Metabolism and health effects of lactose and galactose in milk

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Abstract

Dairy foods are excellent sources of a number of macro-and micronutrients. This review evaluates the most recent literature on dairy and human health, with special reference to lactose and its metabolites, by focusing on findings of systematic reviews and meta-analyses. Conclusions of the vast majority of published studies support an inverse relationship between adequate intake of dairy foods and incidence of overweight, type 2 diabetes, hypertension and cancer. Biological mechanisms responsible for these associations are further explored. Important differences between lactose and other sugars are highlighted, as is lactose intolerance, lactose as a prebiotic and the role of lactose in dental cariogenesis. Finally, an overview of the biological importance of galactose is given. Heterogeneity of studies with regard to study design and age, weight and health status of participants complicates the interpretation of findings. Despite these complexities, there is extensive evidence that moderate consumption of dairy, as part of a balanced diet, is beneficial to health.

Background

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, vitamin D (in fortified products), magnesium, potassium, protein and carbohydrates, and are associated with a number of health benefits. People are generally aware of the benefits of milk and other dairy foods for bone and dental health, but more recently a large body of evidence has linked dairy intake also to other health benefits (Visioli and Strata, 2014; Hirahatake et al., 2014; Pereira, 2014; Keast et al., 2013). Milk and dairy products have a key role in development throughout life(Prado and Dew ey, 2014; Weaver, 2014; Rice et al., 2013).

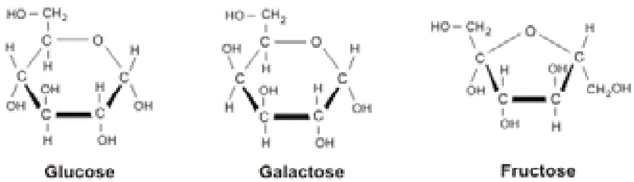
Recently, a Swedish study (Michaëlsson et al., 2014) found that a high intake of milk was associated with higher mortality in one cohort of women and in another cohort of men, and with higher fracture incidence in women. Based on an animal study (Cui et al., 2006), the authors hypothesize that galactose derived from lactose in milk may induce oxidative stress, chronic inflammation, a decreased immune response and neurodegeneration, thus contributing to the risk of mortality and fracture. However, the authors caution that the possibility of residual confounding and reverse causation cannot be ignored (women who were aware that they had osteoporosis may have consumed more milk than women without osteoporosis) and suggest cautious interpretation of the results (Michaëlsson et al., 2014). Commentaries published in response to the study have questioned a number of issues, including that the multivariate model did not adjust for osteoporosis or bone mineral density (Labos and Brophy, 2014). Other criticisms included that large sex differences were not accounted for (Bonneux, 2014) and that vitamin D status and season may have impacted on both fracture risk and all-cause mortality (Hill, 2014). Sundar (2014) also suggested that the synthetic substances used in milk production at the time that cohorts were recruited may have impacted on the mortality reported in the study.

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. Nonetheless, the study has cast doubt on the health benefits of milk. For this reason, the current review 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.

Composition, digestion, absorption and metabolism of lactose

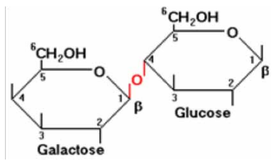
Carbohydrates vary greatly in sweetness, texture, rate of digestion and the degree of absorption following passage through the gastrointestinal tract. Monosaccharides are seldom found in free form, but rather linked into di- and polysaccharide forms.

The smallest carbohydrate unit has the formula (CH2O)*n*, where *n* can be any integer from 3 to 7. Only three monosaccharide hexoses – glucose, galactose and fructose – can be absorbed by humans.



Two monosaccharide units are linked together to form the disaccharides sucrose, maltose and lactose. Lactose β(-D-galactosyl-D-glucose) consists of galactose bound to glucose and is of key importance in animal life as it is the main source of energy from milk.

LACTOSE:



Milk also contains complex sugars called oligosaccharides, which are composed of three to ten sugar molecules linked together. They do not serve as a source of energy, but rather provide nutrients to intestinal bacteria, therefore performing a major role in gastrointestinal health. Human milk contains approximately 1.2% oligosaccharides, while cow's milk contains only 0.1% (Coelho et al., 2015; Pereira, 2014; Zivkovic and Barile, 2011).

Di- and oligosaccharides need to be hydrolyzed as they cannot be absorbed into the bloodstream owing to the absence of transporters to carry them across membranes. The two isomeric forms of lactose (alpha and beta) differ in configuration by the hydroxyl group in position 1 of the glucose moiety. In aqueous solution, alpha and beta lactose exist in equilibrium, with approximately 63% of the lactose in the beta form at room temperature. Intestinal absorption of lactose requires it to be hydrolyzed to its component monosaccharides (glucose and galactose) by the brush-border enzyme lactase (β-galactosidase), which has a special preference for the beta form of lactose. Once lactose is hydrolyzed, the two monosaccharides are absorbed and actively transported from the intestinal lumen into the blood by the sodium-dependent hexose transporter, SGLT1. As the name indicates, this molecule transports a sodium ion together with either D-glucose or D-galactose into the cell; in fact, SGLT1 will not transport a monosaccharide molecule alone.

In contrast, fructose (hydrolyzed from sucrose) is passively transported into the blood via the GLUT-5 transporter. All three dietary mono-saccharides are passively transported from the blood into the liver by the GLUT-2 transporter.

Fructose and galactose are phosphorylated in the liver by fructokinase and galactokinase, respectively, and finally converted into glucose. Glucose tends to pass through the liver and can be metabolized anywhere in the body as a source of energy. Glucose ultimately provides 16 kJ of energyper gram (Deng et al., 2015; Coelho et al., 2015; Schaafsma, 2008).

A deficiency in any of the enzymes involved in lactose digestion and galactose metabolism can lead to metabolic disturbances known as lactose intolerance and galactosemia. Galactosemia develops when the conversion of galactose into glucose in the liver is blocked by a deficiency in any of the enzymes involved in the Leloir pathway. However, this is a rare, congenital error of metabolism. In the absence of any enzyme deficiencies, normal circulating levels of galactose do not cause pathological effects (Coelho et al., 2015; Schaafsma, 2008).

Lactose content of dairy products

Milk from different animals vary in its lactose concentration. Human milk has the highest lactose content while cow's milk contains a notably lower concentration. In fermented cow's milk products, such as yoghurt or buttermilk, the lactose content is about one-third of that in unprocessed milk owing to the conversion of lactose by lactic acid bacteria. During cheese production almost all the lactose in milk is converted to whey and therefore hard cheeses contain virtually no lactose. Any remaining lactose is fully converted into lactic acid by the starter bacteria.

LACTOSE CONTENT OF FOOD ITEMS (scrimshaw And Murray, 1988)

Dairy product	Lactose content (%)
Liquid milk products	
Regular whole milk	3.7–5.1%
2% low-fat milk	3.7–5.3%
Non-fat (skim) milk	4.3–5.7%
Light cream	3.7–4.0%
70% lactose-reduced milk	1.6%
80% lactose-reduced milk	1.1%
Lactose-free milk	0.0%
Cultured milk products	
Sour cream	3.0–4.3%
Buttermilk	3.6–5.0%
Yoghurt, commercial low-fat	1.9–6.0%
Yoghurt, commercial whole-milk	4.1–4.7%
Concentrated milks	
Sweetened condensed milk	11.4–16.3%
Evaporated, whole and skim	9.7–11.0%
Frozen milk products	
Ice cream	3.1–8.4%
Sherbet	0.6–2.1%
Milk fats	
Butter	0.8–1.0%
Powdered milk	
Non-fat milk powder	49.0–52.3%
Instant non-fat milk powder	49.5–54.0%
Whole-milk powder	36.0–38.5%
Cheeses	
Blue	0.0–2.5%
Brie	0.0–2.0%
Camembert	0.0–1.8%
Cheddar (mild)	0.0–2.1%
Cheddar (mature)	2.1%

Dairy product	Lactose content (%)
Cheeses	
Cottage cheese (not creamed)	0.0–3.5%
Cottage cheese (2%)	3.6%
Cottage cheese (1%)	3.6%
Cottage cheese (creamed)	3.6%
Cream cheese	0.4–2.9%
Edam	0.0–1.4%
Feta	4.1%
Gouda	0.0–2.2%
Mozzarella (partly skimmed)	0.0–3.1%
Parmesan (grated)	2.9–3.7%
Parmesan (hard)	0.0–3.2%
Provolone	0.0–2.1%
Ricotta	0.2–5.1%
Roquefort	2.0%
Stilton	0.8%
Swiss	0.0–3.4%

Although all sugars contribute to a sweet taste, the relative intensity differs compared to sucrose (see table), a disaccharide that is broken down to glucose and fructose. The relative sweetness of lactose is only 15% that of sucrose, whereas fructose has a relative sweetness of 170%, making it one of the sweetest naturally occurring sugars (Goldfein and Slavin, 2015). Owing to the low relative sweetness of lactose, it can be used in commercial food products as a thickener and as an additive to improve texture and appearance of food without having a notable impact on the taste or caloric value. Lactose can also be used in pharmaceutical applications as it aids in rapid absorption of drugs and forms an integral part of the composition of most tablets owing to its excellent compressibility properties (Goldfein and Slavin, 2015; Hanover and White, 1993).

Sugar	Relative sweetness
Sucrose	100%
Fructose	170%
Glucose	75%
Maltose	30%
Galactose	30%
Lactose	15%
Mannose	60%
Trehalose	45%

Lactose intolerance

As previously mentioned, the enzyme lactase is needed to hydrolyze lactose to glucose and galactose to facilitate absorption and transport across the intestinal mucosa. Under normal conditions, lactase is produced in the intestinal mucosa of mammals. Full-term newborn infants generally have sufficient lactase activity to digest milk. However, β-galactosidase activity declines after weaning (Deng et al., 2015; McSweeney and Fox, 2009) in most humans (lactase non-persistence), especially those from East Asian and African heritage, resulting in lactose maldigestion (Vandenplas, 2015; Heaney, 2013; Mattar et al.,2012;Brown-Esters et al., 2012). According to Leonardi et al. (2012), only about 35% of the human population can digest lactose beyond the age of about seven or eight years.

Lactose intolerance refers to the digestive symptoms that are associated with lactose maldigestion. Undigested lactose moves from the small intestine to the colon, where it is fermented by bacteria. This sometimes produces gas, which leads to symptoms such as abdominal discomfort, nausea, cramps, bloating, flatulence and diarrhea (Vandenplas, 2015; Mattar etal., 2012).

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; Keithet al., 2011; Wilt et al., 2010; Suchy et al., 2010); however, avoidance of dairy foods is discouraged. Most people who are lactose intolerant can eat small amounts of dairy foods without experiencing discomfort. A number of easily applied strategies can assist in decreasing undesirable symptoms (Vandenplas, 2015; Heaney, 2013;Brown-Esters et al., 2012; Suchy et al., 2010):

- A low lactose load (<6 g present in half a serving of milk) is unlikely to cause symptoms, even in lactose-intolerant persons. Using small amounts of dairy at a time, or taking milk with a meal, slows the release of lactose into the small intestine, which reduces the load to be digested. Less discomfort is subsequently experienced.
- 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.
- 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.
- Tolerance can be built up gradually over a period of time. Consuming lactose-containing foods encourages an intestinal flora population with active lactase. This can improve the ability of the bacteria in the gut to break down lactose and so gradually increase tolerance of lactose-containing foods. 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 milk (possibly owing to a higher osmolality or energy content).
- Probiotics that include lactase-containing organisms can help to relieve symptoms.

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 human health (Petschow et al., 2013). Prebiotics are non-digestible compounds that stimulate the growth and activity of the bacteria in the digestive system (Lukito et al., 2015; Visioli and Strata, 2014). Lactose and oligosaccharides in milk are considered to be bioactive ingredients that may create a healthy microbiota owing to their bifidogenic effects (Vandenplas, 2015; Hirahatake et al., 2014; Zivkovic and Barile, 2011; Chichlowski et al., 2011; Tao et al., 2009; Gopal and Gill, 2000). Oligosaccharides that contain lactose are composed of a lactose core bound to lactose-amine units via b1–3 or b1–6 links and carry fucose or sialic acid in their terminal position (Zivkovic and Barile, 2011; Kuntz et al., 2009). In contrast to the oligosaccharides in fruits and vegetables, those from milk have a branched rather than a linear structure (Zivkovic and Barile, 2011).

In persons with lactase non-persistence, lactose is not fully digested and thus proceeds to the colon where it exerts prebiotic effects. In lactase-persistent persons, most lactose will be digested in the small intestine, although some may reach the large intestine and serve as a prebiotic for the colonic microbiota, including lactic acid bacteria (Lukito et al., 2015). According to Venema (2012). The colonic microbiota hydrolyze and ferment lactose in the colon, producing metabolites such as short-chain fatty acids (primarily acetate, propionate and butyrate) and gases. These metabolites lead to the uncomfortable symptoms experienced by persons with lactose intolerance when large amounts of milk are ingested.

In the colon the short-chain fatty acids provide a source of energy to the micro biota and colonocytes. They can also be absorbed into the portal circulation and transported to the liver, where they may have beneficial systemic effects (Vandenplas, 2015; Vulevic et al., 2015). pH-neutral monosaccharides, such as *N*-acetylglucosamine and fucose, can have immunomodulating effects (Eiwegger et al., 2004), where as acidic oligosaccharides (with sialic acid as monomer) help to prevent pathogen adhesion in the intestinal mucosa (Hickey, 2012; Guggenblichler et al., 1997). In persons with lactase non-persistence, lactose may promote immunity through the cathelicidin antimicrobial peptide (CAMP), which ideally occurs in synergy with other colonic fermentation metabolites such as butyrate (Wahlqvist, 2015).

Hirahatake et al. (2014) have shown that intestinal production of glucagon-like peptide (GLP-1) is influenced by components in foods that provide a substrate for colonic microbiota. In particular, dairy prebiotics and probiotics may influence gut microbiota in such a way that insulin sensitivity and the action of GLP-1 are positively affected (Flint et al., 2012; Zivkovic and Barile, 2011).

The effect of lactose on calcium absorption

Calcium absorption is quite poor in the digestive system, with net absorption averaging about 10% of intake (Heaney and Nordin, 2002). Animal studies have shown that lactose has a positive effect on intestinal calcium absorption (Vandenplas, 2015; Kwak et al., 2012); however, the effect of lactose on calcium absorption in humans has not been confirmed (probably owing to potential confounding factors such as other dietary components that may affect calcium absorption). Replacing lactose with glucose or galactose does not notably influence calcium absorption (possibly because the products of lactose hydrolysis, namely glucose and galactose, also enhance calcium absorption); however, lactose does show enhanced absorption of calcium in humans (Moya et al., 1992) compared with other types of non-absorbable sugars (such as mannitol, lactitol or corn starch). Abrams et al. (2002) have shown that the absorption of calcium was 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.

The exact mechanism by which lactose enhances the absorption of calcium remains to be determined (Kwak et al., 2012). The positive effect of lactose on calcium absorption via passive transport in the small intestine may be due to an effect on intestinal alkaline phosphatase (Areco et al., 2015), increased mineral solubility or enhanced osmotic pressure following fermentation (Schaafsma, 2008).

In persons with lactase non-persistence and who therefore do not digest lactose in the small intestine, calcium absorption from dairy products is enhanced, possibly owing to the prebiotic effect of lactose in sustaining the growth of gut flora such as bifidobacteria and lactobacilli. Kwak et al. (2012) suggest that lactose may encourage the formation of non-digestible oligosaccharides such as *trans*-galacto-oligosaccharides, enhancing the production of short-chain fatty acids and other organic acids that promote the growth of lactic acid bacteria and enhance the absorption of calcium.

Although research is needed to determine the exact mechanism by which lactose enhances calcium absorption, both hydrolyzed and unhydrolyzed forms of lactose seem to enhance calcium absorption in mammals.

The effects of lactose in relation to non-communicable diseases

The inverse association between dairy consumption and a number of health outcomes is supported by a growing evidence base. However, studies reporting on these associations are often heterogeneous in nature. Various study designs have been applied, including observational studies (cross-sectional and longitudinal cohort studies), RCTs, systematic reviews and meta-analyses. The studies did not differentiate on the basis of participants' health status, weight, age or ethnic background. 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).

The role of dairy (and its lactose content) in health and disease is an area of growing interest (Lee et al., 2015;Wahlqvist, 2015;Wahlqvist, 2014). Although various components in milk have been reported to potentially be responsible for health properties, nutrients and foods are habitually eaten in combination, which makes it difficult to determine the component responsible for a specific observed effect. Furthermore, a combination of components may have an effect that would not be visible in isolation. It is thus probable that the role of lactose in health outcomes may be related to other compounds in dairy, its fermentation, and to the habitual diet and lifestyle of study participants (Lukito et al., 2015).

Overweight

A number of systematic reviews and meta-analyses have shown that increased dairy consumption may protect against weight gain and obesity. However, in most reviews, the heterogeneity of studies was emphasized (e.g. initial weight status, differences in energy and calcium intake between control and intervention groups and duration of interventions), resulting in inconsistent findings, making it difficult to draw firm conclusions.

The meta-analysis of Chen et al. (2012) reviewed the effect of 27 RCTs, which included 2101 participants (men and women). The study confirmed that an energy-restricted diet that includes increased milk and dairy consumption lowered body weight and body fat in the short term. However, long-term benefits were not confirmed and the authors concluded that in situations without energy restriction, inclusion of dairy was unlikely to impact on body weight (Chen et al., 2012).

Kratz et al. (2013) conducted a systematic literature review of 16 observational studies investigating the relationship between dairy fat and high-fat dairy foods, obesity and cardiometabolic disease. In 11 of the 16 studies, high-fat dairy intake was inversely associated with measures of adiposity. The authors concluded that "observational evidence does not support the hypothesis that dairy fat or high-fat dairy foods contribute to obesity or cardiometabolic risk".

The meta-analysis of 14 RCTs (883 participants) of Abargouei et al. (2012) showed that 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.

Dror (2014) performed a systematic analysis of 36 cross-sectional, prospective cohort and intervention studies amongst pre-school children, school-age children and adolescents in developed countries to determine associations between dairy intake and adiposity. In adolescents, dairy intake was inversely associated with adiposity, while the association was not significant in school-age or pre-school children.

A systematic review by Louie et al. (2011) examined the association between dairy consumption and obesity in 19 prospective cohort studies (10 in children and adolescents and nine in adults). A beneficial effect was found in eight studies, whereas seven showed no effect, one reported an increased risk (amongst children) and two reported both a decreased and increased risk, depending on the type of dairy eaten.

Most recently, Lu et al. (2016) reviewed 10 prospective cohort studies (46 011 children and adolescents) and published associations between dairy consumption and the risk for childhood obesity. The authors concluded that dairy consumption was inversely associated with body fat and positively associated with an increased body mass index (BMI), indicating that dairy products may promote lean body mass but decrease body fat and so increase BMI.

Of all the bioactive components in milk, it is primarily calcium and vitamin D that have been studied for their effects on body weight and fat mass (Shaharet al., 2010). A high calcium intake may lead to the calcium-mediated formation of insoluble soaps, which prevent fat absorption by binding bile acids (Chen et al., 2012; Kratz et al. 2013; Zemel, 2009; Christensen et al., 2009). However, a number of studies have recently suggested that other milk components may also have a favorable effect on body weight (Weaver, 2014; Rice et al., 2013; Sanders, 2012). For example, dairy proteins (both casein and whey protein) have been suggested to decrease visceral fat mass and body weight (Sanders, 2012; Sousa et al., 2012). Whey seems to have an important role in muscle sparing and lipid metabolism (Pal et al., 2010). In addition, reduced lipogenesis and increased lipolysis may explain the favorable impact of dairy on weight and fat mass.

As far as lactose it concerned, it is possible that its function as a prebiotic may impact on body weight and subsequently also on the comorbidities associated with overweight and obesity. Although not directly related to lactose as a prebiotic, animal studies have shown that prebiotics (fructans) lead to reduced body-weight gain and fat deposition, and protect against hepatic steatohepatitis in obese and Type 2 diabetes rats (Daubioul et al., 2002). Prebiotic-mediated fermentation enhances the production of short-chain fatty acids, which, in turn, stimulate the release of intestinal hormones that influence hypothalamic neuronal activity involved in hormone-based satiety and appetite regulation (Petschow et al., 2013). Prebiotics may further influence the bacterial composition of the gut microbiota, influencing energy homeostasis and insulin sensitivity (Petschow et al., 2013) as well as fat storage and metabolism (Velagapudi et al., 2010).

In view of the described findings, longer-term RCTs with adequate power are needed to better understand the role of dairy products in the prevention of weight gain and the risk of becoming overweight or obese (Rautiainen et al., 2016). According to Petschow et al. (2013), 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.

Diabetes

A growing body of scientific evidence indicates that dairy may significantly reduce the risk of type 2 diabetes (Hirahatake et al., 2014; Zong et al., 2014; Kalergis et al., 2013; USDA, 2010) and associated cardiovascular disease (Huang et al., 2014; Soedamah-Muthu et al., 2011).

A meta-analysis by Elwood et al. (2008) considered four prospective cohort studies. They found that milk or dairy consumption protected against type 2 diabetes and that each additional serving per day was significantly associated with a reduction of 4–9% in diabetes incidence (Elwood et al., 2008). Another meta-analysis, reported by Pittas et al. (2007), included cohort studies that 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.

In a recent systematic review of observational studies that considered the type of dairy consumed, Katz et al. (2013) reported that the consumption of high-fat dairy products was inversely associated with type 2 diabetes. The same association was not found for low-fat dairy. In contrast, Tong et al. (2011) published a meta-analysis of seven cohort studies (328 029 cases). They reported an inverse association between yoghurt and milk consumption (especially skimmed or semi-skimmed milk) and type 2 diabetes, which seemed to be dose dependent. However, high-fat dairy and whole (regular-fat) milk were not found to be associated with diabetes.

In a meta-analysis of 17 prospective cohort and case-control studies, Aune et al. (2013) reported a significant inverse association between intakes of dairy products, low-fat dairy products and cheese and the risk of type 2 diabetes. The meta-analysis of Gao et al. (2013) included 14 studies to clarify the dose–response association of dairy intake and the risk of type 2 diabetes. They found an 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.

A modest increase in daily intake of low-fat dairy, cheese and yoghurt may contribute to the prevention of type 2 diabetes, but needs to be confirmed by RCTs.

The possible mechanisms by which dairy protects against type 2 diabetes remain unclear (Hirahatake et al., 2014; Visioli and Strata, 2014; Kalergis et al., 2013), but may involve a beneficial role of dairy products in obesity and metabolic syndrome, both of which are also risk factors for diabetes. A beneficial effect of dairy on metabolic and inflammation markers relevant to type 2 diabetes and insulin resistance has been found in animal studies (Hirahatake et al., 2014). Components in milk that may be beneficial in reducing risk of diabetes include calcium, vitamin D and dairy fat, with specific reference to *trans*-palmitoleic acid (Kalergis et al., 2013; Kratz et al., 2013; Mozaffarian et al., 2013). *Trans*-palmitoleic acid may improve insulin secretion, triglyceridemia and blood pressure (Hirahatake et al., 2014; Sluijs et al., 2012).

In contrast to the intake of glucose or fructose, lactose intake does not appear to be associated with diabetes incidence (Ahmadi-Abhari et al., 2013), and the use of milk and dairy products is encouraged in persons with diabetes. The relatively low glycemic index of milk assists in blood glucose control (Gunnerud et al., 2012). Hirahatake et al. (2014) have also highlighted the role of the incretin hormones GLP-1 and gastric inhibitory polypeptide (GIP), both of which are affected in type 2 diabetes, in maintaining glucose homeostasis. Panwar et al. (2013) suggest that dairy (especially lactose) may have beneficial effects on the gut microbiota, which may affect GLP-1 and GIP, and encourage further investigation into these effects.

Cancer

The association between dairy intake and cancer remains unclear. The complex etiology of cancer makes it difficult to prove the effect of a single food or nutrient in the development of cancer (Pereira, 2014). Dairy does, however, contain compounds that might exhibit anti-cancer effects (Park et al., 2009). The beneficial or adverse effects of milk and dairy foods have mostly been investigated in relation to ovarian, breast, bladder and colorectal cancers.

Although older studies have reported an association between high lactose consumption and an increased risk of ovarian cancer (Cramer, 1989), more recent evidence does not support this link. Genkinger et al. (2006) conducted a meta-analysis of 12 prospective cohort studies that included 553 217 women, of whom 2 132 had ovarian cancer. No statistically significant associations were found between intakes of milk, cheese, yoghurt, ice cream and dietary and total calcium intake, and the risk of ovarian cancer. However, a non-significant increased risk of ovarian cancer was seen for lactose intakes equivalent to three or more servings of milk per day. Interestingly, Koralek et al. (2006) reported that a higher consumption of total dairy food was associated with a significantly decreased risk of ovarian cancer in their cohort, which included 31 925 women.

Dong et al. (2011) conducted a meta-analysis of 18 prospective cohort studies, which included 1 063 471 participants. The authors found an inverse association between low-fat dairy product intake (excluding milk) and breast cancer in premenopausal women. In contrast, a meta-analysis of more than 20 longitudinal studies, which included 351 041 women, did not find any association between milk intake and breast cancer incidence (Missmer et al., 2002). Similarly, the review of Moorman and Terry (2004) concluded that milk consumption was not associated with breast cancer incidence.

Mao et al. (2011) reported a meta-analysis of 19 cohort case–control studies (7 867 patients with bladder cancer) and found that high milk consumption was associated with a 16% reduction in the risk of bladder cancer. Ethnicity affected results, with the association being stronger in Asian participants and absent in Europeans. In contrast, a meta-analysis by Li et al. (2011) amongst participants with bladder cancer found no association between milk and dairy intake and cancer incidence.

In their systematic review of 19 cohort studies, Aune et al. (2012) reported a significant inverse association between total dairy and milk consumption (not cheese) and the incidence of colorectal cancer. These findings agree with those from other studies (Murphy et al., 2013; Szilagyi et al., 2006).

The possible anti-cancer properties of dairy have been ascribed to its calcium, folate, vitamin D and conjugated linoleic acid content (Pereira, 2014; Norat and Riboli, 2003; Lamprecht and Lipkin, 2001). The role of calcium, folate and vitamin D in regulating cell proliferation may be responsible for their anti-cancer effects (Rodriguez et al., 2003; Lamprecht and Lipkin, 2001). Calcium also binds to fatty acids and biliary salts in the intestine, impacting on their ability to affect the mucosa (Rodriguez et al., 2003), while the role of folate in DNA methylation may protect against cancer (Duthie, 2011). Furthermore, the beneficial effects of prebiotics and probiotics in non-fermented and fermented milk products on the gut microbiota may result in immunomodulatory effects, which may protect against the development of cancer (Amiri et al., 2015).

Hypertension

In view of the high prevalence and major implications of hypertension, attempts to decrease blood pressure are justified. With reference to dietary factors, the relative intake ratios of minerals such as sodium, potassium, magnesium and calcium are related to blood pressure regulation (McGrane et al., 2011; Kris-Etherton et al., 2009; Charlton et al., 2005). The beneficial effects of eating a diet high in fruit and vegetables on blood pressure have been widely reported (Dauchet et al., 2007; Appel et al., 1997). The benefits of a diet rich in fruit, vegetables and low-fat dairy, coupled with reduced total and saturated-fat intake, have also been demonstrated in the Dietary Approaches to Stop Hypertension (DASH) trial (Appel et al., 1997), with about 50% of the reduction in blood pressure associated with the DASH diet ascribed to dairy consumption.
A number of reviews of observational studies and RCTs related to dairy consumption and hypertension have been reported.

A systematic review by McGrane et al. (2011) covered recent RCTs and cohort studies. They found significant inverse associations between both high and low intakes of total dairy, low-fat dairy and fluid dairy foods and hypertension, but none for high-fat dairy and cheese. In a meta-analysis of five cohort studies, involving nearly 45 000 subjects of whom 11 500 had elevated blood pressure, Ralston et al. (2012) found 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 (Ralston et al., 2012; McGrane et al., 2011).

Limitations of the two mentioned reviews included variation in the types of dairy intake and serving sizes amongst different populations. For this reason, Soedamah-Muthu et al. (2012) performed a dose–response meta-analysis of prospective cohort studies in which they evaluated dairy intake and the risk of hypertension in 57 256 subjects (of whom 15 367 were hypertensive) and who were followed up for between two and 15 years. In their analysis, 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 was not significantly associated with hypertension incidence. They recommended that these results need to be confirmed in RCTs.

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 (McGrane et al., 2011; Kris-Etherton et al., 2009). The association between dairy intake and blood pressure is stronger than the association between calcium intake and blood pressure, suggesting that other components in dairy products also contribute to this association (McGrane et al., 2011; Dickinson et al., 2006). Although sodium is the mineral with the most significant effect on blood pressure (Kris-Etherton et al., 2009), calcium and potassium also play a role. Bioactive milk peptides such as lactotripeptides may also contribute to the protective effect of dairy on blood pressure (Ralston et al., 2012; Kris-Etherton et al., 2009; FitzGerald et al., 2004). These compounds are hypothesized to inhibit the action of angiotensin 1-converting enzyme (ACE), thereby preventing blood vessel constriction (Huth et al., 2006; FitzGerald et al., 2004). 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.

Dental caries

It is well known that dietary sugars contribute to the development of dental caries. However, this does not act in isolation. Three factors are required for dental caries to develop, namely the presence of dietary carbohydrate (sugar), dental plaque bacteria and teeth that are susceptible to caries (Aimutis, 2012).

As cariogenic bacteria ferment carbohydrates (sugars) to organic acid metabolites, caries are considered to be an infectious disease of bacterial origin. A complex series of interactions occur in the plaque biofilm that forms on the surface of tooth enamel when cariogenic bacteria interact with dietary constituents, especially sugar. The result is the development of dental caries.

The sweetening power of lactose is only 15% that of sucrose, which makes it an unlikely sweetener choice in processed foods. Although pure lactose has been used in early animal studies to determine the sugar's cariogenic potential (Shaw et al., 1944), the model does not relate directly to real-life situations, as lactose is consumed as part of milk or dairy products. Dairy products contain proteins, fats, vitamins and minerals (calcium and phosphorus), which are known to 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 (Shenkin et al., 2003; Molan, 2001). Milk further also does not increase plaque acidity (Merritt, 2006).

A recent review of 11 observational studies investigated the association between dairy intake and health outcomes in children and adolescents in developed countries (Dror and Allen, 2014). All studies included in the review reported an inverse association between dairy intake and dental caries and some reported that the association was even stronger for yoghurt and cheese consumption.

The follow-up study to the Danish European Youth Heart Study confirmed an inverse association between dairy intake amongst children and adolescents and the risk of dental caries (Lempert et al., 2015). A study by Adegboye et al. (2012) also showed that intake of calcium from dairy sources was associated with a reduced risk of tooth loss, but that the same association was not seen when calcium from non-dairy sources was consumed. A review by Levine (2001) concluded that 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.

Eating cheese increases the concentration of calcium in saliva and plaque (Merritt et al., 2006), which helps to protect tooth enamel (Kashket and DePaola, 2002). Bioactive peptides in caseins protect against caries by preventing demineralization (Aimutis, 2004) and inhibiting the attachment of bacteria to the teeth (Merritt et al., 2006). 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 (Stamatova and Meurman, 2009).

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. 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).

The importance of oral health in preventing the development of caries cannot be emphasized enough (Aimutis, 2012). In addition, 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. The 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 (Merritt, 2006; Aimutis, 2004).

Galactose

Digestion, absorption and metabolism of galactose for normal and excessive intakes

Galactose is a natural aldohexose that differs from glucose only in the configuration of the hydroxyl group in the C4 position. Its presence in bacteria, plants and animals confirms its importance for living organisms (Coelho et al., 2015). Naturally occurring galactose exists stereochemically as alpha or beta anomers, mostly in the cyclic D-configuration instead of the open-chain form. Dietary galactose may be present in free or bound form. The bound forms comprise the disaccharide lactose as well as complex carbohydrates, including oligosaccharides and polysaccharides, glycoproteins and glycolipids (Coelho et al., 2015).

Dietary galactose is released from complex carbohydrates through hydroxylation by salivary and pancreatic amilase, and from lactose by lactase present in the brush border of the small intestine. Similar to D-glucose, free D-galactose is absorbed from the small intestine into the blood through active transport. Galactose is transported via the portal vein to the liver, where almost 90% is retained. The distinctive hepatic capacity to retain and eliminate galactose can be used as a clinical measure of metabolic liver function, which explains the evident galactose intolerance in liver failure (Coelho et al., 2015). The remaining portion (10%) is distributed to other organs and tissues, such as the brain and also the lactating mammary gland for the production of lactose (Cederlund et al., 2013), highlighting its importance in human development.

Galactose exists in two predominant forms in aqueous solution: the α- and β -pyranose structures, which differ in the configuration of the hydroxyl group at the C1 position. Upon its release from lactose, galactose is converted from its β-conformation to the α-anomeric form by galactose mutarotase (Wu et al., 2015). α-Galactose, in turn, is metabolized to glucose by the three principal enzymes in the Leloir pathway, the main pathway of galactose metabolism. These enzymes are, in order of their appearance in the metabolic pathway, galactokinase (GALK), galactose-1 phosphate uridylyltransferase (GALT) and UDP-galactose 4'-epimerase (GALE) (Coelho et al., 2015).

Although this pathway occurs mostly in the liver, it is also active in cells in the brain, lens of the eye and ovaries, as evidenced by the presence UDP-galactose, which acts as the substrate for GALE (Lukito et al., 2015).

Once absorbed, dietary galactose may be converted to UDP-glucose for the production of glycogen and glucose-1-phosphate (Glc-1-P) for the release of energy, or be converted to UDP-galactose and its derivatives, which serve as key substrate donors for the biosynthesis of glycoproteins and glycolipids (Décombaz et al., 2011).

Galactose content of food

Galactose is not derived only from lactose-containing foods. The following tables show food items that are high and moderate in galactose content, respectively.

Foods with a high galactose content (>100 mg/100 g food)(Emms, 2005)

Food	Galactose (mg/100 g or mg/100 ml)
Soy flour (defatted)	7600
Dried figs	4100
Milk (cow's, all types)	9.5–227 (free) plus ~5000 mg lactose, yielding ~2500 mg galactose
Yoghurt (all types)	1150–2600 mg (free) plus ~800–4100 mg lactose, yielding ~400–2050 mg galactose
Black-eyed peas	300–521
Hazelnuts	500
Green split peas	100–493
Chickpeas	100–444
Baby lima beans	175
Red kidney beans	153
Yellow split peas	144
Lentils	116

Foods with a moderate galactose content (<100 mg food)

Food	Galactose (mg/100g or/100ml)
Cheddar cheese (aged 15 days)	94.5–800
Watermelon juice	46.0
Cheddar cheese (aged 78 days)	43.0
Persimmon	35.4
Papaya	28.6
Honeydew melon	26.7
Blueberries	26.2
Tomato	23.0
Orange juice	19.0
Pineapple	18.7
Watermelon	14.7
Apple juice	14.0
Dates	11.5
Capsicum	10.2

Health effects of galactose

As galactose is a precursor to glucose production, it is an essential source of energy. This is particularly important during the developmental stages in mammalian infants, when they depend exclusively on milk as food source (Prado and Dewey, 2014). However, the biological importance of galactose goes beyond its importance as an energy substrate, as it also enhances cellular communication and control processes. As a structural component of glycolipids and glycoproteins, galactose has a critical role in maintaining the integrity both of cell membranes and of the cellular matrix (Coelho et al., 2015).

Apart from its importance in energy production, the Leloir pathway is crucial for the glycosylation of complex molecules such as myelin, which includes galactocerebroside as the predominant glycolipid. Galactose is therefore often 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 (Prado and Dewey, 2014). Galactose is known to serve as a substrate for cerebrosides, gangliosides and mucoproteins in the brain and nervous system. The known role of these molecules in neural and immunological function supports the physiological importance of galactose (Cederlund et al., 2013). Further support for the importance of galactose comes from animal studies focusing on the late fetal and early postnatal period, in which GALT expression has been found to be very high in myelinating oligodendrocytes and Schwann cells after birth. The peak of expression correlates with the period of myelinogenesis, which may be indicative of the high content of the glycolipid galactocerebroside in the complex molecule myelin (Fridovich-Keil and Walter, 2008 as cited by Coelho et al., 2015). It is therefore not surprising that galactose has recently been reported as having a beneficial role in managing a number of diseases, particularly those affecting brain functions (Coelho et al., 2015).

In light of the importance of galactose for development, as evidenced by markedly higher levels of endogenous galactose synthesis observed prenatally versus after birth (Prado and Dewey, 2014), it is not surprising that the human body is able to synthesize galactose *de novo*. It is thus not an essential nutrient.

Galactose also has an important role in maintaining a healthy gastrointestinal tract. Galactose is present in a series of oligosaccharides known as the raffinose-family oligosaccharides or galactose-containing oligosaccharides. Raffinose is a trisaccharide composed of galactose, glucose and fructose, and is found in beans, cabbage, Brussels sprouts, broccoli, asparagus and whole grains. Stachyose is a tetrasaccharide that consists two α-D-galactose units, one α-D-glucose unit and one β-D-fructose unit, and is present in green beans, soybeans and other legumes (Zivkovic and Barile, 2011). These prebiotic oligosaccharides have been shown to stimulate growth of some intestinal microflora and also display anti-adhesive activity. Galactose-containing oligosaccharides have been shown to inhibit infections by enteric pathogens directly through the ability to mimic the pathogen binding sites that coat the surface of gastrointestinal epithelial cells (Schaafsma, 2008).

Unmetabolized or free galactose is toxic only in case of galactosemia, a congenital disorder involving one of the three metabolizing enzymes in the Leloir pathway (Lukito et al., 2015). The most common form of galactosemia (classic galactosemia) is due to a GALT deficiency. Galactosemia is 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 is associated with severe long-term complications, such as cognitive and fertility

CONCLUSION

Scientific evidence confirms that lactose and its metabolites (such as galactose) are unlikely to be detrimental to health. Differential effects of various sugars on health outcomes indicate that lactose, which is naturally present in milk and dairy products, should not be targeted in attempt to reduce dietary sugar intake.

Milk and milk product intake is associated with better dietary quality and has been associated with a reduced risk of overweight and chronic conditions. As shown in this review, there is extensive evidence that moderate daily consumption of dairy, as part of a balanced diet, is beneficial to health.

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