Metabolism and Health Effects of Lactose and Galactose

Corinna Walsh (RD) PhD
Presented by
Louise van den Berg

Pretoria CNE
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Introduction

Scientific evidence supports the essential role of milk and dairy products as part of a healthy eating pattern.
• Dairy foods are excellent sources of the nutrients calcium, magnesium, potassium, protein and carbohydrates

• Benefits of milk and other dairy foods for bone and dental health are well-known

• Dairy intake also linked to other health benefits

• Key role in development throughout life

Visioli and Strata, 2014; Hirahatake et al., 2014; Pereira, 2014; Keast et al., 2013; Prado and Dewey, 2014; Weaver, 2014; Rice et al., 2013
Hypothesize that galactose from lactose in milk may induce:

- oxidative stress → chronic low grade inflammation
- a decreased immune response and
- neurodegeneration

Michaëlsson et al., 2014; Cui et al., 2006
Criticisms

- Possibility of reverse causation (women who knew that they had osteoporosis may have consumed more milk)

- Multivariate model did not adjust for osteoporosis or bone mineral density

- Large sex differences not accounted for

- Vit D status may have impacted on fracture risk and all-cause mortality

- Synthetic substances used in milk production at the time that cohorts were recruited may have impacted on mortality

Michaëlsson et al., 2014; Labos and Brophy, 2014; Bonneux, 2014; Hill, 2014; Sundar, 2014
Aim of presentation

• In view of the mentioned limitations and in the absence of evidence from randomized controlled trials (RCTs), the results of the Michaëlsson study need to be interpreted with caution

• Yet, the study has cast doubt on the health benefits of milk

• This presentation will aim to evaluate the evidence on the health effects of dairy, with special reference to lactose and its metabolites, which are naturally present in milk
Content

- Composition, digestion, absorption and metabolism of lactose
- Lactose intolerance
- Lactose as a prebiotic
- Lactose in calcium absorption
- Non-communicable diseases:
  - Type 2 Diabetes Mellitus
  - Hypertension
  - Dental caries
Composition, digestion, absorption and metabolism of lactose

- Lactose consists of galactose bound to glucose

- The enzyme lactase is needed to hydrolyse lactose to glucose and galactose to facilitate absorption and transport across the intestinal mucosa
• Galactose and glucose are absorbed and actively transported from the intestinal lumen into the blood by the sodium-dependent hexose transporter, SGLT1

They are then passively transported from the blood into the liver by the GLUT-2 transporter

Deng et al., 2015; Coelho et al., 2015; Schaafsma, 2008
• Galactose is then **phosphorylated** in the **liver** and finally converted into glucose

• Glucose tends to pass through the liver and can be metabolised anywhere in the body as a **source of energy**

Deng et al., 2015; Coelho et al., 2015; Schaafsma, 2008
Galactose

- Galactose is metabolized to glucose by 3 enzymes in the Leloir pathway, the main pathway of galactose metabolism

- These enzymes are:
  - galactokinase (GALK)
  - galactose-1 phosphate uridylyltransferase (GALT) and
  - UDP-galactose 4’-epimerase (GALE)

- Although this pathway occurs mostly in the liver, it is also active in cells in the brain, lens of the eye and ovaries

Coelho et al., 2015; Lukito et al., 2015
Galactose

- The presence of galactose in bacteria, plants and animals confirms its importance for living organisms.

- It is found in lactose as well as in complex carbohydrates, including oligosaccharides and polysaccharides, glycoproteins and glycolipids.

Coelho et al., 2015
Functions of Galactose

Apart from its importance in energy production:

- Referred to as ‘brain sugar’ in lay terms owing to its role in supporting brain structure and development during the neonatal period and early life

- Important role in maintaining a healthy GIT - present in the raffinose-family oligosaccharides that stimulate growth of some intestinal microflora

- Display anti-adhesive activity - inhibit infections by enteric pathogens

Prado and Dewey, 2014; Schaafsma, 2008; Zivkovic and Barile, 2011
Galactosemia

- A congenital disorder involving one of the three enzymes in the Leloir pathway - classic galactosemia is due to a GALT deficiency

- Particularly serious during the **neonatal period** and affects a number of organs, including the liver and brain

- **Dietary restriction** of galactose resolves the symptoms of galactosemia, but

- Associated with severe **long-term complications** cognitive and fertility impairments, even in patients who follow a galactose-restricted diet rigorously

Lukito et al., 2015; Waisbren et al., 2012
Lactose intolerance

- Under normal conditions, lactase is produced in the intestinal mucosa of mammals.

- Full-term newborn infants generally have sufficient lactase activity to digest milk.

Deng et al., 2015; McSweeney and Fox, 2009; Vandenplas, 2015; Heaney, 2013; Mattar et al., 2012; Brown-Esters et al., 2012; Leonardi et al., 2012
Lactose intolerance

• However, lactase activity declines after weaning in most humans (lactase non-persistence), especially those from East Asian and African heritage, resulting in lactose maldigestion

Deng et al., 2015; McSweeney and Fox, 2009; Vandenplas, 2015; Heaney, 2013; Mattar et al., 2012; Brown-Esters et al., 2012; Leonardi et al., 2012
Lactose intolerance refers to the digestive symptoms that are associated with lactose maldigestion:

- abdominal
- discomfort,
- nausea,
- cramps,
- bloating,
- flatulence,
- diarrhoea

Deng et al., 2015; McSweeney and Fox, 2009; Vandenplas, 2015; Heaney, 2013; Mattar et al., 2012; Brown-Esters et al., 2012; Leonardi et al., 2012
Lactose intolerance

Those who consider themselves lactose intolerant may decrease their dairy intake, resulting in compromised intake of the nutrients and other beneficial compounds in dairy

Bailey et al., 2013
Strategies to improve lactose intolerance

• A low lactose load (<6 g present in half a serving of milk) is unlikely to cause symptoms.

• Using small amounts of dairy at a time, or taking milk with a meal, slows the release of lactose into the intestine, which reduces the load to be digested - less discomfort.

Vandenplas, 2015; Heaney, 2013; Brown-Esters et al., 2012; Suchy et al., 2010
Strategies to improve lactose intolerance

• Dairy foods such as cheese (especially hard cheeses), active-culture yoghurt and fermented products such as buttermilk contain limited lactose and can be eaten without causing gastrointestinal discomfort.

• These foods are fermented by lactic acid bacteria, which convert some of the lactose to lactic acid during production.

Vandenplas, 2015; Heaney, 2013; Brown-Esters et al., 2012; Suchy et al., 2010
Strategies to improve lactose intolerance

• Although more expensive, reduced-lactose or lactose-free milk is also available - this milk has many health benefits over dairy substitutes such as soy milk

• Taking a lactase tablet with milk improves digestion

• Probiotics that include lactase-containing organisms can help to relieve symptoms

Vandenplas, 2015; Heaney, 2013; Brown-Esters et al., 2012; Suchy et al., 2010
Strategies to improve lactose intolerance

• **Tolerance** can be built up gradually over a period of time:
  • consuming lactose-containing foods encourages an intestinal flora population with active lactase
  • intake can be increased gradually by, for example, adding half a glass of milk to one meal on the first day, half a glass to two meals on the next day, etc.

• **Chocolate milk** is better tolerated than white (higher osmolality or energy content)

Vandenplas, 2015; Heaney, 2013; Brown-Esters et al., 2012; Suchy et al., 2010
Do people with lactose intolerance need to avoid dairy?

D - Drink milk with food.
A - Add natural cheeses to your diet, such as Cheddar, Colby and Swiss, which are low in lactose.
I - Introduce dairy slowly. Gradually increase the amount.
R - Reduce it. Enjoy lactose-free milk and milk products.
Y - Yogurt with active cultures helps digest lactose.

UFS UV
There may be an evolutionary reason why only about 35% of the human population can digest lactose beyond the age of about 7 / 8 years.

Deng et al., 2015; McSweeney and Fox, 2009; Vandenplas, 2015; Heaney, 2013; Mattar et al., 2012; Brown-Esters et al., 2012; Leonardi et al., 2012
Effects of lactose as a prebiotic

• The recent emphasis on the structure and function of the human microbiome has focused attention on the potential role of probiotics and prebiotics in promoting health.

• Prebiotics are non-digestible compounds that stimulate the growth and activity of the bacteria in the digestive system.

• Lactose and oligosaccharides in milk are considered to be bioactive ingredients that may create a healthy microbiota owing to their bifidogenic effects.

Petschow et al., 2013; Lukito et al., 2015; Visioli and Strata, 2014; Vandenplas, 2015; Hirahatake et al., 2014; Zivkovic and Barile, 2011
Effects of lactose as a prebiotic

Lactose non-persistent persons

Lactose is not fully digested and thus proceeds to the colon where it exerts prebiotic effects.

Lactase-persistent persons

Most lactose will be *digested* in the small intestine, but some may reach the large intestine and serve as a prebiotic for the colonic microbiota, including lactic acid bacteria.

Lukito et al., 2015; Venema, 2012
Effects of lactose as a prebiotic

The colonic microbiota **hydrolyse and ferment lactose** in the colon, producing metabolites such as **short-chain fatty acids** (primarily acetate, propionate and butyrate) and gases.

Lukito et al., 2015; Venema, 2012
Lactose and oligosaccharides

Vandenplas, 2015; Vulevic et al., 2015; Eiwegger et al., 2004; Hickey, 2012; Flint et al., 2012; Zivkovic and Barile, 2011
Effects of lactose as a prebiotic

- Dairy prebiotics and probiotics may influence gut microbiota in such a way that **insulin sensitivity** and the action of the incretin hormone glucagon-like peptide (GLP-1) are positively affected.

Vandenplas, 2015; Vulevic et al., 2015; Eiwegger et al., 2004; Hickey, 2012; Flint et al., 2012; Zivkovic and Barile, 2011
Effect of lactose on calcium absorption

Heaney and Nordin, 2002; Vandenplas, 2015; Kwak et al., 2012; Abrams et al., 2002
Effect of lactose on calcium absorption

- Net calcium absorption about 10-30% of intake

- **Animal studies**: lactose has a positive effect on intestinal calcium absorption

- Effect in **humans** has not been confirmed (probably owing to potential confounding factors such as other dietary components that may affect calcium absorption)

Heaney and Nordin, 2002; Vandenplas, 2015; Kwak et al., 2012; Abrams et al., 2002
Effect of lactose on calcium absorption

• Lactose does show enhanced absorption of calcium in humans compared with other types of non-absorbable sugars (such as mannitol, lactitol or corn starch)

• Absorption of calcium significantly higher in infants fed a lactose-containing formula than in those fed a lactose-free formula that contained corn maltodextrin and corn syrup solids

Heaney and Nordin, 2002; Vandenplas, 2015; Kwak et al., 2012; Abrams et al., 2002
Effect of lactose on calcium absorption

The exact mechanism by which lactose enhances the absorption of calcium unclear:

- may be due to an effect on intestinal alkaline phosphatase
- increased mineral solubility
- enhanced osmotic pressure following fermentation

Kwak et al., 2012; Areco et al., 2015; Schaafsma, 2008
Effect of lactose on calcium absorption

In persons with lactase non-persistence, calcium absorption from dairy products is enhanced due to the prebiotic effect of lactose:

- sustaining the growth of gut flora such as bifidobacteria and lactobacilli
- encouraging the formation of short-chain fatty acids that promote the growth of lactic acid bacteria

Kwak et al., 2012
So, yes...there are apparent advantages to being lactose non-persistence after all...

Deng et al., 2015; McSweeney and Fox, 2009; Vandenplas, 2015; Heaney, 2013; Mattar et al., 2012; Brown-Estes et al., 2012; Leonardi et al., 2012
Why are some people lactose non-persistence and others not?

Originally milk was not tolerated >7-8yrs

After the onset of cattle farming

Developed ways to tolerate milk by fermenting it

In Europe 7500 yrs ago: a single gene mutation emerged that caused lactose persistence

In Europe the DNA base cytosine changed to thymine in a genomic region (LP allele) not far from the lactase gene

Pockets of lactase persistence in West Africa, Middle East and South Asia → due to different mutations

Curry, 2013, Nature, 500
Why did the mutation persist?

1. Opened up a new nutrient rich food source

2. When the LP allele appeared, it offered a major selective advantage -> how?
   Still debated....
     - vit D?
     - malaria?

In a 2004 study researchers estimated that people with the mutation would have produced up to 19% more fertile offspring than those who lacked it.

Compounded over several hundred generations, that advantage could help a population to take over a continent. But only if “the population has a supply of fresh milk and is dairying”

“It’s gene-culture co-evolution. They feed off of each other.”

Curry, 2013, Nature, 500
A growing evidence base supports the inverse association between dairy consumption and health outcomes.
Dairy: Chronic diseases of lifestyle?

- Studies often heterogeneous:
  - Various **study designs** have been applied, including observational studies (cross-sectional and longitudinal cohort studies), RCTs, systematic reviews and meta-analyses
  - Studies do not differentiate on the basis of **health status, weight, age or ethnic background**
• Studies often heterogeneous (cont.):

• Although **differences in nutrient composition** of dairy products may affect outcomes differently, some studies evaluated the effect of **total dairy product intake**, whereas others differentiated between low-fat dairy products, high-fat dairy products, yoghurt, cheese, and liquid versus solid foods.

• Other factors that may impact on health outcomes and which should ideally be adjusted for include **smoking, alcohol consumption** and other **dietary confounders** (such as calcium and total energy intake).
Overweight and obesity: Evidence

Chen et al. (2012): 27 RCTs, 2101 participants

- Confirmed that an energy-restricted diet that includes increased milk and dairy consumption lowered body weight and body fat in the short term.

- However, in situations without energy restriction, inclusion of dairy was unlikely to impact on body weight.
Overweight and obesity: Evidence

Kratz et al. (2013):  
16 observational studies

• Relationship between dairy fat and high-fat dairy foods, obesity and cardio-metabolic disease

• In 11 of the 16 studies, high-fat dairy intake was inversely associated with measures of adiposity
Overweight and obesity: Evidence

Abargouei et al. (2012): 14 RCTs, 883 participants

- Including dairy products in weight-loss diets, reduced fat mass and waist circumference and accelerated weight reduction, while increasing lean mass significantly more than conventional weight-loss diets.
Overweight and obesity: Evidence

Dror (2014):

36 cross-sectional, prospective cohort and intervention studies amongst pre-school children, school-age children and adolescents in developed countries

• In adolescents, dairy intake was inversely associated with adiposity, while the association was not significant in school-age or pre-school children
Overweight and obesity: Evidence

Louie et al. (2011):
19 cohort studies (10 in children and adolescents and 9 in adults)

A beneficial effect was found in 8 studies, whereas 7 showed no effect, 1 reported an increased risk (amongst children) and 2 reported both a decreased and increased risk, depending on the type of dairy eaten
Lu et al. (2016):
10 cohort studies (46 011 children and adolescents)

Dairy consumption was inversely associated with body fat and positively associated with an increased BMI, indicating that dairy products may promote lean body mass but decrease body fat and so increase BMI.
Overweight and obesity: Mechanisms

• A high calcium intake may lead to the calcium-mediated formation of **insoluble soaps**, which **prevent fat absorption** by binding bile acids

• Whey protein seems to have an important role in **muscle sparing** and lipid metabolism

• Dairy may induce **reduced lipogenesis** and **increased lipolysis**

• Lactose may influence the **bacterial composition** of the gut microbiota, influencing energy homeostasis and insulin sensitivity as well as fat storage and metabolism

Chen et al., 2012; Kratz et al. 2013; Zemel, 2009; Christensen et al., 2009; Weaver, 2014; Rice et al., 2013; Sanders, 2012; Sousa et al., 2012; Pal et al., 2010; Petschow et al., 2013; Velagapudi et al., 2010
“The application of prebiotics and probiotics in manipulating the microbiota to improve lipid metabolism and insulin resistance is a field of research that may come to have an important role in addressing overweight and obesity”

Petschow et al., 2013
Type 2 Diabetes Mellitus: Evidence (6)

Elwood et al. (2):  
4 prospective cohort studies

Milk or dairy consumption protected against T2DM

Each additional serving per day was significantly associated with a reduction of 4-9% in diabetes incidence
Type 2 Diabetes Mellitus: Evidence

Pittas et al. (2007) cohort studies

• Compared the effect of high and low dairy intakes (3-5 servings per day vs 1.5 servings per day)

• Higher dairy intake was associated with a lower risk of diabetes
Type 2 Diabetes Mellitus: Evidence

Kratz et al. (2013)

- Consumption of high-fat dairy products was inversely associated with T2DM
- Same association was not found for low-fat dairy
Type 2 Diabetes Mellitus: Evidence

Tong et al. (2011): seven cohort studies (328 029 cases)

- Inverse association between yoghurt and milk consumption (especially skimmed or semi-skimmed milk) and type 2 diabetes, which seemed to be dose dependent
Type 2 Diabetes Mellitus: Evidence

Aune et al. (2013):
17 prospective cohort and case-control studies

• Significant inverse association between intakes of dairy products and the risk of type 2 diabetes
Type 2 Diabetes Mellitus: Evidence

Gao et al. (2013):
14 studies

• To clarify the dose-response association of dairy intake and risk of T2DM

• Inverse linear association of consumption of all dairy products (13 studies), low-fat dairy products (8 studies), cheese (7 studies) and yoghurt (7 studies) and the risk of type 2 diabetes
Type 2 Diabetes Mellitus: Mechanisms

• A beneficial effect of dairy on metabolic and inflammation markers relevant to T2DM and insulin resistance found in animal studies

• Dairy fat - trans-palmitoleic acid - may improve insulin secretion, triglyceridaemia and blood pressure

• Relatively low glycaemic index of milk assists in blood glucose control

• Lactose may have beneficial effects on the gut microbiota which may affect GLP-1 and gastric inhibitory polypeptide (GIP), both of which are affected in T2DM

Hirahatake et al., 2014; Kalergis et al., 2013; Kratz et al., 2013; Mozaffarian et al., 2013; Sluijs et al., 2012; Gunnerud et al., 2012; Panwar et al., 2013
Hypertension: Evidence

Appel et al., 1997: Dietary Approaches to Stop Hypertension (DASH) trial

- A diet rich in fruit, vegetables and low-fat dairy, with reduced total and saturated-fat intake reduces blood pressure

- About **50% of the reduction in blood pressure** associated with the DASH diet ascribed to **dairy consumption**
Hypertension: Evidence

McGrane et al. (2011): RCTs and cohort studies

- Significant inverse associations between intakes of total dairy, low-fat dairy and fluid dairy foods and hypertension, but none for high-fat dairy and cheese
Hypertension: Evidence

Ralston et al. (2012):
5 cohort studies, 45 000 subjects of whom 11 500 had elevated blood pressure

- Significant inverse associations between intakes of total dairy, low-fat dairy and fluid dairy foods (milk and yoghurt) and blood pressure

- Fat-free and low-fat dairy products, especially milk, appear to have an even more significant lowering effect on blood pressure than other dairy products
Hypertension: Evidence

Soedamah-Muthu et al. (2012): dose-response meta-analysis of cohort studies, 57 256 subjects (of whom 15 367 were hypertensive)

Followed up for between 2 and 15 years

• Intakes of total dairy, low-fat dairy and milk were all linearly associated with a lower risk of hypertension

• Consumption of high-fat dairy, total fermented dairy, yoghurt and cheese not significantly associated with hypertension incidence
Hypertension: Mechanisms

- Dairy products are low in sodium and rich in protein, minerals (calcium, magnesium, potassium and phosphorus), vitamins (riboflavin, folate, and vitamin D in fortified milk) and trace elements (iodine, selenium and zinc), which may contribute to a reduction in blood pressure individually or in combination.

- Although sodium is the mineral with the most significant effect on blood pressure, calcium and potassium also play a role.

McGrane et al., 2011; Kris-Etherton et al., 2009; Dickinson et al., 2006; Ralston et al., 2012; FitzGerald et al., 2004; Huth et al., 2006
Hypertension: Mechanisms

Bioactive milk peptides such as lactotripeptides may also contribute to the protective effect of dairy on blood pressure.

These compounds inhibit the action of angiotensin 1-converting enzyme (ACE), thereby preventing blood vessel constriction.

The prebiotics and probiotics in dairy products may have a positive effect on body weight and thus potentially also on the comorbidities associated with overweight and obesity, of which hypertension is one.

McGrane et al., 2011; Kris-Etherton et al., 2009; Dickinson et al., 2006; Ralston et al., 2012; FitzGerald et al., 2004; Huth et al., 2006
Dental Caries

Dietary sugars contribute to the development of dental caries

- However, this does not act in isolation:
  **3 factors** are required for dental caries to develop:
  - the presence of dietary carbohydrate (sugar)
  - dental plaque bacteria and
  - teeth that are susceptible to caries

Aimutis, 2012
Dental Caries

• Sweetening power of lactose is only 15% that of sucrose - unlikely sweetener choice in processed foods

• Dairy products contain proteins, fats, vitamins and minerals (calcium and phosphorus), which protect against dental caries

• When replacing other sugars, such as sucrose and fructose, lactose has been shown to be the least cariogenic of all dietary sugars

• Milk further also does not increase plaque acidity

Merritt, 2006; Shenkin et al., 2003; Molan, 2001
Dental Caries: Evidence

Dror and Allen, 2014:
11 observational studies

• Association between dairy intake and health outcomes in children and adolescents in developed countries

• All studies reported an inverse association between dairy intake and dental caries and some reported that the association was even stronger for yoghurt and cheese consumption
Dental Caries: Evidence

Adegboye et al. (2012):

- Intake of calcium from dairy sources associated with a reduced risk of tooth loss, but the same association was not seen when calcium from non-dairy sources was consumed.
Dental Caries: Evidence

Levine (2001):

• Consumption of sweetened dairy foods, such as chocolate milk, does not increase the risk of dental caries and therefore dairy beverages are considered a healthier option than sweetened soft drinks.
Dental Caries: Mechanisms

• Eating **cheese** increases the concentration of **calcium in saliva and plaque**, which helps to protect tooth enamel

• **Bioactive peptides** in **caseins** protect against caries by preventing demineralization and **inhibiting the attachment of bacteria** to the teeth

• Probiotics in milk also result in **lower bacterial counts**, possibly because the composition of the salivary film changes and there is reduced adhesion of bacteria

Merritt et al., 2006; Kashket and DePaola, 2002; Aimutis, 2004; Stamatova and Meurman, 2009
Dental Caries: Infant feeding

• Most infants are exposed to lactose during breastfeeding or formula feeding and in the presence of cariogenic bacteria, milk could potentially be cariogenic.

• The reportedly higher cariogenecity of human milk (and some infant formulas) compared with cow’s milk may be due to the comparatively higher lactose content and lower protein, calcium and phosphorus content in these milks.

Koletzko et al., 2005
Dental Caries: Infant feeding

- When babies go to sleep with a **bottle**, milk may remain in the mouth for several hours, resulting in decreased salivary flow and extended exposure of dental plaque to fermentable carbohydrates.

- Formulas that contain **other sweeteners**, such as high-fructose corn syrup or sucrose, are also more cariogenic than those containing only lactose.

Koletzko et al., 2005
Dental Caries: Prevention

• Importance of **oral health** in preventing development of caries

• **Different foods** can affect oral pH, plaque formation and salivary flow

• **Healthy eating** has a critical role in the growth, development and maintenance of oral tissues throughout life

• Intake of **milk and dairy products** is an essential component of healthy eating, and the **calcium and bioactive components** in dairy may have an important role in **preventing** dental caries and periodontitis

Aimutis, 2012; Merritt, 2006; Aimutis, 2004
Conclusion

There is extensive evidence that moderate consumption of dairy, as part of a balanced diet, is beneficial to health!
Thank You!
References


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