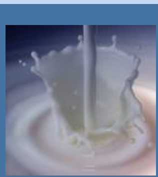
SPLASH! milk science update: April 2015 Issue



SPLASH! milk science update
April 2015 Issue

This month's issue features the regenerative powers of milk molecules, dairy and insulin resistance, breastfeeding and vitamin D deficiency, and an infection-fighting formula.

The Regenerating Powers of Human Milk Molecules

- **Previous research has shown that the body releases specialized chemical signals that help resolve infections.**
- **A new study identifies previously undescribed chemical signals present in human breast milk that accelerate tissue repair and regeneration in addition to resolving infections.**
- **The discovery of these molecules may improve our understanding of the beneficial properties of breast milk and could lead to new approaches to treating infections and several human diseases.**

What do breast milk, regenerating flatworms, and infected mice have in common? That might sound like a particularly cryptic riddle, but the answer may improve our understanding of the beneficial properties of breast milk and could potentially lead to new therapies for many diseases.

In a new study, Charles Serhan and his team from Brigham and Women's Hospital identified new chemical signals that help resolve bacterial infections and speed up tissue repair and regeneration [1]. They isolated these molecules from human breast milk, mice with self-limiting bacterial infections, and regenerating flatworms called planaria.

"The primary response in an infection and in an inflammatory response is to recruit cells to the site of injury or bacterial invasion," explains Serhan, a biochemist and experimental pathologist. Serhan studies how the human body stops this cell recruitment and shuts down the inflammatory response before it can become harmful. Uncontrolled inflammation has been implicated in a number of diseases, including cardiovascular disease, asthma, Alzheimer's disease, and arthritis. Finding new ways to stop the inflammatory response could potentially help treat many of these ailments.

Serhan's previous work has helped show that the resolution of inflammation is an active process, mediated by molecules dubbed 'specialized pro-resolving mediators' or SPMs [2,3,4,5]. "This is a pretty novel concept," says Serhan. SPMs are small molecules made at the site of an infection that promote the clearance of bacteria and cellular debris from the infection site and stimulate the resolution of the inflammatory response.

But that may not be all they do. In a recent study, Serhan and his team showed that in pigs with periodontitis—a gum infection that destroys the bone supporting teeth—using pro-resolving molecules to control inflammation actually allowed the tissue to regenerate [6]. Serhan recounts that the team "started to think hard about how all these specific signals in the resolution response can actually stimulate tissue regeneration."

In the new PNAS study, Serhan and his team isolated chemical signals from self-limited bacterial infections in mice, and then examined whether these could promote tissue regeneration. They looked at the effects of these signals on flatworms called planaria, which have an amazing ability to regrow body parts that have been injured or cut off [7]. According to Serhan, "They're an ideal model for looking at tissue regeneration. You can cut those planaria in half, and then they'll regenerate on their own, and we looked at whether these specific signals would regulate this."

Serhan and his team cut off the heads of planaria and found that the heads grew back faster in the presence of these chemical signals. They characterized the molecules responsible for this regenerative effect as lipid-protein conjugates, and called them sulfido-conjugated product I (SCI) and sulfido-conjugated product II (SCII) based on their structures.

Next, they decided to look for similar chemical signals in human milk. Serhan says that "anything important is present in human breast milk." The team was able to isolate chemical signals from human milk that also promoted regeneration in planaria. This discovery, he remarks, "really clinched it for us that this could be important in human biology."

Jesmond Dalli, a biochemical pharmacologist at Brigham and Women's Hospital and the first author on the PNAS study, estimates that "if these signals are as important as we think they are, then they have to be conserved in evolution."

"So, we started with a mouse, and then we went to planaria, to see whether these processes were active there," says Dalli. Looking at human milk, "gave us a way to look at regeneration in humans," he says. "We can't really chop someone's fingers off and look at what's happening, so these regenerative processes that are happening in infants that are developing, that was our validation."

The team had good reason to think that these signals might be present in milk. Human breast milk has been previously shown to contain chemicals and nutrients that play a role in infant development and immunity [8]. A recent study also found high concentrations of certain types of SPMs in human breast milk [9]. Moreover, many SPMs, including SCI and SCII, are synthesized from fatty acid precursors such as docosahexaenoic acid, or DHA. Serhan says that "Another reason we were interested in milk was because we know that in mother's milk, there's a high concentration of DHA." DHA from breast milk is thought to play a role in early neural development, and is added to some infant formulas, although, according to the FDA, it is still unclear whether DHA in infant formula is beneficial [10].

Serhan is currently working on determining therapeutic uses for SPMs. The compounds found in the PNAS paper and in another more recent study by Serhan's team enhance the killing and clearance of E. coli [11]. He explains, "They're actually enhancing the anti-microbial action of the innate immune system." The ability of SPMs to control inflammation could prove useful against the many diseases where unresolved inflammation may play a role. In fact, he says, "There are a couple of these molecules and their analogs that are already in clinical trials for things like periodontal disease, and eye inflammation." What makes SPMs particularly handy is that unlike many common anti-inflammatory molecules, they do not suppress the overall immune system, so they wouldn't disrupt the body's ability to respond to other infections.

There's also the question of what natural role these molecules might be playing in human breast milk. We don't have specific answers yet, but Serhan thinks we can speculate. From his work, "what becomes even more exciting is the possibility that these agents are present in milk to enable growth and tissue development," he says. Given that breast milk carries many immune mediators, these molecules could also be important for the infant's immune development. Serhan says, "Those are really exciting possibilities, and I guess more reason why breast milk is very important."

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3. Chiang N, et al. (2012) Infection regulates pro-resolving mediators that lower antibiotic requirements. Nature 484(7395):524–528.
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Dairy Foods and Insulin Resistance

- **Type 2 diabetics have low insulin sensitivity and require more insulin to maintain healthy blood sugar levels.**
- **Dairy foods, particularly their whey proteins, are believed to have positive effects on glucose metabolism by increasing insulin sensitivity.**
- **While numerous randomized studies have investigated the potential health benefits of dairy to diabetics, not all have identified a positive relationship between dairy intake and insulin sensitivity.**
- **Discrepancies are present even in studies that control for weight loss/gain, factors known to strongly influence insulin sensitivity.Dairy products, vegetables, fruits, grains, and some other foods are associated with lower blood levels of uric acid and lower incidence of gout.**
- **New review papers suggest that contradictory results of previous research are likely the result of the complex nature of glucose metabolism. They provide direction for future studies on dairy and insulin sensitivity.**

Can being more sensitive make you healthier? It can, if you are one of the nearly 30 million Americans living with type 2 diabetes. Although type 2 diabetics produce insulin, they have a very low sensitivity to this hormone. Without injecting additional insulin, blood sugar levels reach unhealthy levels that, over time, can result in damage to the kidneys, nerves, and blood vessels. While diabetics are instructed to avoid foods that raise blood sugar levels, there are other foods that could be ideal for diabetics because they can increase the body's sensitivity to insulin. Topping this list are dairy foods such as milk and yogurt that have bioactive factors that increase the body's response to insulin and a low glycemic index. But despite these demonstrated physiological actions, many studies have failed to show any effect of increased dairy intake on blood glucose metabolism. Two new review papers (1, 2) help make sense of these conflicting findings and suggest the discrepancy may have more to do with the complexities of studying a metabolic disease, than the biological effects of dairy on insulin tolerance.

Sensitivity training

We often think of sugar as something we need to avoid in our diet, but sugar (specifically glucose) is the fuel that our body runs on. It is used both for immediate energy needs by cells and also stored for future use by the liver and muscles. When we eat foods that contain glucose, such as fruits, vegetables, starches, and dairy, the pancreas responds by producing insulin, a protein tasked with moving glucose from the bloodstream into the cells. If the cells already have enough glucose, insulin also plays a role in converting glucose into its storable form, glycogen.

This whole system is disrupted in individuals that have low insulin sensitivity, or what is commonly referred to as insulin resistance. Although their pancreas produces insulin in response to glucose in the bloodstream, their cells have a decreased sensitivity to the action of insulin. As a result, more insulin is needed to transfer glucose into the cells. The pancreas responds by increasing insulin production. Type 2 diabetes occurs when pancreatic insulin production can no longer keep up with insulin requirements. Without the addition of synthetic insulin, heightened blood glucose levels (called hyperglycemia) can result in kidney damage, blindness, heart disease, and stroke.

So, why would cells that were once sensitive to insulin become resistant to its chemical actions? Extra body fat, especially that stored around the abdomen, appears to be the most important non-genetic factor explaining the decrease in insulin sensitivity. Fat cells, or adipocytes, produce hormones and pro-inflammatory molecules that interfere with the signals insulin uses to transport glucose into cells (1-4). The more abdominal fat cells, the greater amount of disruptive molecules are produced, the more insulin is needed to get the job done.

Dairy knows the whey

There is one piece of good news about low insulin sensitivity: it is not permanent. Just as an increase in fat cells can reduce sensitivity, a decrease in fat cells, through weight loss or muscle-building exercise can increase it. Exercise is also able to improve insulin sensitivity, even without changes in body weight (1, 2). And because many foods contain bioactive components (e.g., phytoestrogens in soy, antioxidants in fruit), it is not surprising that dietary changes may exert positive effects on glucose metabolism as well.

Numerous studies have examined dairy foods for their potential preventative role in the development of insulin resistance, as well as their ability to increase sensitivity in type 2 diabetics (1, 2). Dairy limits post-prandial hyperglycemia, which is a fancy way of saying how much your blood glucose levels rise after consuming a meal. The smaller the rise in blood sugar, the less insulin needs to be produced. This is believed to be the result of actions of whey proteins that are unique to milk and milk-derived foods. Whey proteins contain essential amino acids that have been demonstrated to stimulate the pancreas to produce insulin (1). And when digested, these proteins are believed to form bioactive peptides (chains of amino acids) that enter the bloodstream and influence glucose metabolism (1). Finally, both whey-derived peptides and calcium may also influence the types of chemicals and hormones secreted by fat cells that can interfere with insulin's ability to move glucose from the bloodstream into the cells (1).

Dairy, dairy quite contrary

Given this list of ways in which dairy foods influence glucose metabolism, it may seem surprising that it is still unclear whether adding dairy to the diet has any effect on insulin sensitivity. Two recent reviews on the topic (1, 2) suggest that the complexity of the topic — glucose metabolism—is partly to blame.

Insulin sensitivity is influenced by numerous factors, all of which interact with one another. Simply changing one factor, such as diet, could unknowingly affect many other factors, such as body fat. Are the results because of the dietary change, or because of some other factor that was not accounted or controlled for? It is not possible to establish causality, because so many factors can cause changes in insulin sensitivity. In their review, Turner et al. (2) were specifically interested in removing the potentially confounding variable of weight loss (or gain). But even among the ten weight-stable, randomized, controlled trials they compare, there are major discrepancies in results: four studies show a positive effect of dairy on insulin sensitivity, one showed a decrease, and five found no effect at all.

And herein lies the next likely reason for differences in findings: methodological variation, particularly the timing of the intervention studies. Short-term studies (in Turner et al.'s review, those < 8 weeks in duration) failed to identify any significant changes, while those between 12 and 24 weeks found a positive effect of dairy on insulin sensitivity. At first glance, this seems to indicate that dairy foods have a cumulative effect on the action of insulin that can only be measured in longer randomized studies. However, only one of three six-month studies reviewed by Turner et al. (2) reported an increase in insulin sensitivity as a result of increased dairy consumption.

Turner et al. (2) believe that there are simply just too few studies that effectively test for the relationship between dairy intake and insulin sensitivity, and among those that have, it is not possible to directly compare the results because of differences in the type of dairy foods used (low-fat milk, yogurt), outcome measures (e.g., fasting insulin, glucose tolerance), and study participants (normal weight, obese, diabetic). Ballard and Bruno (1) echo these frustrations. They believe there is a strong foundational basis for the mechanisms by which dairy interacts with glucose metabolism and increases insulin sensitivity, but it has yet to be clearly demonstrated in long-term randomized trials because of a failure to control for confounding variables, such as changes in body weight or carbohydrate intake, that can accompany dairy intervention studies.

Given that diabetes is the seventh leading cause of death in the U.S., this seems like a conflict that requires quick resolution. Both review papers provide important signposts for future research projects on dairy and insulin resistance. Although the effect of dairy on insulin resistance may not be as profound as that of weight loss or exercise (2), a lifestyle change that can be easily implemented could have a large impact on the fight against diabetes.

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Breastfeeding and Vitamin D Deficiency

- **Breast milk does not provide babies with enough vitamin D; instead, babies rely on transplacental transfer, skin synthesis, or supplementation of vitamin D.**
- **Vitamin D deficiency in pregnant women and breastfeeding mothers and infants is a global problem further compounded by the lack of a standardized way of analyzing and comparing data.**
- **A new study compared the vitamin D status of breastfeeding mothers and infants in North America, Latin America, and China—highlighting large variations in the prevalence of vitamin D deficiency between those populations.**
- **The study showed that a person's vitamin D level depends on sun exposure behavior and vitamin D supplementation, including formula feeding.**

Breastfed babies get all the nourishment they need from their mother's milk—right? Almost. One nutrient they don't get enough of from breast milk is vitamin D, a hormone essential for babies' growth and health. Instead, infants rely on vitamin D transferred from their mother via the placenta during early pregnancy; vitamin D produced in the baby's skin after sun exposure; or vitamin D supplied via infant formula. Recently, it's become clear that vitamin D deficiency in pregnant women is widespread in many parts of the world (1). This means that many babies who are exclusively breastfed and also kept out of the sun— as recommended by health authorities—are lacking in vitamin D. To tackle this global health problem, a new study (2) calls for greater attention to the vitamin D levels in pregnant mothers and newborns.

Vitamin D is essential for the body's ability to maintain adequate levels of calcium in the blood and various tissues. Calcium, in turn, enables cells to communicate with each other, helps muscles contract, and gives strength to bones. Lack of vitamin D is therefore detrimental to health, especially bone health.

Only a few foods—including fatty fish, fortified dairy products, and egg yolk—contain vitamin D. For most people, a major source of this vital substance is sunlight, which stimulates our skin to produce vitamin D. But even in many countries that have plenty of sunshine, there is growing concern that vitamin D deficiency is a common and likely underdiagnosed health problem. The reported prevalence ranges from some 30% in the USA to upwards of 70% in some countries, including India and the United Arab Emirates. Severe cases can lead to rickets— a childhood disease in which bones soften and become prone to fractures and deformity—and this condition may represent the tip of the iceberg.

Comparing vitamin D levels in Cincinnati, Mexico City, and Shanghai

While moderate to severe vitamin D deficiency appears common among sun-deprived and unsupplemented pregnant mothers and breastfed infants, an accurate depiction of the global prevalence is lacking because there is no standardized way to analyze and compare the data. To get a clearer picture, researchers in North America, Latin America, and China recently joined forces to examine vitamin D in breastfeeding mothers and babies in these three parts of the world (2). A unique aspect of their research was its use of a standardized study design across different international sites— in Cincinnati, Mexico City, and Shanghai. Furthermore, the study participants' blood levels of vitamin D were all measured using the same protocol in the same laboratory in Cincinnati.

The study examined about 120 pairs of mothers and babies at each location. Nurses visited the families at set intervals between four and 108 weeks after each birth, recording information about their vitamin D supplementation and sun exposure. Blood samples from all the mothers and around a third of the babies were also collected at certain time points.

After analyzing the data, Dawodu and colleagues (2) found that vitamin D deficiency was common in breastfeeding mothers from Shanghai and Mexico City and less common in Cincinnati mothers—somewhat ironically, perhaps, considering the sunshine available at each latitude. Four weeks after giving birth, 62% of the mothers in Mexico City (latitude 19° N), 52% of the mothers in Shanghai (latitude 31° N), and 17% of the mothers in Cincinnati (latitude 39° N) were deficient in vitamin D.

The higher amount of vitamin D in the Cincinnati mothers was clearly linked to their much higher sun index—calculated from the body surface area exposed to sunlight and the weekly hours of exposure—and vitamin D supplementation compared with the Shanghai and Mexican mothers. The very limited sun exposure of the latter was likely related to cultural practices in Shanghai and Mexico, where new mothers are restricted from outdoor activities while being cared for by family members.

As for the babies, the results were somewhat different. The proportion of infants lacking in vitamin D was lowest in Shanghai—not Cincinnati, as it was for the mothers. At 26 weeks of age, 62% of the Mexican, 28% of the Cincinnati, and 6% of the Shanghai infants were vitamin D deficient. Notably, the Shanghai babies' sun index during the fall/winter season was about twice as high as that of the other babies. This probably contributed to their higher levels of vitamin D. Besides, most breastfeeding infants in Shanghai would be likely to receive vitamin D supplements because it's encouraged by health authorities, although the information about vitamin D supplementation among the surveyed infants was incomplete.

Unsurprisingly, the study showed that a higher sun index and formula feeding, which increased the babies' vitamin D intake, were predictors of higher amounts of vitamin D in infants.

Vitamin D deficiency—a significant, global problem

The study had a number of limitations, including limited blood sampling and time points, lack of comparison across seasons, and no evaluation of the role of skin pigmentation. But in taking the first steps toward objectively mapping the prevalence and risk factors for vitamin D deficiency in different populations, it calls greater attention to what appears to be a significant global problem—especially for pregnant women, breastfeeding mothers, and infants.

Healthcare providers and caregivers need to pay close attention to this problem and promote vitamin D supplementation where necessary. This is particularly important in view of the current trend to increase the prevalence and duration of exclusive breastfeeding, which does not provide babies with enough vitamin D. Additionally, careful attention to sun exposure is equally crucial because, while sun exposure clearly boosts an individual's vitamin D status, it can also increase the risk of skin cancer, especially in the very young.

Another question that needs to be sorted out through future comprehensive clinical studies is what constitutes optimal vitamin D status and supplementation during pregnancy—a topic that remains controversial (1).

So, while the near 100-year old practice of fortifying commercial cow's milk with vitamin D has had a profound impact on human nutrition, many children and adults are still not getting enough of this essential nutrient. Clearly, the last word is yet to be had on vitamin D.

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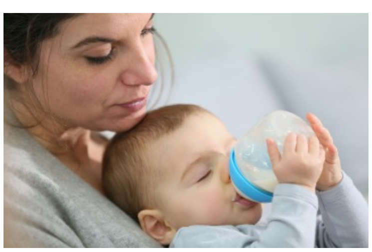
Infection-Fighting Formula

- **An experimental infant formula has been found to cut the rates of several kinds of early-life infections, relative to standard infant formula.**
- **This experimental mixture has lower concentrations of protein and energy, but the key difference when it comes to fighting germs is this formula's supplement of milk fat globule membranes from cow's milk.**
- **So far, only Scandinavian infants have been studied in this way. Much larger reductions in infection rates are likely to be found in areas of the world where infections during infancy are a bigger health problem.**

There is a plethora of ways in which the composition of infant formula differs from that of breast milk. For one, the latter has a far greater diversity of ingredients, which are still not exhaustively known. But there are also plenty of known constituents of breast milk that are absent from infant formula. One team of researchers is dedicated to figuring out the implications of adding one kind of missing ingredient in particular—milk fat globule membrane (MFGM)—on infants' health and development. Recently, this group identified some benefits to infants' abilities to cope with infections when the infant formula they consume contains this supplement [1].

The research team in question is mainly drawn from Umeå University in Sweden and Finland's National Institute for Health and Welfare. Their experimental formula is different from standard formulas in a few extra ways. Namely, while the experimental formula is supplemented with MFGMs, it also has some protein and energy content removed, compared to infant formulas that are available in stores. The source of MFGM is cow's milk, which is likely to be subtly different from the MFGM found in human milk. Nonetheless, an earlier study by this team found apparent advantages in the neurodevelopment of infants' who were fed this novel formula containing the globules, compared to formula that lacked them [3 4].



The new study [1] focuses on infants' abilities to fight infection rather than their brain development, and compares three groups: infants who were exclusively fed breast milk for the first six months of life, infants fed only un-supplemented, standard formula from two to six months, infants who uniquely consumed the experimental, globule-containing formula from two to six months. For a whole year, parents kept diaries of their little darlings' infections, stool types, and visits to the doctor. The researchers separately measured the infants' antibodies, and made regular house calls to keep the parental data collection on track.

The results are fairly impressive, particularly given the generally well-kept conditions of the infants in the study. (Their families hailed from sanitary, suburban Scandinavia, rather than, for example, the streets of Calcutta, so the infants in this study were unlikely to suffer lots of infections.) When it came to the incidence of a common ear infection in children (acute otitis media), just one of the 80 infants on the experimental formula succumbed by the age of 12 months; yet seven (also out of 80) infants fed normal formula had caught the infection. Moreover, only a quarter of the infants fed experimental formula by their parents needed fever-lowering drugs in their first year of life, while 43% of those fed standard formula group did. The study was double-blinded, meaning that none of the parents could have known whether their child received experimental or standard formula.

The evidence that the experimental formula helps infants fight infections goes more than skin-deep. The antibody tests showed that the immune systems of the infants consuming MFGMs in formula were found to be less likely to flair up, or to 'hyper-respond'. These infants had lower concentrations of antibodies that act against pneumococcal infections (specifically, various serotypes of serum immunoglobulin G), than the infants fed standard formula.

As in the neurodevelopment study [3, 4], all of these differences suggest that formula-fed infants with MFGMs in their diet are more similar to breast-fed infants than to infants fed standard formula. Put simply, the globule supplement seems to make infants who for whatever reason do not receive breast milk, healthier as well as smarter.

Why should this be? Science has a way to go in figuring out all the parts of breast milk that help babies fight infections, but some of breast milk's known germ-fighters are components of MFGMs. The lipids in these membranes have been shown in laboratory studies to have an antiviral effect. And various proteins (as well as proteins with carbohydrate attachments) that are embedded in these lipids perform their own antimicrobial acts. Among them, the proteins known as butyrophilins, lactadherin, and mucins, have particular, germ-combating effects.

In short, the new study gives further support to the idea that swapping out the vegetable oils that are currently used for making infant formula, and swapping in fat globules from cow's milk, would be a generally good idea. How much confidence should we have in the results? On the one hand, the number of infants involved in this study is quite small, and the researchers did not find differences in as many measures of infection-fighting as they had perhaps hoped. But, on the other hand, the substantive benefits of cutting infant infections are far less likely to be found in Scandinavia than in places where infants more commonly catch nasty bugs—which suggests we should be pretty confident. To that end, researchers elsewhere have found that adding MFGMs to the diets of Peruvian infants reduced their incidence of diarrhea [2]. Thus, to resoundingly convince the world that the new, experimental mixture is the future of infant formula, a bigger trial in a dirty, developing world city, would probably generate even more impressive results.

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