies reporting varied outcome measures and demonstrating effects of small magnitude.

References

1. Gremse DA, Greer AS, Vacik J, et al. Abdominal pain associated with lactose ingestion in children with lactose intolerance. *Clin Pediatr (Phila).* 2003;42(4):341-345.

2. Nielsen OH, Schiotz PO, Rasmussen SN, et al. Calcium absorption and acceptance of low-lactose milk among children with primary lactase deficiency. *J Pediatr Gastroenterol Nutr.* 1984;3(2):219–223.

3. Johnson AO, Semenya JG, Buchowski MS, et al. Correlation of lactose maldigestion, lactose intolerance, and milk intolerance. *Am J Clin Nutr.* 1993;57(3):399–401.

4. Haverberg L, Kwon PH, Scrimshaw NS. Comparative tolerance of adolescents of differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks. I. Initial experience with a double-blind procedure. *Am J Clin Nutr.* 1980;33(1):17-21.

5. Kwon PH, Jr, Rorick MH, Scrimshaw NS. Comparative tolerance of adolescents of differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks. II. Improvement of a double-blind test. *Am J Clin Nutr.* 1980;33(1):22–26.

6. Paige DM, Bayless TM, Huang SS, et al. Lactose hydrolyzed milk. *Am J Clin Nutr.* 1975;28(8):818–822.

7. Rorick MH, Scrimshaw NS. Comparative tolerance of elderly from differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks: a double-blind study. *J Gerontol.* 1979;34(2):191–196.

8. Suarez FL, Adshead J, Furne JK, et al. Lactose maldigestion is not an impediment to the intake of 1500 mg calcium daily as dairy products. *Am J Clin Nutr.* 1998;68(5):1118–1122.

9. Suarez FL, Savaiano D, Arbisi P, et al. Tolerance to the daily ingestion of two cups of milk by individuals claiming lactose intolerance. *Am J Clin Nutr.* 1997;65(5):1502-1506.

10. Vesa TH, Korpela RA, Sahi T. Tolerance to small amounts of lactose in lactose maldigesters. *Am J Clin Nutr.* 1996;64(2):197–201.

11. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med*. 1995;333(1):1–4.

12. Brand JC, Holt S. Relative effectiveness of milks with reduced amounts of lactose in alleviating milk intolerance. *Am J Clin Nutr.* 1991;54(1):148–151.

13. Rosado JL, Solomons NW, Lisker R, et al. Enzyme replacement therapy for primary adult lactase deficiency. Effective reduction of lactose malabsorption and milk intolerance by direct addition of beta-galactosidase to milk at mealtime. *Gastroenterology.* 1984;87(5):1072–1082.

14. Lybeck Sorensen K, Vergara Meersohn M, Sonne J, et al. A new type of low-lactose milk. Tolerance by lactose malabsorbers and evaluation of protein nutritional value. *Scand J Gastroenterol.* 1983;18(8):1063–1068.

15. Unger M, Scrimshaw NS. Comparative tolerance of adolescents of differing ethnic backgrounds to lactose-containing and lactose-free dairy drinks. I. Initial experience with a double-blind procedure. *Am J Clin Nutr.* 1980;33(1):17–21.

16. Cheng AH, Brunser O, Espinoza J, et al. Long-term acceptance of low-lactose milk. *Am J Clin Nutr.* 1979;32(10):1989–1993.

17. Lisker R, Aguilar L. Double blind study of milk lactose intolerance. *Gastroenterology.* 1978;74(6):1283–1285.

18. Montalto M, Nucera G, Santoro L, et al. Effect of exogenous beta-galactosidase in patients with lactose malabsorption and intolerance: a crossover double-blind placebo-controlled study. *Eur J Clin Nutr.* 2005;59(4):489–493.

19. Jarvinen RM, Loukaskorpi M, Uusitupa MI. Tolerance of symptomatic lactose malabsorbers to lactose in milk chocolate. *Eur J Clin Nutr.* 2003;57(5):701–705.

20. Xenos K, Kyroudis S, Anagnostidis A, et al. Treatment of lactose intolerance with exogenous beta-D-galactosidase in pellet form. *Eur J Drug Metab Pharmacokinet.* 1998;23(2):350–355.

21. Vesa TH, Lember M, Korpela R. Milk fat does not affect the symptoms of lactose intolerance. *Eur J Clin Nutr.* 1997;51(9):633–636.

22. Lin MY, Dipalma JA, Martini MC, et al. Comparative effects of exogenous lactase (beta-galactosidase) preparations on *in vivo* lactose digestion. *Dig Dis Sci.* 1993;38(11):2022–2027.

23. Rask Pedersen E, Jensen BH, Jensen HJ, et al. Lactose malabsorption and tolerance of lactose-hydrolyzed milk. A double-blind controlled crossover study. *Scand J Gastroenterol.* 1982;17(7):861–864.

24. Reasoner J, Maculan TP, Rand AG, et al. Clinical studies with low-lactose milk. *Am J Clin Nutr.* 1981;34(1):54–60.

25. Jones DV, Latham MC, Kosikowski FV, et al. Symptom response to lactose-reduced milk in lactose-intolerant adults. *Am J Clin Nutr*. 1976;29(6):633–638.

26. Mustapha A, Jiang T, Savaiano DA. Improvement of lactose digestion by humans following ingestion of unfermented acidophilus milk: influence of bile sensitivity, lactose transport, and acid tolerance of *Lactobacillus acidophilus*. *J Dairy Sci.* 1997;80(8):1537–1545.

27. Jiang T, Mustapha A, Savaiano DA. Improvement of lactose digestion in humans by ingestion of unfermented milk containing *Bifidobacterium longum*. *J Dairy Sci.* 1996;79(5):750–757.

28. Vesa TH, Marteau P, Zidi S, et al. Digestion and tolerance of lactose from yoghurt and different semi-solid fermented dairy products containing *Lactobacillus acidophilus* and bifidobacteria in lactose maldigesters—is bacterial lactase important? *Eur J Clin Nutr.* 1996;50(11):730–733.

29. Lerebours E, N'Djitoyap Ndam C, Lavoine A, et al. Yogurt and fermented-then-pasteurized milk: effects of short-term and long-term ingestion on lactose absorption and mucosal lactase activity in lactase-deficient subjects. *Am J Clin Nutr.* 1989;49(5):823–827.

30. Martini MC, Smith DE, Savaiano DA. Lactose digestion from flavored and frozen yogurts, ice milk, and ice cream by lactase-deficient persons. *Am J Clin Nutr.* 1987;46(4):636–640.

31. Lin MY, Yen CL, Chen SH. Management of lactose maldigestion by consuming milk containing lactobacilli. *Dig Dis Sci.* 1998;43(1):133–137.

32. Savaiano DA, AbouElAnouar A, Smith DE, et al. Lactose malabsorption from yogurt, pasteurized yogurt, sweet acidophilus milk, and cultured milk in lactase-deficient individuals. *Am J Clin Nutr.* 1984;40(6):1219–1223.

33. Newcomer AD, Park HS, O'Brien PC, et al. Response of patients with irritable bowel syndrome and lactase deficiency using unfermented acidophilus milk. *Am J Clin Nutr.* 1983;38(2):257–263.

34. Hertzler SR, Savaiano DA. Colonic adaptation to daily lactose feeding in lactose maldigesters reduces lactose intolerance. *Am J Clin Nutr.* 1996;64(2):232–236.

35. Briet F, Pochart P, Marteau P, et al. Improved clinical tolerance to chronic lactose ingestion in subjects with lactose intolerance: a placebo effect? *Gut.* 1997;41(5):632–635.

36. Cappello G, Marzio L. Rifaximin in patients with lactose intolerance. *Dig Liver Dis.* 2005;37(5):316–319.

Behavioral Factors Related to Lactose Intolerance and Bone Consequences

Susan L. Johnson, Ph.D.

Lactose intolerance describes a group of gastrointestinal symptoms associated with incomplete digestion of lactose including abdominal discomfort, cramps, flatulence, and nausea.[1] It is estimated that 29% of Americans have a reduced ability to digest lactose.[2,3] Among some ethnic groups in America, the estimated prevalence is much higher with approximately 15% of whites, 50% of Hispanics, and 80% of blacks being lactose intolerant.[2,4] These incidence rates, however, may greatly overestimate the percentage of those who experience symptoms after consuming usual amounts of dairy products. Individuals with lactose maldigestion (i.e., low lactase levels) may or may not experience the symptoms of lactose intolerance.[2] In many instances, lactose intolerance is either self-diagnosed or diagnosed by a physician using subjective information (i.e., description of symptoms or elimination of foods) instead of objective testing.[1,5,6] It has been suggested that the perception of being lactose intolerant is more influential than actual diagnosed lactose intolerance, as people who perceive they are lactose intolerant change their behavior due to the gastrointestinal symptoms they associate with dairy consumption.

Consuming adequate dairy foods is suggested to be important to achieve optimal health, particularly in relation to bone health. Research has revealed that milk, milk products, and calcium may reduce the risk of disorders including osteoporosis, hypertension, excess body weight and fat, and colorectal cancer.[1,7,8] Dairy products offer high calcium content and bioavailability at a relatively low cost.[1,7] Fluid milk is fortified with vitamin D to a level of 400 IU per quart, which has positive implications for bone mineral accretion.

The 2005 Dietary Guidelines for Americans recommends two to three servings of low-fat milk or milk products per day based on age.[9] It was found that 81% of all individuals surveyed in the 1999–2002 National Health and Nutrition Examination Survey (National Dairy Council, unpublished data) did not meet their dairy food intake recommendations. Specifically, more than 50% of children age 2 to 8, 77% of preadolescents and adolescents (age 9 to 19), and close to 90% of adults age 20 to 50 did not meet the recommendation. It is not clear what percentage of suboptimal dairy food consumption is attributed to lactose intolerance, but perceived lactose intolerance may unnecessarily discourage many people from consuming adequate amounts of dairy foods. For example, in a longitudinal study of 1,521 adolescent males and females in Minnesota (Project EAT), survey data revealed that perceived lactose intolerance in males was the only factor found to be associated with lower calcium intake at follow-up and with longitudinal decreases in calcium intake.[10]

Several psychosocial predictors of calcium intake have been identified for adolescent girls including knowledge of calcium-containing foods, self-efficacy for consuming calcium-rich foods, and availability of calcium-containing foods in the home.[11] The effects of the home environment on girls' calcium intake and bone mineral content have suggested that when milk is offered more often and when mothers reported drinking milk, girls consumed more dietary calcium from milk and had a higher bone mineral content.[12] Whether parental perceived lactose intolerance relates to child feeding practices and intake of lactose-containing foods has not been adequately investigated and represents an important opportunity for future research.

Prevalence rates of lactose intolerance may be lower than originally suggested among some ethnic groups.[13] Despite estimates of lactose intolerance in 80% of blacks,[14] only 24% of blacks surveyed in a nationally representative sample actually reported being lactose intolerant.[15] Cultural factors may impact low dairy consumption in this population, and the diet of African Americans is more likely to contain low amounts of certain nutrients including calcium, magnesium, and phosphorus, because blacks report lower consumption of dairy foods.[16] According to a study conducted on the adherence of minorities to the food guide pyramid, the Hispanic population has suboptimal consumption of dairy foods ranging from 1.5 to 1.9 average servings per day regardless of whether they were born in the United States or born in Mexico, South America, or Central America.[17] The low intake of calcium-rich dairy foods and other nutrients by these populations is of particular concern, since it potentially contributes to bone loss and hypertension.[2]

Several factors may contribute toward individuals perceiving themselves to be lactose intolerant. Recent studies indicate that perceived lactose intolerance, particularly among minorities, may start at an early age. One study that conducted focus groups to determine the perception of preadolescent and adolescent Asian, Hispanic, and white girls found that Hispanic girls were most likely to relate lactose intolerance symptoms with milk consumption.[18] This group also had the most negative perceptions of milk. Another study reported that approximately 20% of white, Asian, or Hispanic preadolescent and adolescent girls age 10 to 13 considered themselves to be milk intolerant. However, of those who considered themselves to be milk intolerant, more than half were actually not lactose maldigesters.[19]

A recent study was designed to (1) understand the actual prevalence of lactose intolerance and its practical significance among blacks, Hispanics, and whites, and (2) to understand the concerns lactose-intolerant individuals have with respect to dairy consumption. The aim included identifying strategies that can be implemented to facilitate and increase dairy food consumption to the recommended levels among these individuals.[20]

Adults who were screened for symptoms related to lactose intolerance participated in a focus group conducted using the Nominal Group Technique.[21] Participants' insights, knowledge, and experiences were tapped to identify strategies they used to deal with their perceived lactose intolerance and problems they encountered due to lactose

intolerance. Consequently, each participant selected what he or she individually perceived as (1) the three most significant facilitative strategies related to reducing problems with their lactose intolerance, or (2) the three most significant problems they encountered with having lactose intolerance. These data yielded a rank-ordered list. In Tables 1 and 2, the six most commonly ranked items are listed for each question.

Table 1. Most Important Things That Worked To Reduce Problems With Lactose Intolerance

Item	Responses
1	Avoid all dairy products
2	Use alternatives to dairy products such as soy-based products
3	Limit the intake of whole-milk dairy products
4	Use lactase-free milk
5	Use lactase pills
6	Use medications such as Gas-X

Table 2. Most Important Problems Encountered With Having Lactose Intolerance

Item	Responses
1	Not able to eat certain foods that you like
2	Worry about embarrassment at social events because of lactose intolerance
3	Limit your physical activity because of lactose intolerance
4	Concern about not getting enough calcium
5	Concern about developing osteoporosis or other bone diseases
6	Limit activities that take you away from available restrooms

It is of note that the most common strategies opted for are the exclusion of dairy products, even if these foods are liked, and that pursuing this option results in a concomitant concern regarding calcium intake and the development of osteoporosis. These data suggest that even though individuals are informed about the consequences of chronic low calcium intake, they will choose that option to avoid the negative side effects of (perceived) lactose maldigestion.

The consequences for choosing diets low in calcium are most significantly related to lower bone mineral content. One study of adolescent girls (a substudy of the Adequate Calcium Today study) reported that girls who perceived themselves to have lactose maldigestion self-selected diets restricted in dairy products, had lower calcium intakes (212 mg less calcium), and lower spinal bone mineral content values (although no difference in total body mineral content was observed).[19]

In adult populations in Estonia, the self-perception of lactose intolerance has been reported to be a better predictor of milk consumption than hypolactasia (LCT gene as measured by C/T_{-13910} variant). Furthermore, milk consumption was among the predictors of bone mineral density, whereas neither the LCT genotype nor the lactase phenotype predicted bone mineral density.[22] Similar findings were reported in a 12-year longitudinal study in Finland in which lactase genotype was not related to differences in bone mineral content or bone mineral density. However, males with lactase nonpersistence (C/C_{-13910} genotype) had the highest loss of bone mass in the lumbar spine.[23]

Summary

Individuals who perceive themselves to be lactose intolerant alter their diets, whether or not they have the genetic variant associated with lactose maldigestion. These changes in food selection appear to be driven by social concerns and lead to ambivalence on the part of individuals who perceive that they are lactose intolerant. On one hand, they wish to avoid unpleasant consequences associated with lactose-containing products; on the other hand, they are concerned about the consequences of poor calcium intake and reduced physical activity levels. The outcome for those who perceive they are lactose intolerant is an increased risk for poor bone health. Additional research investigating the intergenerational transmission of beliefs and feeding practices within families who perceive they manifest symptoms of lactose maldigestion would inform future intervention development and practice at the primary care level.

References

1. Miller GD, Jarvis JK, McBean LD. *The Handbook of Dairy Foods and Nutrition.* 3rd ed. Boca Raton, LA: CRC Press; 2007.

2. Jarvis JK, Miller GD. Overcoming the barrier of lactose intolerance to reduce health disparities. *J Natl Med Assoc.* 2002;94:55–66.

3. Suarez FL, Savaiano DA. Diet, genetics, and lactose intolerance. *Food Tech.* 1997;51:74–76.

4. Sabi T. Hypolactasia and lactase persistence. Historical review and terminology. *Scand J Gastroenterol Suppl.* 1994;202:1–6.

5. Montes RG, Perman JA. Lactose intolerance. Pinpointing the source of nonspecific gastrointestinal symptoms. *Postgrad Med.* 1991;89:175–178, 181–174.

6. Lovelace HY, Barr SI. Diagnosis, symptoms, and calcium intakes of individuals with self-reported lactose intolerance. *J Am Coll Nutr.* 2005;24:51–57.

7. Nicklas TA. Calcium intake trends and health consequences from childhood through adulthood. *J Am Coll Nutr.* 2003;22:340–356.

8. Huth PJ, DiRienzo DB, Miller GD. Major scientific advances with dairy foods in nutrition and health. *J Dairy Sci.* 2006;89:1207–1221.

9. U.S. Department of Health and Human Services and U.S. Department of Agriculture. *Dietary Guidelines for Americans, 2005.* 6th ed. Washington, DC: U.S. Government Printing Office; 2005. health.gov/dietaryguidelines/dga2005/document/pdf/DGA2005.pdf. Accessed November 19, 2009.

10. Larson NI, Neumark-Sztainer D, Harnack L, Wall M, Story M, Eisenberg ME. Calcium and dairy intake: longitudinal trends during the transition to young adulthood and correlates of calcium intake. *J Nutr Educ Behav*. 2009;41:254–260.

11. Sharma SV, Hoelscher DM, Kelder SH, Day RS, Hergenroeder A. Psychosocial, environmental and behavioral factors associated with bone health in middle-school girls. *Health Educ Res.* 2008;24;173–184.

12. Fisher JO, Mitchell DC, Smiciklas-Wright H, Mannino ML, Birch LL. Meeting calcium recommendations during middle childhood reflects mother-daughter beverage choices and predicts bone mineral status. *Am J Clin Nutr.* 2004;79:698–706.

13. McBean LD, Miller GD. Allaying fears and fallacies about lactose intolerance. *J Am Diet Assoc.* 1998;98:671–676.

14. National Digestive Diseases Information Clearinghouse. Lactose Intolerance. Washington, DC: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 2004. digestive.niddk.nih.gov/ddiseases/pubs/lactoseintolerance/. Accessed November 19, 2009.

15. Wooten WJ, Price W. Consensus report of the National Medical Association. The role of dairy and dairy nutrients in the diet of African Americans. *J Natl Med Assoc.* 2004;96:5S–31S.

16. Fulgoni V 3rd, Nicholls J, Reed A, et al. Dairy consumption and related nutrient intake in African-American adults and children in the United States: continuing survey of food intakes by individuals 1994–1996, 1998, and the National Health and Nutrition Examination Survey 1999–2000. *J Am Diet Assoc.* 2007;107:256–264.

17. Sharma S, Murphy SP, Wilkens LR, et al. Adherence to the food guide pyramid recommendations among African Americans and Latinos: results from the multiethnic cohort. *J Am Diet Assoc.* 2004;104:1873–1877.

18. Auld G, Boushey CJ, Bock MA, et al. Perspectives on intake of calcium-rich foods among Asian, Hispanic, and white preadolescent and adolescent females. *J Nutr Educ.* 2002;34:242–251.

19. Matlik L, Savaiano D, McCabe G, VanLoan M, Blue CL, Boushey CJ. Perceived milk intolerance is related to bone mineral content in 10- to 13-year-old female adolescents. *Pediatrics.* 2007;120:e669–e677.

20. Nicklaus TA, Hughes SO, Shewchuk RM, Qu H. Understanding perceived lactose intolerance in white, black, and Hispanic adults. (Manuscript in preparation; personal communication.)

21. Kull M, Kallikorm R, Lember M. Impact of molecularly defined hypolactasia, self-perceived milk intolerance and milk consumption on bone mineral density in a population sample in Northern Europe. *Scand J Gastroenterol.* 2009;44:415–421.

22. Laaksonen MML, Impivaara O, Sievanen H, et al. Associations of genetic lactase non-persistence and sex with bone loss in young adulthood. *Bone.* 2009;44:1003–1009.

23. Miller D, Shewchuk R, Elliot TR, Richards S. Nominal Group Technique: a process for identifying diabetes self-care issues among patients and caregivers. *Diabetes Educ.* 2000;26:305–310, 312, 314.

Psychological Impacts: Strategies Effective in Managing Individuals Diagnosed With Lactose Intolerance

Janet E. Taylor, M.D., M.P.H.

There are many chronic diseases related to underconsumption of recommended dietary nutrients including vegetables, fruits, and whole grains,[1] dietary patterns,[2] underlying physiologic conditions, and psychological factors.[3] Chronic medical conditions such as osteoporosis, cardiovascular disease, and, in particular, hypertension and stroke have been associated with a deficiency in calcium. This may be more serious and consequential in ethnic minority groups. African Americans, Hispanics, and Native American Indians have higher than average risks for the development of hypertension and stroke[4] while demonstrating low calcium and dairy food consumption. In the United States, low calcium intakes may be found in up to 75% of individuals.[4] Dairy foods account for up to 72% of calcium, and low calcium intake is widely seen as a public health problem.[5] Physiologic functions such as nerve conduction, muscle contraction, cell adhesiveness, mitosis, blood coagulation, and structural support of the skeleton are all related to calcium.[5]

Health behaviors such as the consumption of dairy foods are influenced by social context. Social context is important in understanding the distribution of health behaviors and health outcomes[6] and are determined by socioeconomic position, income, race/ethnicity, gender, and level of education. Cultural beliefs about health and illness also may impact health behaviors.

A goal of the United States (Healthy People 2010) has been to reduce health disparities such as overweight and obesity between many ethnic and racial groups.[7] Rising obesity rates in the United States contribute to chronic disease, with obesity resulting in many efforts to moderate the food environment. Multi-focused efforts have placed a focus on “individual responsibility,” altering the food environment in neighborhoods and schools, suggestions on governmental intervention with proposals to restrict sales of fats and sweets or impose taxes, and a push to limit advertising and improve access to healthier foods within at-risk communities.[8] Food access can be defined as both a financial and physical need. Underconsumption of dairy foods has been related to medical conditions such as hypertension, bone loss, and colon cancer[4] and remains a physiologic and psychological challenge for many in ethnic communities.

The health impact of decreased calcium intake in ethnic populations has been well documented. A diet that consists of three or more consumptions of dairy foods per day is usually adequate.[9] Less than half of African Americans eat one or more servings of dairy foods daily.[2] A study of 168 Asian and Asian American college students indicated that the majority consumed low amounts of daily calcium and did not take supplements

nor know how much they should take.[10] A survey of 405 Latina women diagnosed with lactose intolerance indicated that more than half were unsure of what foods caused discomfort, and 12% removed dairy completely from their diet.[11] Children of all ethnic groups are influenced by their parental choices and their own perceived milk intolerance.[12]

A major barrier to adequate daily calcium intake is *lactose intolerance*. This term refers to the occurrence of gastrointestinal symptoms resulting from the incomplete digestion of lactose, a carbohydrate. It is caused by a shortage of the enzyme, lactase. There are three basic types:

a. Primary lactose intolerance is the most common form and is genetically determined. Symptoms do not usually become apparent until late adolescence or early adulthood.

b. Secondary lactose intolerance occurs as a result of disease, surgery, radiation, or medications. Lactase activity is restored when the underlying condition resolves.

c. Congenital lactose intolerance, a lifelong complete absence of lactase, is a rare condition.[2]

The prevalence of lactose intolerance in U.S. populations varies. Within the United States, 80–90% of African Americans, 95–100% of Native Americans, 80–90% of Asian Americans, and 50–55% of Latinos may be lactose intolerant.[2] Globally, it is estimated that lactose nonpersistence may affect up to 70% of the world's population.[9] It is important to note the difference between lactose maldigestion (incomplete lactose digestion secondary to low levels of lactase) versus lactose intolerance (symptoms of bloating, cramping, and diarrhea that may or may not occur with undigested lactose in the intestinal tract).[13] Clinical tests should be performed to establish a definitive diagnosis, as opposed to allowing patients to self-diagnose.

Confusion, public awareness campaigns, and misperceptions about lactose intolerance continue to contribute to nutrient deficiencies and can worsen lactose intolerance and affect underconsumption of dairy foods within families. There is a potential benefit of healthcare providers having the capacity to implement individualized approaches to the treatment of lactose intolerance. A successful healthcare outcome, in addition to an accurate diagnosis and actionable treatment option, also requires an understanding of the psychological factors in lactose intolerance. The American public also needs to understand the health benefit of consuming foods that are high in calcium.

An underlying food intolerance like a food allergy, irritable bowel syndrome, and lactose intolerance may present with a clear constellation of gastrointestinal symptoms as well as psychological sequelae. Undiagnosed individuals with gastrointestinal complaints may present with somatization preoccupation[14] and psychological dysfunction (i.e., depression, anxiety, and quality of life impairment.[15] A recent survey of more than 400

African American women reported that 75% of them were self-diagnosed, and almost one-third had not contacted a healthcare provider to confirm the diagnosis.[16] The social impact was significant, as almost two-thirds reported feeling inconvienced by the diagnosis and worried about symptoms occurring during social events. Latina women had similar concerns and were unsure about what foods caused discomfort. In both groups, almost 12% totally removed dairy foods from their dietary regimen. Asian populations also had inadequate knowledge about calcium intake and minimal contact with healthcare providers.[10]

The role of physicians and health professionals to make the right diagnosis, discuss treatment and food options, as well as provide psychosocial education and support is critical. It has been widely reported that "public awareness and misunderstandings of lactose intolerance are at an all-time high."[3] Children who have a perceived milk intolerance will self-impose a milk restriction, starting as early as age 10.[12] These early attitudes can affect bone mineral growth in adolescents who restrict calcium intake. As in adults, lactose maldigestion in adolescents does not equal lactose intolerance.[12] Individuals who self-diagnose are at risk for unnecessary dietary restrictions, expense, possible nutritional shortcomings, and a failure to treat other causes.[3] Patients also should be aware that a diagnosis does not predict the occurrence of symptoms of intolerance.

Effective disease management of lactose intolerance includes an understanding of the psychological burden for the patient and the role and need of the clinician to be aware of psychological challenges that may impact an individual and his/her family's quality of life, adherence and compliance, and dietary intake of calcium.

Psychological strategies must be implemented after a correct diagnosis has been made of lactose intolerance.[13] An awareness of the patient's psychosocial factors (i.e., attitudes and knowledge, social norms, and perceived control) can determine the use of healthcare facilities in a timely manner.[17] Patient knowledge can have a direct impact on action. Self-efficacy, or the perception of an individual of his or her own ability to perform an action to achieve a desired outcome, is a powerful determinant of health behaviors and outcomes.[18] Shared decision-making in healthcare decisions can honor the patient by respecting his or her choices, culture, social context, and specific needs.[19,20] The acceptance by patients of their own physical state by practicing mindfulness and acceptance can improve outcomes by promoting openness and exploring thoughts and feelings. Providers can encourage patients to self-monitor their mental and physical state by providing them with the tools of self-awareness.[21,22] Peer support and strong social networks have been associated with changes in fruit and vegetable intake, and may be applicable to increasing social support and information for lactose-intolerant patients.[6] The utilization of technology (i.e., emails, texts, video games) and education has been utilized to stimulate dietary change and to promote health-related behavior changes.[1,23]

Understanding the patient's belief about lactose intolerance can inform the provider about coping responses that can influence health outcomes. Illness beliefs have five aspects: identity (how the patient describes illness), cause, timeline (duration of symptoms), consequences (expected outcome and effects of the illness), and perceived controllability/self-management.[24] Another psychological strategy is to increase capacity and confidence in healthcare providers about discussing the role of nutrition, calcium intake, and lifestyle risk factors for patients who have lactose intolerance. One study taught pharmacists utilizing their own nutritional status. Findings were consistent with an increased willingness to talk to healthcare consumers.[7,25]

References

1. Madlensky L, Natarajan L, Flatt S, Faerber S, Newman V, Pierce J. Timing of dietary change in response to a telephone counseling intervention. *Health Psychol.* 2008;27(5):539–547.

2. McBean L, Miller G. Allaying fears and fallacies about lactose intolerance. *J Am Diet Assoc.* 1998;671–676.

3. National Medical Association. Lactose Intolerance and African-Americans. *J Nat Med Assoc Suppl.* 2009;101(10).

4. Jarvis J, Miller G. Overcoming the barrier of lactose intolerance to reduce health disparities. *J Nat Med Assoc.* 2002;94(2):55–66.

5. Miller G, Jarvis J, McBean L. The importance of meeting calcium needs with foods. *J Am Coll Nutr.* 2001;20(2):168S–185S.

6. Sorensen S, Stoddard A, Dubowitz T, et al. The influence of social context on changes in fruit and vegetable consumption: results of the Healthy Directions Studies. *Am J Public Health.* 97(7):1216–1227.

7. Chang L, Popovich N, Iramaneerat C, Smith E, Lutfiyya M. A clinical nutrition course to improve pharmacy students' skills and confidence in counseling patients. *Am J Pharm Educ.* 2008;72(3):66.

8. Drewnowski A, Darmon N. Food choices and diet costs: an economic analysis. *J Nutr.* 2005;135(4):900–904.

9. Byers K, Savalano D. The myth of increased lactose intolerance in African-Americans. *J Am Coll Nutr.* 2005;24(6)5695–5735.

10. Nguyen D, O'Connell M. Asian and Asian-American college students' awareness of osteoporosis. *Pharmacotherapy.* 2002;22(8):1047–1054.

11. Hispanic PR Wire. New research finds Latinas with lactose intolerance manage their conditions by limiting or avoiding dairy. September 21, 2009.

12. Matlik L, Savalano D, McCabe G, VanLoan M, Blue C, Boushey C. Perceived milk intolerance is related to bone mineral content in 10- to 13-year-old female adolescents. *Pediatrics.* 2007;120:669–677.

13. Lovelace H, Barr S. Diagnosis, symptoms and calcium intakes of individuals with self-reported lactose intolerance. *J Am Coll Nutr.* 2005;24(1):51–57.

14. Teufel M, Biederman T, Rapps N, et al. Psychological burden of food allergy. *World J Gastroenterol.* 2007;3(25):3456–3465.

15. Lackner J, Jaccard J, Krasner S, Katz L, Gudleski G, Blanchard E. How does cognitive behavior therapy for IBS work?: a mediational analysis of a randomized clinical trial. *Gastroenterology.* 2007;133(2):433–444.

16. Richard Day Research. Lactose Intolerance in Multicultural Communities Survey. 2009.

17. Bradley E, McGraw S, Curry L, et al. Expanding the Andersen model: the role of psychosocial factors in long-term care use. *Health Sciences Res.* 2002;37:5.

18. Franks P, Chapman B, Duberstein P, Jerant A. Five factor model personality factors moderated the effects of an intervention to enhance chronic disease management self-efficacy. *Br J Health Psychol.* 2009;14(3)473–487.

19. Butz A, Walker J, Pulsifer M, Winkelstein M. Shared decision making in school age children with asthma. *Pediatr Nurs.* 2007;33(2):111–116.

20. Goff S, Mazor K, Meterko V, Dodd K, Sabin J. Patients' beliefs and preferences regarding doctor's medication recommendations*. J Gen Intern Med. 23*(3):236–241.

21. Naliboff B, Frese M, Rapgay L. Mind/body psychological treatments for irritable bowel syndrome. *eCAM.* 2008;5(1)41–50.

22. Gaylord S, Whitehead W, Coble R, et al. Mindfulness for irritable bowel syndrome: protocol development for a controlled clinical trial. *BMC Complementary and Alternative Med.* 2009;9:24.

23. Baranowski T, Buday R, Thompson D, Baranowski J. Playing for real: video games and stories for health-related behavior change. *Am J Prev Med.* 2008;34(1):74–82.

24. Brown C, Battista D, Sereika S, Bruehlman R, Dunbar-Jacob J, Thase M. Primary care patients' personal illness models for depression: relationship to coping behavior and functional disability. *Gen Hosp Psychiatry.* 29(6):492–500.

25. Ampt A, Amoroso C, Harris M, McKensie S, Rose V, Taggart, J. Attitudes, norms and control influencing lifestyle risk factor management in general practice. *BMC Fam Pract.* 2009;10:59.