Lactose Intolerance: An Unnecessary Risk for Low Bone Density

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Abstract

The potential for lactose intolerance causes 25–50 million Americans and an unknown number of people around the world to avoid milk. Milk avoidance is a significant risk factor for low bone density. Individuals who avoid milk, due to intolerance or learned aversion, consume significantly less calcium and have poorer bone health and probable higher risk of osteoporosis. Lactose intolerance is easily managed by: (1) regular consumption of milk that adapts the colon bacteria and facilitates digestion of lactose; (2) consumption of yogurts and cheeses and other dairy foods low in lactose; (3) consumption of dairy foods with meals to slow transit and maximize digestion, and (4) use of lactose-digestive aids. As dairying spreads around the world to new markets and dairy foods become the dominant source of calcium in these markets, the potential for lactose intolerance will grow. Management of lactose intolerance globally will require both education and product development.

The potential for lactose intolerance causes 25–50 million Americans and an unknown number of people around the world to avoid milk. Milk avoidance is a significant risk factor for low bone density. Individuals who avoid milk, due to intolerance or learned aversion, consume significantly less calcium and have poorer bone health and probable higher risk of osteoporosis. Milk is also an excellent source of high quality protein and other nutrients, such as potassium, sodium, and B vitamins, plus water. Research over the past 30 years demonstrates that lactose intolerance is easily managed by: (1) regular consumption of milk that adapts the colon bacteria and facilitates digestion of lactose; (2) consumption of yogurts and cheeses and other dairy foods low in lactose; (3) consumption of dairy foods with meals to slow transit and maximize digestion, and (4) use of lactose digestive aids.
Lactose intolerance can cause moderate and acute symptoms of excessive flatulence, stomach discomfort and diarrhea. Typically, initial symptoms include initial stomach distension and discomfort followed by flatulence. If maldigestion is severe, diarrhea can quickly follow. The occurrence of symptoms depends on several variables. Those variables include dose, gastrointestinal motility, individual digestibility, and microflora profile.

**Dose:** Typically, one cup of milk (containing 12 g of lactose) or lactose in water served alone or with a meal is well tolerated by maldigesters, even those claiming severe intolerance (table 1). As the results below demonstrate in a double-blinded, randomized protocol, physiological relevant symptoms occur only when more than 12 g of lactose is consumed.

If milk (or in the example below, food supplement containing lactose) is consumed with breakfast, it remains well tolerated (fig. 1). Dairy sources vary considerably in lactose content. Lactose is water soluble and thus found in the whey portion when curds and whey are separated during cheese production. Thus, hard cheeses have minimal lactose and soft cheeses are intermediate in lactose content. Yogurts are well tolerated due to microbial β-galactosidase that is active in vivo during digestion, supplementing the body’s own lactase activity. The primary source of lactose in the diet is fluid milk.

**Gastrointestinal Motility:** The rate at which the lactose passes into the intestine is a function of stomach emptying and meal feeding. Lactose tolerance is significantly improved when lactose is fed with a meal. The effect is more difficult to demonstrate with individual foods such as whole milk compared to fat-free milk.

**Digestibility:** The residual lactase activity in the small intestine presumably varies among individuals and likely influences tolerance. However, this variance is not well understood or evaluated relative to tolerance.

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**Table 1.** Intolerance symptoms from lactose in water consumed on an empty stomach for breakfast [1]

<table>
<thead>
<tr>
<th>Lactose dose</th>
<th>Flatus frequency (over 5 h)</th>
<th>Flatus ratings</th>
<th>Abdominal pain ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 g</td>
<td>4.0 ± 1.3a</td>
<td>3.4 ± 1.0a,b</td>
<td>1.7 ± 0.8a</td>
</tr>
<tr>
<td>2 g</td>
<td>4.3 ± 1.8a</td>
<td>3.8 ± 1.4b</td>
<td>1.7 ± 0.9a</td>
</tr>
<tr>
<td>6 g</td>
<td>5.1 ± 0.6a</td>
<td>1.9 ± 0.9a</td>
<td>1.2 ± 0.5a</td>
</tr>
<tr>
<td>12 g</td>
<td>4.6 ± 1.1a</td>
<td>3.5 ± 1.3b</td>
<td>3.4 ± 0.8b</td>
</tr>
<tr>
<td>20 g</td>
<td>9.0 ± 2.6b</td>
<td>6.6 ± 1.8c</td>
<td>5.3 ± 1.8b</td>
</tr>
</tbody>
</table>

a,b,c Treatments not sharing the same letter are significantly different (p < 0.05); ratings of symptoms of hours 1–8.
**Microflora:** The ability of the large intestine bacteria to compensate for maldigestion depends on how well the microflora are adapted to metabolize lactose.

Regular consumption of lactose in both double-blinded and free living studies suggests that diet history and adaptation are major factors in determining tolerance. In the example below (fig. 2), subjects were adapted to either dextrose or lactose over a 10-day period and then challenged with a breath hydrogen test.
Table 2. Intolerance symptom ratings to the lactose challenges after the dextrose and lactose feeding periods [2]

<table>
<thead>
<tr>
<th></th>
<th>After dextrose</th>
<th>After lactose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flatus ratings (n = 20)</td>
<td>8.1 ± 1.6</td>
<td>4.5 ± 1.0(^a)</td>
</tr>
<tr>
<td>Flatus frequency (n = 6)</td>
<td>23.0 ± 2.8</td>
<td>11.0 ± 2.6(^b)</td>
</tr>
</tbody>
</table>

Data are the sum ratings for hours 1–8 after the lactose challenge (mean ± SEM).
\(^a\) \(p = 0.025\), \(^b\) \(p = 0.028\), significantly different from after dextrose.

Table 3. Impact of lactose intolerance and lactose maldigestion on bone density

<table>
<thead>
<tr>
<th>Population</th>
<th>Sample size</th>
<th>Age years</th>
<th>Summary</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal women</td>
<td>58</td>
<td>57 ± 7</td>
<td>No significant difference between LI and non-LI women</td>
<td>Corazza et al. [3]</td>
</tr>
<tr>
<td>Young adults</td>
<td>103; includes 55 with LI</td>
<td>28 ± 2</td>
<td>↓ BMD with LI</td>
<td>Di Sefano et al. [4]</td>
</tr>
<tr>
<td>Adults</td>
<td>66 with LI</td>
<td>20 – 78</td>
<td>↓ BMD and ↑ bone turnover with LI</td>
<td>Segal et al. [5]</td>
</tr>
<tr>
<td>Adults</td>
<td>218; 115 with LI; 103 controls</td>
<td>58 ± 11</td>
<td>No significant difference in BMD; ↑ risk of vertebral fracture among LI subjects</td>
<td>Kudlacek et al. [6]</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>33 with idiopathic osteoporosis</td>
<td>54 (31–65)</td>
<td>↓ lactose absorption among osteoporotic subjects</td>
<td>Finkenstedt et al. [7]</td>
</tr>
<tr>
<td></td>
<td>33 controls</td>
<td>56 (33–67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>745</td>
<td>≥60</td>
<td>↑ dairy → ↑ BMD (hip) in males, not females</td>
<td>McCabe et al. [8]</td>
</tr>
<tr>
<td>Young women</td>
<td>291; 100 with LI</td>
<td>10–13</td>
<td>Perceived LI (even at 10 years) → ↓ BMD reflecting low milk intake</td>
<td>Matlik et al. [9]</td>
</tr>
<tr>
<td>Children</td>
<td>19</td>
<td>9.6 ± 1.9</td>
<td>Low lactose intake → low Ca intake and low BMD among LI children</td>
<td>Stallings et al. [10]</td>
</tr>
</tbody>
</table>

BMD = Bone mineral density; LI = lactose intolerance.
The amount of gas and gastrointestinal symptoms were dramatically reduced when subjects were adapted to lactose (table 2).

The primary clinical issue of concern related to lactose maldigestion and intolerance is reduced calcium intake, leading to low bone density and thus increasing the risk for osteoporosis. Studies that typify these concerns are summarized in table 3 and illustrated in figure 3.

The preponderance of evidence among those with perceived and diagnosed lactose intolerance indicates that there is an increased risk of decreased bone mineral density. This clinical presentation increases the risk of bone fractures, such as vertebral bone. The poor bone health status reflects avoidance by consumers to eat dairy products, even among children, vs. the evidence that those with lactose intolerance can consume and tolerate at least 8 oz (240 ml) of milk or related products. This is consistent with the numerous studies that indicate a strong relationship between dietary calcium and vitamin D with bone fragility, particularly the spine [11].

The incidence of symptoms resulting from intolerance to milk and dairy products in various populations has been well documented [12–15]. The FDA’s Consumer Health Information website [16] states that NIH ‘estimates that 30–50 million Americans are lactose intolerant’. The NIH’s website contains a substantial amount of information on this condition [17]. Numbers of individuals who avoid milk worldwide are not known. But, it is likely that this number will grow dramatically in the years ahead as dairying is expanded in global markets such as China and the Middle East, and worldwide dietary patterns evolve.

Dairy foods account for 73% of the calcium available in the US food supply [18] and 51% of the total calcium intake [19]. Calcium intakes of most Americans are far below recommendations [20–22]. Fleming and Heimbach [23] provide specific data of the amount of calcium intake in the US by sex, age, ethnic group, region, and food group. Further, it is difficult to get ade-
quate calcium in a western diet without dairy foods [23–25]. It is hypothesized that adequate calcium not only helps reduce the risk of osteoporosis and hypertension [26, 27], but also possibly reduces the risk for several cancers [9, 26].

An estimated 75% of the world’s population and 25% of Americans are maldigesters of lactose. Like all other mammals, these maldigesters lose 90+% of their infantile levels of lactase during early childhood development. Thus, they have limited ability to digest lactose into its component sugars (galactose and glucose) in the small intestine. The NIH estimate of 30–50 million milk avoiders is supported by a survey by Elbon et al. [28] demonstrating that 17% of Whites and 35% of Blacks indicated a perceived milk intolerance. The National Dairy Council African American Lactose Intolerance Study [28] reported that 24% of respondents considered themselves lactose intolerant, and 49% reported some physical discomfort at some time following dairy food consumption, of which 27% said they experience discomfort all the time. Evidence suggests that all maldigesters have a similar potential for intolerance [29, 30]. If the conservative estimate of 24% of the entire African-American population is used for extrapolation (i.e. 35% of African-American maldigesters are estimated to be intolerant since only 75% of African-Americans are maldigesters) to the general US population, at least 25 million (1/3 of 75 million) Americans are avoiding dairy foods due to lactose intolerance. If the 17% figure from Elbon et al. [28] is used, 50 million Americans are avoiding dairy foods.

As the dairy industry continues to develop worldwide, and dairy foods become a dominant global source of calcium in the diet, the potential for symptoms of lactose intolerance among maldigesters will continue to grow. Education and new product development can address this issue.

References

Lactose Intolerance

16 http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm094550.htm.

Discussion

Dr. Anderson: I was really impressed by your point that if you give lactose and you change the microbiology in the large intestine then you may have an impact on obesity, appetite control and food intake regulation. Maybe people should be recommended to take lactose to change their gut population and combat obesity. There was a discussion earlier that obese people have different microflora than lean people. One
would argue you don’t know which is the chicken and which is the egg, so perhaps it is not a simple solution. I think your point that you can change the bacteria quite quickly depending on the type of diet is a very important observation. I think it’s the same thing with dietary fiber, and as you know many people say they cannot tolerate fiber when it fact it is due to healthy activity in the colon. However, with constant application they do adapt. Do both amount and type of bacteria change?

Dr. Savaiano: We have a paper on soy, a soy isolated product that’s high in stachyose and raffinose showing adaptation increase in the bifidus. My graduate student just had it accepted. I have a colleague who is a microbiologist, we are also in the middle of the study trying to do the similar kind of work with lactose. It’s clear that it looks like bifidus will change, from everything we know about bifidus it will rather go up. But the difference between change in the number of bacteria, the species of bacteria and the metabolic capacity of bacteria hasn’t been given enough attention because one might not change the nature of the bacteria in terms of their species, but one might induce an enzyme activity or metabolic pathway as we have shown with lactose, where you can increase hydrogen utilization and increase β-galactosidase. But the numbers of bacteria do not change at all, there may simply be an induction or you might see an increase in certain populations, or both. The molecular tools we are now developing I think will start to allow us to answer some of those interesting questions, but they are not easy questions to answer.

Dr. Haschke: We have discussed that gene polymorphisms are associated with lactose intolerance. At least in European countries, screening to detect those polymorphisms is done in many hospitals when pediatric or adult patients are suspected to have lactose intolerance. The diagnosis is then confirmed by positive hydrogen breath testing. Could you elaborate on this and on polymorphisms which have been detected in populations other than the Caucasian?

Dr. Savaiano: We thought there were three genetic polymorphisms for persistence, one originated out of northern Europe, one originated out of the Middle East and one originated out of central Africa. It now looks like there are at least seven or eight polymorphisms, most of them in Africa. There is new evidence of finding six polymorphisms in parts of Africa where we have persistence. So this move to persistence is a very easy change that happens in a number of environments for a number of reasons, and it’s probably different in those seven or eight different populations. How that difference influences tolerance, we don’t have any idea. Whether that actually influences tolerance, we don’t know. The genetic testing that’s going on is highly correlated with the hydrogen test, it seems to work quite effectively, but the hydrogen testing in a clinical setting is a challenge. In a research setting it’s actually quite easy. But yes, the new tools are growing, and I think clinicians will find their use probably a lot easier. Will they tell us something different than what we already know, I am not sure.

Dr. Prentice: Over coffee, we were talking about the change in the microbiota that occurs between a milk-based diet and a rice-based diet. Given what you have just told us about inducing lactase in the microbiota, is the ability to digest lactose going to depend on the type of carbohydrate that is generally the staple in the population?

Dr. Savaiano: Presumably, you would need a galactose-glucose bond, the β-galactosidic bond, in order to induce the pathway. So in theory, one would find compounds that have that bond potentially doing the same thing. I think that’s probably all I have to say on that given what we are doing commercially, but certainly I do believe that if you took stachyose or raffinose and you fed it, you would get β-galactoside induction at least, you might secondarily get some of that but clearly you get changes in the microbiota. I live in a place where there are lots of soybean farmers, and the soybean farmers tell me that if they eat soy for a couple of weeks they are fine, they don’t have any symptoms of flatulence or intestinal distress, so my soybean farmer friends tell
me they adapt. Microbiota are incredibly adaptable. Many of us who traveled over the world probably have had some changes in our microbiota with the change in diet, some of us for the better and some for the worse, and as we go back we go back to those environments again. I think it’s a huge area of research.

*Dr. Prentice:* I was thinking more about inducing tolerance to lactose if your carbohydrate background was different.

*Dr. Savaiano:* I think that the microbiota are incredibly responsive to whatever you feed them; so if you feed them something, they are going to adapt to use it to continue to grow and prosper in their microenvironment. Any carbohydrate you feed them, they will adapt to that carbohydrate. Bread, for example, has about 10% nondigestible starch, that’s probably another place where there is some potential for adaptation.

*Dr. Hernell:* If you analyze small intestinal biopsies from patients with congenital lactase deficiency, the residual activity is extremely low, it is virtually absent. But if you do the same on individuals with hypolactasia, you always find residual activity which, as you showed, varies considerably. What is your opinion, which fraction of these individuals do lose 90% or more of their activity, because probably 10% residual activity is what most people would need to remain lactose tolerant.

*Dr. Savaiano:* There is an interesting study by Levett in the US that was done in the 1970s I believe, where he demonstrated that in nonpersistent individuals about half of lactose was still digested in the small bowel. So the residual lactase is very important. And, in fact, if you feed lactulose which is completely nondigested vs. lactose, you have to feed about twice much lactose to get the same hydrogen curves. That would be indirect evidence that would suggest that this residual lactase also is important. Now the variation in that residual lactase I think is interesting, I would love to do that study. I am not quite sure how to do it because of the difficulties with biopsy in human subjects and so forth, but that would be a wonderful study to determine if there are populations where there is variation that has relevance to digestion. It’s a very good question. I wish I had a better answer.

*Dr. El Barbary:* Does lactose intolerance increase with age in the same individual?

*Dr. Savaiano:* It probably increases with age between the ages of 3 and 5, that’s not your question I understand, but that’s what the evidence would suggest. There are some indications in the elderly that small bowel overgrowth can have an influence on lactose intolerance, and if you treat the small bowel with antibiotics you get some recovery. So that’s a microbiota issue though, not a lactase issue. We have done a study with Asian American young and elderly and found absolutely no difference in their nonpersistence in terms of symptoms and maldigestion. I believe that a lot of the incidence we see of individuals who claim as they get older to have a symptom of intolerance has to do in fact with infection, malnutrition, traveling, a change in colon flora, that I don’t think would be accounted for to the extent that it is important.

*Dr. El Barbary:* Yes, but I just wanted to know whether lactase activity as enzyme decreases with age in the same person.

*Dr. Savaiano:* I don’t believe the evidence is there to support that reduction.

*Dr. Sankaranarayanan:* I presume your focus is more on lactose intolerance in the adult.

*Dr. Savaiano:* Yes, correct, all the studies are with adults.

*Dr. Sankaranarayanan:* Could you answer some questions on pediatric lactose intolerance?

*Dr. Savaiano:* I can at least review the literature for you and give you an indication of what is there.

*Dr. Okai Brako:* What is the extent of nonpersistence in children younger than 3 years old?
Dr. Savaiano: The scientific literature would suggest that it's extremely low, that almost all mammals or humans between the birth and 3 years have high levels of lactase. There are few examples of congenital abnormalities where there is no lactase at all, but very few examples. I would ask the question about milk protein and milk protein allergy because oftentimes those issues can be confused. If one takes milk proteins early in development and the gut is not closed up and you get immune response and allergic response, and as you will know that's a whole different clinical scenario; but I think oftentimes those scenarios get confused. There isn't very much evidence that would support low lactase levels prior to the age of 3 years, and I know clinically you may have experiences that are different, but I am not suggesting those are not real experiences, the literature doesn't have much.

Dr. Sarwar Ferdaus: As pediatricians, we often deal with diarrheal diseases. After rotaviral diarrhea, infants or small children do not digest milk. In those cases, we don't see too much flatulence or gas production, but what we see is that lactic acid comes out in the stool. There are perianal disorders apparent with lactic acid, and in those cases we do a test that reduces lactic acid in the stool, we give the children some other products and their condition improves. So, can we replace the hydrogen test with reducing the substances in the stool in adults?

Dr. Savaiano: I don't know the answer to that question. On a theoretical basis, there are perhaps a lot of factors that will reduce the acidity or increase the acidity, lower the pH of the colon. I showed you that hydrogen is adaptable, so in that sense it's not a good test either. The future I think is the genetic testing. There is a literature that compares those tests, and in general what we find is the hydrogen test is the most sensitive and it's the least likely to have false positives.

Dr. Johansson: With hydrolyzed lactose you have a release of glucose and galactose, and one should consider if one is turning a noncariogenic milk product into a cariogenic milk product, which might be an issue to be studied.

Dr. Savaiano: I agree, these are control studies attempting to distinguish this hypothesis. But when you do split lactose and make lactose-hydrolyzed products, you do have a different carbohydrate composition, and that needs to be considered, and in the US these products are sold widely.

Dr. Haque: You said that the incidence of lactose intolerance is very rare in the pediatric population. But in our place, we come across many children with watery diarrhea, and when we restrict lactose and give them lactose-free milk they respond quite dramatically. How do you explain this?

Dr. Savaiano: The lactase enzyme is very sensitive to all influences that come through the intestinal lumen. It's one of the only two enzymes that sit outside the cell attached with a carbohydrate moiety into the membrane, so anything that comes by that influences it, ethanol, alcohol, infection. You could even hypothesize that certain food components might influence whether that enzyme gets knocked off or not. If you are eating fiber components, anything that could influence that enzyme is going to cause a secondary intolerance, and so I would argue that what you are likely seeing is a secondary intolerance which is very common. Don't get me wrong, it's very common and important, but once you resolve the issue of what is causing the secondary intolerance, whether it's infection, malnutrition or whatever, you can get the individual healthy. You should go back to a situation where they are tolerant, at least that's what the data would suggest.

Dr. Garg: I have one comment and one question. The comment is about lactase deficiency or activity in the <3 years age group. Let's remember that premature babies have less than normal lactase activity, and you said that even at 34 weeks there is only 30% of lactase activity compared to term newborns, and that is the logic behind formulating preterm infant formula with low lactose and glucose polymers. Still, whether
this is clinically significant is not certain. We must remember that preterm newborns
tolerate mother's milk very well, and mother's milk contains lactose as the only carbo-
hydrate source.

My question is about children 2--3 years old. Apart from lactose, they also consume
other sugars, and some of them take large amounts of fruits, juices and candies, and
can lead to the symptoms of flatulence and abdominal discomfort. So when a
child of this age group consumes both lactose and a lot of other sugars, how do you see
which one is causing the symptoms?

Dr. Savaiano: I don't know. I am not a clinician. Theoretically, simple sugars at
even fairly high concentrations should be cleared through the small bowel very rap-
idly. They should not reach the large bowel.

Dr. Gibson: Just a question about the general applicability of your observation
that you can induce tolerance to lactose by giving increasing doses of small doses,
which sort of parallels what we do to overcome bee sting intolerance and inducing
small amounts of bee venom. I was just wondering, in relation to celiac disease and
the intolerance to gluten, do you think this could be a method? What’s the literature
on this?

Dr. Savaiano: Let me answer different questions. Many gastroenterologists in the
western world deal with irritable bowel syndrome (IBS). There is something wrong
and they don't know what it is. It's the wonderful label that says we don't know what’s
wrong with you, you have recurring diarrhea. Could it be that in the western world we
are eating such a refined diet with so few fibers, so few complex carbohydrates that we
have created intestines that essentially starve the microbiota, starve these compounds
that they evolved on? I don't know. Celiac disease is probably a different mechanism.
That mechanism in terms of immune function and immune response might not fit this
model. IBS though might fit this model, I really don’t know. Actually we are starting to
take a look at some of those questions with IBS.

Dr. Neves: It's a very practical question. We used to tell our mothers and teenagers
not to drink milk during meals because of iron absorption and now you are telling us
to allow this. What should we do?

Dr. Savaiano: So, is it more important to have adequate iron status or have tol-
erance to lactose, that's the answer to the question. It depends on the individuals. If
their iron status is fine and they feel that they are lactose intolerant, then my advice is
probably sound. If they will tolerate lactose and they are iron deficient, it's probably a
good advice. It's probably situational.