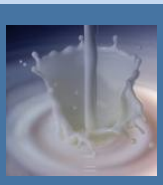
SPLASH! milk science update: December 2014 Issue



SPLASH! milk science update

December 2014 Issue

This month's issue features novel vitamin B12 absorption via dairy, a breast pump hackathon, dairy's value for Samburu children, and chemical messages from our mother's milk.

A Case for Vitamin B12 "Smuggling"

- **Many people suffer from vitamin B12 deficiency, either as a result of dietary deficiency or malabsorption.**
- **Vitamin B12 deficiency causes a range of health issues related to anemia and nerve damage.**
- **Research suggests that a protein in cow's milk—transcobalamin—stimulates uptake of vitamin B12 in the gut via an alternate route than the generally accepted route.**
- **Transcobalamin-vitamin B12 complex extracted from cow's milk might be used as a natural bioavailable alternative in overcoming vitamin B12 malabsorption.**

Memory loss, depression, numbness, seizures—those are some of the potentially irreversible symptoms suffered by people lacking vitamin B12. The deficiency is relatively common, especially in vegetarians and in people with dysfunctional uptake of the vitamin in the gut. A recent study (1) suggests that a protein found in cow's milk stimulates vitamin B12 uptake via an alternate route. This protein might be used as a natural source to treat vitamin B12 malabsorption.

Our body needs vitamin B12 to support the metabolism, produce red blood cells, and to make sure our nerve cells work properly. But our body can't make vitamin B12—a molecule produced by certain bacteria that, for instance, reside in the rumen of cows. Therefore, we need to get vitamin B12 from our diet, or from supplements.

Many people consume well above the recommended daily intake of 2.4 micrograms—an amount you could get from two or three glasses of milk—but some don't consume enough. This is the case for many vegetarians, especially vegans (2), as the only natural source of vitamin B12 is animal products. Others can't absorb the vitamin properly into their gut cells. These are mainly elderly people, but also people affected by gastrointestinal disorders or gastrointestinal surgery.

Consequently, vitamin B12 deficiency is relatively common, leading to a range of health problems, including anemia and nerve damage. Potentially severe or even irreversible, the symptoms are many: fatigue, loss of appetite, 'pins and needles' in the hands and feet, balance disorders and dementia, to name but a few. To treat these debilitating effects in those suffering vitamin B12 malabsorption, doctors typically prescribe monthly intramuscular shots—no doubt a hassle for the patient and often painful—or very large oral doses of vitamin B12—a daily routine that can be difficult to follow (1). Therefore, scientists are looking for new ways of delivering vitamin B12 to people at risk of deficiency.

The vitamin B12 "trafficking route"

Many studies have indicated that vitamin B12 from milk products is absorbed more easily than vitamin B12 from other natural sources, as well as the synthetic form found in supplements. The secret of this greater bioavailability of dairy vitamin B12 may lie in the proteins that attach themselves to the vitamin. But before getting to the secret, let's take a quick tour along the vitamin B12 "trafficking route".

Several proteins produced in our gastrointestinal tract help absorb vitamin B12 through the cells lining our small intestine and into our bloodstream. Holding onto and letting go of the vitamin at certain places en route, the proteins function more or less as chauffeurs and bodyguards, providing cross-border transport and unlocking doors. It's here—at any of these "checkpoints"—that an inherited or acquired dysfunction can cause malabsorption and vitamin B12 deficiency (1, 3). Once inside the bloodstream, vitamin B12—also known as cobalamin—is escorted to various body tissues by a protein called transcobalamin.

The transcobalamin alternative

Besides its blood-trafficking role, there is some evidence to suggest transcobalamin can also promote uptake of vitamin B12 from the intestine. Recently, Hine et al. added further evidence to this notion (1). They showed that the bovine version of transcobalamin, extracted from cow's milk, stimulated uptake of vitamin B12 into lab-grown cells derived from cows, mice, and humans. This indicated an uptake mechanism that is similar across different animal species, even though transcobalamin itself varies somewhat between species. For example, the series of amino acids that make up the protein is around 70 percent similar between cows and humans. And while the protein largely ferries around in the blood of humans, it acts as an "escort" for vitamin B12 in cow's milk.

Hine and colleagues also reported that the transcobalamin-vitamin B12 twosome from cow's milk was much more effective than vitamin B12 alone in traversing specialized human intestinal cells. These cells are commonly used as a laboratory model for what goes on inside the gut. Interestingly, the experiments indicated that the transcobalamin "route" was distinctly different from the regular route—and did not involve any of the protein "smugglers" working the regular route.

This alternate route could be good news for those people whose "regular route" for vitamin B12 uptake has been cut off. Hine et al. proposed that transcobalamin-vitamin B12 complex extracted from cow's milk might be used as a natural bioavailable alternative in beating vitamin B12 malabsorption.

But there's a long way from observations in lab-grown cells—no matter how promising—to real, viable treatments based on studies in humans. And while cow's milk is rich in vitamin B12, milk-processing procedures would likely need to be optimized to extract the complex in a cost-effective and practical way. Furthermore, the kinds of doses required still need to be identified.

In the meantime, enjoying regular doses of dairy products will continue to provide an excellent source of this important vitamin for all those blessed with an intact trafficking "route".

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MIT's Hackathon Revolutionizes the Breast Pump

- **Today's breast pumps have numerous design faults that make pumping an unpleasant and time-consuming experience.**
- **One prototype redesign, called Second Nature, aims to mimic the action of an infant suckling.**
- **Another prototype redesign, called the Mighty Mom Utility Belt, comes with an app to monitor the volume of milk pumped.**

If there were a relatively expensive technology, several decades older than the motor car, and purchased by many thousands of people each year, you would expect it to have gone through multiple rounds of innovation and refinement. Alas, the breast pump has no equivalent to the Lamborghini. Instead, its users invariably complain that it is uncomfortable to the point of painful, noisy (but not in a sexy Lamborghini way), and physically prevents them from performing other tasks. In both the verbal and adjectival sense, the breast pump sucks in its current forms. Which is why MIT Media Lab recently hosted a "hackathon"—a collective and competitive brain storming session with the aim of redesigning the breast pump from scratch.

Among the offerings of the dozen or so teams that took part, two newfangled pump ideas have caught ***SPLASH!***'s eye. They have one important common aspect to their designs; unlike breast pumps currently on the market, both take a woman's experience of pumping as their starting point and then try in different ways to help women be less enslaved by the machine.

One design, named Second Nature, explicitly aims to make pumping more like nursing an infant. The team was founded when former experimental physicist, Kirsty Johnston, gave a one-minute pitch at the start of the hackathon, an appeal for biomimicry. Johnston used a breast pump for a year because her son had trouble latching, and she says that the trials of that time compelled her to attend the hackathon.

Pumping was, “tedious, painful, and kinda dehumanizing,” says Johnston. She noticed a multitude of design problems. “When I was pumping in the hospital, you had to sit up, and you have these things literally suctioned to you. It is not discrete. It’s loud. The bottles attach directly to the flanges so you can’t put a sweater on. And you have to sit forward. Sitting up and sitting forward was uncomfortable, as a new mom.”

At the hackathon, Johnston’s team decided they had to do more than merely re-engineer one part of the breast pump to solve all of these issues. They began with altering the shape of the flange, which they thought of as equivalent to an infant’s mouth, and something that should not be so bulky that it could not fit under a bra.

When an infant breastfeeds directly from her mother, she uses her tongue to massage the nipple to the top of her mouth, creating a cavity at the back of her mouth. The lower pressure in the cavity then helps her to swallow. The Second Nature team has come up with three options to replicate the tongue mechanism, but Johnston admits that this is where their prototype needs some work.

The flanges attach to tubes that lead the milk under low and constant suction, which is provided by a small motor, to a collection bottle in a shoulder sling. “When you’re done you can just detach the tubing from the flange. Say you’re a bus driver, you could pump while you’re driving the bus. Or you could pump during a video conference. It would just be a quite humming noise in the background, which is the motor muffled in the bag.”

The second hackathon product of note won the competition. Called the Mighty Mom Utility Belt, it is somewhat like the belts worn by marathon runners to hold sugary gel snacks. This team began with a Facebook survey, asking moms what they wanted to see in a breast pump redesign.

Like the Second Nature design, the Mighty Mom team also brought the milk collection bottles and the motor components of the breast pump down to waist level, to free a user’s hands to get on with basic manual tasks, and without so much noise from the motor. One of their main contributions was a tube to carry milk from a flange to a belt, which could be effectively unzipped along its length, and washed in a dishwasher. But the emphasis of the Mighty Mom design is on customizability, and on an App that monitors the volume of milk reaching the collection bottles.

“We had a guy on our team who works on optic sensors, and uses them in water quality tests to study different chemicals in water,” explains Robyn Churchill, a midwife and prominent team member. “If you’re hiding the bottles away in a bag behind you—rather than right in front of you—you definitely need a quantity monitor.”
This kind of data is likely to be especially useful for women who pump in order to increase their breast milk output, by allowing them to monitor their progress over time.

Down the line, the sensor might also monitor alcohol content. “The Facebook survey showed that women really wanted that. To be able to go out an have a couple of glasses of wine, and then test whether there’s any alcohol in the milk,” adds Churchill.

It is early days for both of these breast pump hacks. The Mighty Mom team has some prize money to spend on a trip to Silicon Valley, to do the rounds of venture capital firms there. At present, they are trying to figure out who among the 20-odd team members could quit their day job and focus on developing the product full time. The Second Nature folks could do with a week where a group of engineers sit down and optimize the tongue mechanism. Neither of these prototypes has yet been perfected. But, if either of them eventually make it to market, they will revolutionize the experience of pumping—and, perhaps more importantly, they will facilitate discrete pumping for working women that barely interrupts their day.

To find out more about the hackathon, go to the website: http://breastpump.media.mit.edu/

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Dairy's Value for Samburu Children

- **The Samburu are a pastoralist population in Kenya that once depended heavily on animal milk for nutrition but have recently shifted to a more agricultural lifestyle that includes less milk.**
- **A new study combines detailed dietary intake data with measures of child weight and height to determine how the dietary shift has influenced Samburu nutrition and child health.**
- **Child milk consumption did not predict height or weight measures, but reduced household milk production was associated with child undernutrition.**
- **Although cultivated foods can make up for the calories once provided by milk, they are poor substitutes for the protein, fat, and micronutrients needed for optimal growth and development.**
- **Policies to increase livestock holdings and milk consumption can positively impact child growth and population health.**

Among the earliest human populations to drink milk were pastoralists from East Africa. Over 3,000 years ago, they evolved the genetic mutations associated with lactose tolerance (1). Milk has remained integral to pastoralist livelihoods, providing between 50 to 90% of their daily caloric intake (2). Over the last several decades, however, environmental changes and political pressures have forced many populations, such as the Samburu of Kenya, to abandon their nomadic herding lifestyle for one focused more on agriculture. In addition to becoming more sedentary, these populations have decreased their livestock holdings, and with that, their milk consumption. What does this dramatic shift in livelihood mean for the health of a population with such a long history of milk dependence?

This important question is addressed by a new study that combines longitudinal data on diet and subsistence practices with measures of weight and height in children among the Samburu population (2). The results suggest that milk may play a critical role in preventing nutritional deficiencies and improving child health outcomes.

A population in transition

The Samburu are a population of roughly 200,000 people living in North Central Kenya. They have a long history of herding livestock, which includes indigenous breeds of cattle, sheep, and goats (3). Agricultural practices were introduced during the 1960s and since that time cultivation of crops (primarily maize and beans) has been integrated to varying degrees into the livelihoods of Samburu people. Since the 1980s, there also has been an increase in the reliance on wage labor for family income. While livestock are still considered central to their lifestyle, the Samburu, like many other pastoralist populations, are transitioning toward a more diversified livelihood strategy (2).

Study authors Iannotti and Lesorogal hypothesized that departures from the pastoralist mode of subsistence would be associated with reductions in milk consumption, which in turn would influence childhood nutrition and health (2). To test their hypothesis, they administered comprehensive surveys to 158 households at three time points over a 10-year period (2000, 2005, and 2010). Survey questions were designed to give the authors a clear picture of what each household was consuming and how each household made a living. For example, 24-hour dietary recalls were administered to each household and used to determine how well individual family members were meeting nutritional requirements. Because of the specific interest in milk and childhood growth, detailed questions also were included that allowed the authors to estimate each child's milk consumption — down to the milliliter!

Unlike the dietary data, growth data (height and weight) were not longitudinal, collected at just one time point from the same children that provided 24-hour recall information on milk consumption (218 children from 55 households). As a result, the study did not measure how each individual child grew over a set period of time. Rather, data on children's height and weight were compared to reference data (matched for age and sex) from the World Health Organization (WHO). Specifically, researchers wanted to determine what proportion of Samburu children could be characterized by underweight (low weight for age), wasting (low weight for height), and stunting (low height for age). Low is defined as

being in the lowest 5th percentile, or more than two Z scores away from the mean, for weight and height by age, or weight by height.

All calories were not created equal

When all of the data are combined, a detailed picture emerges of where Samburu get their calories and nutrients from, and what this means for their overall health. Maize provided the majority of the calories (50-55%) across all time points in the study. In comparison, only 10% of their calories were from milk. Despite its small contribution to their caloric budget, milk was responsible for 20% of total dietary fat, 20% of protein, and more than 50% of micronutrient intake (e.g., calcium, vitamin A, B12,). From this, it is clear to see how even small differences in milk consumption could produce large differences in nutrition, particularly for growing children. Indeed, the study found that reduced milk consumption at the household level was associated with child undernutrition.

It may seem surprising then, that Iannotti and Lesorogal report individual child milk intake was not predictive of any child growth measures (2). Compared to WHO reference standards, the Samburu certainly face issues of stunting, underweight, and wasting (for Samburu < 5 years of age, the prevalence was 30.6%, 23.9%, and 8.6%, respectively)(2). But children with higher milk intakes were not taller, heavier, or heavier for their height than their Samburu peers. How can these results be reconciled with their findings of widespread child undernutrition?

Iannotti and Lesorogal suggest that height and weight may not be the most appropriate measurements to understand the effect of reduced milk consumption on child health. Linear growth and weight gain may be sustained simply through sufficient energy intake. While maize is lower in protein and fat than milk, and lacks many of milk's micronutrients, it may provide sufficient calories for growth.

But not all calories are created equal. Although milk intake may not influence children's height or weight, it may have profound impacts on numerous other health outcomes that are not as easily quantified at one study visit. Based on analysis of dietary recall information, Iannotti and Lesorogal propose that Samburu are at high risk for having inadequate intake of vitamin A, vitamin B12, folate, zinc, and calcium (2). Deficiencies in any of these nutrients can result in poor child development or health outcomes. For example, zinc deficiency can influence linear growth, but is also associated with impaired immune function and an increased risk of diarrhea and pneumonia (4).

Improving outcomes

The goal of this type of research project is to identify ways in which to improve child growth and overall health. Despite the lack of relationship between individual child milk intake amounts and height and weight measurements, there were numerous factors that were demonstrated to improve child (and adult) nutrition. Cattle ownership at the household level was associated with improved child growth measurements and milk consumption ensured adequate micronutrient nutrition. Therefore, policies that promote and support the maintenance of livestock and continued milk production among the Samburu have the potential to positively influence child nutritional status, and subsequently, population health of Samburu and other pastoralist groups in transition.

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Stop, Slow, & Go: Hormonal Signals from Mother's Milk

- **Animal scientists pioneer "lactocrine programming" hypothesis.**
- **Research is ongoing in rodents, pigs, monkeys, and humans.**
- **Relaxin, cortisol, and leptin in milk affect offspring growth, reproduction, and behavior.**
- **Maternal-origin hormones are a key element for offspring development.**

Hormones are not just for women! From babies to the elderly, both females and males have these chemical messengers circulating throughout their bodies. Astonishingly, milk contains hormones too.

Getting the message via milk

Hormones are like a group email or a Facebook message with many recipients. Just as a Facebook status may be received by only certain ("friended") people, hormone messages are only received by tissues that have the right receptors. In this way, specialized glands secrete a hormone to convey the body's "status," and the "friended" tissues—those with the receptor—are updated. This is known as the endocrine system. "Endo" means 'within' our own bodies. But what about hormones we get from someone else… like from our mother through her milk? This system is clearly not endocrine… the hormones are coming from another body via her mammary glands during lactation. For this reason they are termed "lactocrine" and the numerous bioactives in milk, including proteins, peptides, and steroids, might be messages from mother to baby.

Professors Frank "Skip" Bartol at Auburn University, and Carole Bagnell at Rutgers have been tackling hormones in mother's milk and the consequences in piglets for over a decade. They and their team have found an exquisite synchrony between hormones in mother's milk and hormonal receptors in piglets that together affect piglet development, particularly in their reproductive tract. Their discoveries motivated them to coin the term "lactocrine programming" for hormonal signaling from the mother to the neonate through the milk the young ingests (1-5). Quoting Socrates, Skip reminds us, "to understand a thing you must first name it." The name—lactocrine programming—implies both that the message comes from the lactating mammary gland, and that the message "programs" the infant's development.

Programming baby's future reproduction with milk relaxin

In piglets, reproductive tissues have a critical window of development in the first days after birth (6-7). Women, too, develop tissues to make future babies while they themselves are babies. These reproductive tissues—uterine glands, cervical tissue, and the endometrium—wait for a "start development" message. That message is conveyed by the hormone "relaxin." Here's the crazy part: relaxin is delivered by the mother via her milk. Piglets that are allowed to suckle have relaxin in their blood stream, but not piglets fed a milk-replacer (8-9). Relaxin activity in pig milk is highest in the first few days of lactation, and is similar to findings from dogs and humans (10). Experimental manipulations have shown that as little as one colostrum feeding in the first 12 hours after birth can make a difference. For example, just a single colostrum feeding bout in the first hours after birth allows for typical cervical cell proliferation and development—an important predictor of future litter size (11).

So far, these studies predicted long-term effects of milk relaxin but did not yet demonstrate them. That all changed last July, when Bartol and Bagnell, with Dr. Jeff Vallet at the USDA-ARS/RLH Meat Animal Research Center, revealed new evidence that early life-disruptions in access to mother's milk had persistent effects well into adulthood. In a retrospective study of 381 gilts and over 1,500 litters produced by those gilts, they found that female pigs with limited access to maternal-origin hormones via milk as piglets had reduced litter size as adults (12). So, it is safe to conclude, at least in pigs, that the number of babies born in any generation was partly programmed by their grandmothers via milk hormones.

Programming baby's growth and temperament with milk cortisol

It's not enough for a hormone like cortisol to be in milk. Somehow, the baby has to be able to receive the message by having the right receptor for that hormone. This November, Sharon Donovan and colleagues demonstrated how much of cortisol's receptor—the glucocorticoid receptor—is in a human baby's intestinal tract (13). The glucocorticoid receptor gene in the intestinal tract of breastfed babies had five times higher expression than in formula-fed babies. So, babies do indeed have a receptor for cortisol in their digestive tracts, and its presence is responsive to human milk.

Given that babies have the right receptor, the milk cortisol message must be pretty important. What is that message? This November, Hinde and colleagues published a large study in monkeys (N=108) revealing what monkey babies seemingly do with that message (14). Monkey mothers who had higher concentrations of cortisol in their milk had daughters who were more “nervous” and less “confident.” For sons, though, how much cortisol increased across time was correlated with being more “nervous” and less “confident.” Nervous was a temperament score that combined ratings by a trained observer on how “nervous, fearful, timid, NOT calm, and NOT confident” the infant was after a 25-hour assessment during peak lactation. Confidence was the temperament score combining “confident, bold, active, curious, playful” traits. Mothers who had produced more infants had higher available milk energy but lower cortisol, whereas younger “earlier reproductive career” mothers produced lower levels of available milk energy and higher cortisol. And most intriguingly, higher cortisol in milk was also associated with better infant growth. All of these findings suggest that cortisol in milk sends this message: play less and prioritize milk calories on growth.

Programming baby’s growth with milk leptin

Cortisol is not the only hormone in milk linked to infant growth. Also this November (seriously, so many amazing milk papers in November!), EA Quinn and colleagues reported leptin values in breast milk among women living in Cebu, Philippines (15). Leptin is a hormone made by fat cells. The leptin message influences appetite and body fat storage. Filipino women had some of the lowest reported concentrations of leptin in milk, probably because they were particularly lean with fewer fat cells to secrete leptin. Even in this lean population, leptin concentrations were correlated with maternal percent body fat. Up to a year of age, infants were bigger for their age if their mothers synthesized milk with lower leptin levels than the infants whose mothers produced higher concentrations of milk leptin… and if they were daughters. Milk leptin showed a much stronger association with daughter size than with the size of sons. This result echoes partly the findings in rhesus and rodents, insofar as there seem to be differential degrees of sensitivity or windows of sensitivity among developing males and females to maternal origin hormones.

When the milk stops

Sometimes the milk stops flowing too soon during a bout or across time. This can occur naturally as a consequence of mastitis, insufficient milk supply, or, in litter bearing species, competition for the teat among siblings. In humans, lactocrine disruption can occur as a result of cultural practices, medical conditions, or economic realities. Among some traditional peoples, cultural practices of colostrum avoidance and replacement are not uncommon (16). Depending on context, breastfeeding can be contraindicated if mothers have certain infectious diseases or are taking medication that affects milk production or has effects in infants (17). Lastly, in the U.S., the lack of paid maternity leave prevents many mothers from breastfeeding. Given how easily and often the milk stops flowing, it seems important to understand the implications of lactocrine disruption—the disruption of the delivery of breast milk hormones like relaxin, cortisol, and leptin.

Collectively, the studies demonstrate that mammalian young have physiology specific to using the hormonal signals from their mother’s milk to influence their daily functioning, and shape their development. But we still know relatively little about these pathways, and many more questions are generated. What does it mean when hormones are absent during lactocrine disruption, or when hormones are dialed to 11 with the “knob” broken off? We don’t know. Do we expect either of these to necessarily be catastrophic in typically developing mammalian young? No, we don’t, but it is possible that formula-fed infants are missing out, or that the human population is less resilient when adaptation to the current environment is missing. Perhaps disruptions in milk hormones influence animal science and dairy productivity as well. Subtle differences in individual fitness can manifest in lower production of young or milk that may cumulatively add up across an animal’s life or aggregated across a herd. It will certainly be worthwhile to find out.

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