SPLASH! milk science update

July 2014 Issue

This month's issue features articles about night-time milking, the effects of dairy foods on cholesterol, the optimal amount of DHA in breast milk, and how milk polyamines affect gut health.

Night Milk

- **Infrequent nursing produces richer milk; frequent nursing produces more milk.**
- **Co-sleeping and "on demand" suckling is typical in most primates.**
- **Night milking of dairy cows increases milk yield and a different composition.**
- **Consumption of night milk is associated with better sleep-wake cycles.**

Among many mammals, lactating females may have extended periods of time in between nursing bouts. This is often the case for females who "cache" or "park" their young in nests, dens, or burrows while they depart to forage more efficiently unencumbered by the presence of the young (parents, you know what I am talking about). The egg-laying echidna is an excellent, if totally weird, example. After hatching from the egg inside the mother's pouch, the young—known as a puggle—consumes milk secreted from a patch on the mother's tummy. Once the puggle is too large for the pouch, lactating echidnas dig nursery burrows. Here the young waits to nurse 3–6 days between mother's visits (1). Maternal foraging trips and inter-nursing intervals have also been well-studied in other species, particularly in seals (2) and rabbits (3). These inter-nursing intervals are generally characterized by energetically dense milk (4, 5). A comparison among prosimian primates showed that indeed the species that "parked" their young had higher fat concentrations than did closely related species that carried young while foraging (6).

However, among most primates, mothers carry young with them throughout the day as they forage, socialize and even occasionally when the mother is locomoting. Infants have what is known as "on demand" nipple access, especially in the early infancy period. Sustained access to the mother is not just during the daytime, if anything it increases at night when primate mothers and infants co-sleep (7). Indeed co-sleeping and night-time breastfeeding characterize much of the world's diverse cultures and human evolutionary history (8–10). Nightime nursing, especially in the context of safe bed-sharing, is implicated in sustaining lactation and achieving breastfeeding goals for mothers (8). The likely mechanism of longer breastfeeding duration likely rests within the behavioral biology of milk production—greater demand generates greater output. And co-sleeping can facilitate more frequent nursing and evacuation of the mammary gland. This nursing pattern increases lactose synthesis, pulling more water into the milk and increasing milk yield (11). In this way infant demand can increase milk production in the mother, insofar as mothers behaviorally accede to that demand (12, 13). They don't always—I have watched monkey mothers lie down on the ground to prevent the infant from gaining nipple access. Human mothers typically attempt behavioral distraction or object pacification if they are disinclined to nurse at the moment of infant demand.

The best understanding of the milk demand-production dynamic emerges from animal science research in dairy cows. Increasing frequency of milking improves milk production, and increasing milking frequency often involves night milking. In an elegant inter-mammary, within cow design, researchers showed that milking four times a day (every six hours) produced higher yields than did twice daily milking (every 12 hours) (14). This increased milk production continued even after the frequency of milkings was reduced to twice daily, revealing that milk "demand" in early lactation increased milk production throughout lactation (14). The persistent changes in mammary gland gene expression underlying this effect were recently documented (15).

But night-milking is not just about increasing milk production; the composition of milk collected at night differs from day milk. Of particular interest to our purposes here are hormones that are implicated in sleep cycles, such as melatonin. Concentrations of melatonin in milk can be up to ten times higher when cows are milked at night compared with daytime (16). And when that night milk was fed to rats, their circulating melatonin increased AND had improved sleep (as assessed via concentrations of a sleep-associated metabolite urinary sulfatoxymelatonin) (16).

That's in rats, what about in humans? Consumption of melatonin-rich milk, collected via night milking of dairy cows, increased daytime activity of some, but not all, elderly patients in rest homes, without altering their nighttime sleep patterns (19). Taken together, these studies suggest that there are potential applications for improving human health through strategic night milking. Moreover, there are many other bioactive hormones in milk that likely vary across the 24 hours of the day, and what they do when consumed remains poorly explored (17, 18). Unlocking milk hormones and strategizing animal management practices to enhance healthy concentrations of milk bioactive compounds is an exciting and developing area of dairy and food science.

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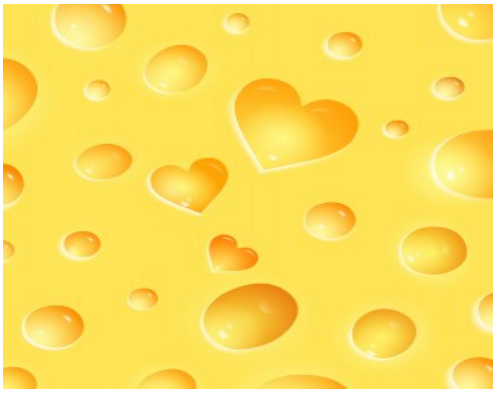
Cholesterol—What's (Love of) Cheese Got to Do With It?

- **Intake of dairy foods is inversely related to cardiovascular disease.**
- **Milk and cheese consumption may counteract the cholesterol-raising effect of saturated fat.**
- **The calcium in dairy products stimulates excretion of saturated fat through feces.**

Lamb chops, chips, chocolate, cheese—what's not to love? Yet, an affair with such fatty foods is prone to be marred by worry. Health authorities tell us that foods high in saturated fats increase our "bad" cholesterol and, along with it, our risk of heart disease. But research shows that calcium-rich dairy products such as cheese—despite their high content of saturated fat—may not wreck our hearts after all.



The pooling of results from lots of studies have indicated there is no reason to believe milk and dairy foods cause cardiovascular disease (1, 2). On the contrary, many studies suggest that eating plenty of dairy may actually protect against clogged arteries, stroke and heart attack (3).

Much of the evidence comes from so-called observational studies, where researchers observe what happens in a group of study participants living normally without any intervention. Observations often span decades, and might include what participants eat and whether or not they develop certain diseases. The researchers can then calculate the health risks associated with consumption of the food(s) in question. The Achilles' heel of observational studies is that they cannot determine cause and effect; at best, they provide circumstantial evidence and hypotheses.

Carefully controlled intervention or experimental studies, on the other hand, are considered the gold standard for directly testing the health effects of various substances, diets, or treatments. Recently, Danish scientists have undertaken several short-term intervention studies to verify the hypothesis that calcium in milk and dairy products can counteract the harmful effect of saturated dairy fat (4-6).

"Among leading scientists in this field, there is a strong consensus that you cannot make judgments about health effects of a food only by reading the food label—you need to study the whole food. And that is what we have been doing over the last five years," says Professor Arne Astrup, Head of the Department of Nutrition, Exercise and Sports at the University of Copenhagen, Denmark.

Of Pigs and Men

In one study, the scientists fed two groups of pigs a high-fat diet. During an adaptation period, the two weight-matched groups received the same diet. In a subsequent intervention period, one group of pigs received the high-fat diet, now supplemented with milk minerals, predominantly calcium. The other (control) group received a placebo, that is, the same high-fat diet without milk minerals. In a similar human study, healthy non-smoking young men were put through two intervention periods, consuming a high-fat diet with or without added milk minerals, respectively. The diet was tailored to the men's individual energy requirements, calculated from their basal metabolic rate and physical activity level (4).

In both studies, the researchers measured various parameters in the blood, urine and feces of the study subjects. The blood samples showed that when the high-fat diets were supplemented with milk minerals, the pigs' and the men's total cholesterol and "bad" low-density lipoprotein (LDL) cholesterol increased significantly less than when the milk minerals were not added. The milk minerals did not affect the "good" high-density lipoprotein (HDL) cholesterol.

The human study was a sub-study of an experiment where the main source of calcium was dairy products rather than mineral supplements (5). The scientists realized their original data might be confounded by differences in diet compositions owing to the wide range of nutrients present in the milk. So they included the sub-study to keep the number of experimental variables to an absolute minimum, relying on a milk mineral concentrate instead of potentially variable dairy minerals. The sub-study and the pig study confirmed the original results.

Flushing Out the Bad Fats

So the calcium in dairy evidently makes amends for the supposed badness of saturated fat, which—ironically—endows dairy products with their creamy deliciousness. But how?

Cranking up the calcium in the high-fat diets of the Danish study participants stimulated their bodies (pigs and men alike) to excrete much more fat in their feces (4, 5). This seems, at least partly, to confirm the proposed mechanism in which calcium binds to fatty acids inside the intestines, forming insoluble soap particles that get flushed out with the feces.

However, the study authors pointed out that the increased fecal fat excretion could only partly explain the cholesterol-reducing effect they observed. They suggested that another, so far unidentified mechanism, was also at play, possibly involving aggregation of bile acids and other minerals such as phosphate or magnesium.

What about Different Types of Dairy?

Another question that keeps nutrition researchers busy is whether different dairy products such as butter, milk, yogurt, or cheese differ in their ability to influence cholesterol levels. This would seem plausible, given that dairy products differ a great deal in terms of their physical makeup, such as how their calcium and fat molecules are assembled. Some observational studies have suggested that particularly cheese and yogurt consumption is related to good cardiovascular health (3). But the body of evidence has been somewhat confusing.

To provide some experimental data, Danish scientists recruited another batch of healthy young men willing to go on a series of highly controlled diets for a few weeks. The experimental design involved milk- and cheese-based diets in which all the nutritional values, including fat and calcium content, were strictly matched, making it possible to confirm any dairy-related differences (6).

Compared with the control diet, the milk- and cheese-based diets attenuated the cholesterol-raising effect of saturated fat and stimulated fecal fat excretion, consistent with the findings from the other studies. Milk and cheese appeared to have the same effect; however, as Astrup points out: “There might be a difference that the study did not have the statistical power to pick up, which actually could have important public health implications in favor of cheese.”

Clearly, the jury is still out on precisely how—and how much—dairy foods influence the body’s cholesterol levels. Likewise, a complete picture of the health effects of dairy food consumption is probably still some way off. What the latest research is telling us though, is that the saturated fat in dairy products does not deserve its tainted reputation.

So while ditching the chips from fish ‘n’ chips is still sound health advice, dairy lovers may take comfort in the knowledge that their calcium-laden objects of desire are not such baddies after all. Pass that cheese, please!

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How Much DHA Should Be in Human Milk?

- **Docosahexaenoic acid (DHA) is a long-chain polyunsaturated fatty acid found in breast milk that plays a role in neurodevelopment.**
- **Breast milk DHA concentration is influenced by DHA in the mother's diet.**
- **Researchers examined the concentration of DHA in breast milk, infant blood and maternal blood in four populations in Tanzania with different dietary DHA intakes.**
- **All lactating mothers, regardless of DHA intake, lost body stores of DHA.**
- **Mothers with optimal DHA status produced milk containing 1% DHA.**
- **Prenatal and postnatal DHA supplementation would benefit breastfeeding mothers who do not eat a lot of fish.**

The goal of infant formula is to mimic breast milk composition as closely as possible. But when considering milk components that vary widely across and within populations, whose breast milk should be used as the gold standard? Take, for example, docosahexaenoic acid (DHA), a long-chain polyunsaturated fatty acid implicated in brain growth and development. DHA is one of the most variable fatty acids in human milk, its concentration being directly influenced by the amount of DHA in the mother's diet. Current formula recommendations are between 0.2–0.5% DHA (g DHA/100 g of total fatty acids), which most closely resembles values in milk from mothers consuming a Western diet. Many have argued that the Western diet is a poor model (being notably low in DHA) and optimal DHA may be as much as two to three times this concentration (1–3). Adding to this debate is a recent report from a team of Dutch researchers investigating milk in a non-Western population with high DHA intake (4). They argue that optimal milk DHA comes from mothers with optimal DHA status, further supporting the position that (at least when it comes to DHA) formula might be mimicking milk from the wrong population of breastfeeding mothers.

If some is good, is more better?

DHA concentration in breast milk varies more than 20-fold across human populations (0.06–1.4% by weight). The lowest values are found in milk from mothers with little or no preformed sources of DHA (eg, fatty fish) in their diets and the highest values are found in milk from mothers who consume fish products daily (5). Although it is well known that milk with no (or very little) DHA compromises infant health, particularly visual and cognitive development (1; reviewed in 6, 7), the concentration that leads to optimal infant outcomes is still under investigation.

It is all too easy to fall into the trap of thinking that if some DHA is good, then more must certainly be better. We are so familiar with diseases and syndromes that result from dietary deficiencies that we can forget it is possible to have too much of a good thing. DHA decreases platelet aggregation, and too much DHA could potentially cause excessive bleeding (8). Assuming that the maximum amount of DHA is the same as the optimal amount could compromise infant health.

Further complicating matters is an understanding of how (and when) to measure optimal infant development. For example, is an IQ test the appropriate method to assess cognitive development? Should cognitive skills be evaluated during infancy, childhood, or at some point later in time? Early nutritional input (both positive and negative) can show effects at later points in the individual's lifetime (9), which means longer-term studies that integrate multiple measures of cognition might be the most appropriate. However, these studies can be both logistically and financially difficult to undertake.

Whereas optimal DHA status in infants is unknown, optimal DHA levels in adults is better studied. Researchers measure the percentage of DHA n the membranes of red blood cells (RBC-DHA) as an estimate of the amount of DHA generally found in the body's cell membranes. In adults, RBC-DHA of 8 g% fatty acids is considered optimal for cardiac and mental health (eg, reduced incidence of cardio-vascular disease, depression) (2, 4, 10). How much DHA do breastfeeding mothers need to consume to maintain their optimal levels?

In a recently published study, Luxwolda et al (4) take advantage of the natural range of variation in DHA concentration in breast milk. Rather than perform randomized controlled trials on infants consuming formulas with various milk DHA levels, they focused their investigations on four Tanzanian populations that vary in freshwater fish, and thus DHA, intake (Maasai = no fish; Pare = 2–3 serving fish/week; Sengerema = 4–5 servings/week; Ukerewe = >7 servings/week). They were interested in both maternal and infant status, determined by quantifying the concentration of DHA in red blood cells (g% fatty acids RBC-DHA), and how both of these factors related to breast milk DHA concentration.

The ups and downs of DHA

The researchers anticipated differences in milk DHA concentration among the four populations. Previous studies (eg, 5, 11) had demonstrated the strong influence of maternal fish consumption on milk DHA composition. Their research questions focused on determining how this variation in milk DHA concentration was related to changes in maternal DHA status from delivery through three months postpartum, and, more importantly, how it influenced infant DHA status (as a proxy for the concentration of DHA in infant brains, body fat and other membranes) over this same time period.

At birth, RBC-DHA levels for infants were between 4–5 g% DHA in fatty acids for the low fish intake populations (0–3 servings) and between 6.5–8 g% for the high fish intake populations (4+ servings). Maternal RBC-DHA at birth also varied across mothers with respect to their DHA intake. Mothers with high DHA intake began the lactation period with a RBC-DHA near 9 g% fatty acids, but mothers with low DHA intake (the Maasia and Pare) had RBC-DHA levels of approximately 4 g%. As a result, these mothers (and presumably any mother with low DHA intake, such as mothers on a Western diet) began the lactation period in a depleted DHA state (4). And, it appears, they were never able to recover their losses or improve their infants' DHA status during the postpartum period; low DHA status at birth resulted in a postpartum decrease in RBC-DHA in both mothers and infants as measured at three months postpartum.

Contrast this with the pattern observed in infants born to mothers with high freshwater fish intakes. Both the Sengerema and Ukerewe infants had increases in their RBC-DHA levels from birth to three months of age. Furthermore, Ukerewe infants were the only group to reach 8 g% RBC-DHA, an observation that the study authors attribute both to their high DHA status at birth and high DHA intake (1% DHA) during early infancy (4).

The magic number?

At age three months, RBC-DHA status of Ukerewe infants was more than double that of the mostly vegetarian Maasai. But what does this difference mean for their neurodevelopment, growth, or overall health? That is totally unknown. What is known is the optimal RBC-DHA for adults (8 g% fatty acids) so the data could be viewed in the context of what is optimal for the breastfeeding mother. The study showed that all mothers lost RBC-DHA over three months postpartum, regardless of their intake. The percentage of DHA in milk that corresponds to mother's optimal DHA levels is 1% (4). Therefore, it seems logical that 1% DHA is a reasonable target for milk.

Unquestionably, the optimal DHA for breastfeeding mothers is much higher than typically provided by most diets around the world (low consumption of wild-caught fatty fish). Both prenatal and postnatal supplementation with DHA would likely benefit both breastfeeding mothers and their babies. This is certainly more practical than expecting the whole world to live like the Ukerewe.

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Polyamines Promote a Healthy Gut Microflora

- **The number of bacterial cells in the human gastrointestinal system is ten times the combined total of all other cells in the body.**
- **Seeding of the bacteria populations occurs during neonatal life.**
- **The resulting composition of gastrointestinal microflora is incredibly important for establishing nutrient and energy balance, a healthy immune system and development of other physiological systems.**
- **This study looked at the influence of a polyamine supplement on neonatal gut bacteria in mice.**
- **Bacterial species in the gut of mice with polyamine-supplemented formula more closely resembled that of breast-fed mice.**

For many years the gastrointestinal (GI) tract was considered as a body compartment that primarily existed to digest food into nutrients that were in a useable form for the body. This is of course still the case, but we have come to appreciate that the GI tract and its contents contribute far more to the development and overall health of many physiological systems in the body. The bacteria that live in the GI tract, collectively referred to as the microbiota, are central to these effects. There is an astounding number of individual bacteria in a mammalian GI tract, in fact the number of bacterial cells in the human gastrointestinal system is approximately ten times the combined total of all other cells in the body (1).

Over the past decade, but particularly in the past five years, there has been an explosion of interest and associated research into GI tract microflora. Armed with genomic science, researchers have been able to more readily answer some long-standing questions about the species of bacteria that are represented and what influences them. At birth, our underdeveloped GI tract is essentially free from bacteria, and during neonatal life, seeding the species that will colonize the gut determines what develops in subsequent years (2, 3). There are broadly two components to seeding: the bacteria themselves and the nutrients that are supplied to allow them to expand, which are generically referred to as prebiotics.

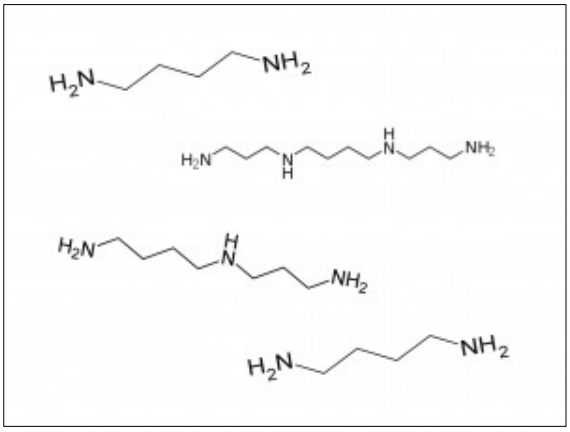
The outcome of the seeding process is a GI tract microflora whose composition is incredibly important for establishing nutrient and energy balance, a healthy immune system and development of other physiological systems. The bacteria that live in the gut, referred to as commensal bacteria, help to digest food and provide nutrients that may not otherwise be available. One example of this is the supply of folate, an essential vitamin that is synthesized by gut bacteria and supports infant growth and development, especially the developing brain and immune systems (4).

In the immune system, commensal bacteria contribute to an intestinal environment that is conducive to immune “education.” The GI tract contains large numbers of lymphocytes and other immune cells that provide a gateway to the protected physiological environment of the body. During development and neonatal maturation, these cells undergo extensive interactions that lead to the establishment of a stable and sensitive system that is finely tuned to distinguish

what is “self” from “non-self.” This process includes identification of commensal bacteria, which instruct the neonatal immune system to accept them as normal residents (5).

In breast-fed infants, commensal bacteria are predominantly from species of *Bifidobacterium*, *Streptococcus*, *Lactococcus* and *Lactobacillus*. They are believed to originate almost entirely from the mother, including directly from colostrum and breast milk, which also provide the essential nutrients or prebiotics to expand the number of bacteria. Most of the prebiotic content of breast milk is not yet replicated in infant formulas. With the aim of examining how these prebiotic differences may be narrowed, Gomez-Gallego et al (1) supplemented formula with polyamines and tested their formulation on neonatal mice.

Polyamines are compounds with two or more primary amino groups (-NH_2). They are essential factors for normal cellular function and have been recognized for many years as bacterial growth factors. They are important for the developing gut mucosa. However, the concentrations of the polyamines—spermidine, spermine and putrescine—are lower in dairy cow milk compared with human milk. The goal of Gomez-Gallego et al (6) was to recapitulate the breast-fed intestinal bacterial profiles of neonates that were formula-fed.



Polyamines

The researchers used a mouse model system and provided supplemented feeding from two weeks of age with formula containing various concentrations of polyamines, similar to those found in breast milk. Bacterial species colonizing the GI tract were enumerated for each section of the gut from the oral cavity to the large intestine. They first profiled the bacteria of formula-fed mice and breast-fed mice to establish differences in total bacterial numbers and patterns of colonization. When those animals fed the formula diet supplemented with polyamines were compared with those fed formula alone, they found a shift in bacterial content and compartmental species towards that identified in breast-fed mice. Although dose effects were generally weak for the range of doses used, for each group there was at least one dose that shifted the bacterial composition from a non-supplemented formula value and towards a breast-fed value. This comparison needs to be repeated in humans, but potentially represents a relatively simple solution that could have substantial benefits.

With the introduction of metagenomic analyses of commensal microbiomes, and increasing attention to the importance of bacterial colonization for neonatal gut health and lifetime well-being, we can expect that genomic technologies will continue to contribute to advancing the science of infant formulation.

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