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This review gives a brief overview of inflammation and summarises current research that evaluates the role of dairy products in inflammation.

A publication for health professionals

The effect of dairy products on inflammatory biomarkers

Inflammation is a biological process that occurs when the body activates an immune response to protect itself from environmental stimuli such as dietary triggers, pathogens or toxins.[1,2] During the inflammatory process, special chemical messengers are released, which initially may lead to redness, swelling or even pain. This is a normal reaction and is generally short lived, and consequently referred to as acute inflammation. However, if the inflammatory response presents more persistently, it leaves the body in a state of distress, which can trigger disease and illness. This type of inflammation is considered to be chronic. It is well known that dietary components in the foods we consume can potentially have either an anti- or a pro-inflammatory effect. In recent years, dairy has received increased interest regarding its effect on inflammation, often unfairly fuelled by media claims and so-called 'research documentaries', which do not always have a scientifically balanced perspective. This sparked a growing interest in evidence-based research on dairy and inflammation. However, the nutritional composition of dairy, such as its lipid profile, relative leucine content or fermentation status, can affect its inflammatory potential. This review reports the most recent research on dairy and the inflammatory response which suggests that the consumption of milk and dairy protein have a neutral or beneficial effect on inflammatory biomarkers.

Types of inflammation

Acute inflammation is characterised by an acute-phase response during which a cascade of various cytokines are activated, including interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α). These cytokines activate inflammatory cells such as neutrophils, macrophages and monocytes, which, in turn, secrete further additional cytokines and trigger the acute-phase response through the manifestation of fever and leukocytosis, increased synthesis of adrenocorticotropic hormones and the production of various acute-phase proteins (e.g. C-reactive protein, CRP). This response occurs in order to protect the host or repair tissue damage.

In contrast, when chronic inflammation sets in, mononuclear cells such as lymphocytes, macrophages and plasma cells are activated, which contributes to further tissue destruction, necrosis and illness. This shift from acute to chronic inflammation can be characterised by an over-production of cytokines, which further contribute to a breakdown of immune tolerance and major alterations in tissues. Immune tolerance refers to a state in which the immune system is unresponsive to substances or tissues that would normally induce an immune response.[3] This cascade response further increases the risk for various non-communicable diseases in both young and older individuals.[2,4,5]

Characteristics of the acute and chronic inflammatory response are summarised in Table 1. An acute inflammatory response is typically initiated during times of infection. Pathogen-associated or damage-associated molecular patterns develop in response to physical, chemical or metabolic stimuli.[4] In contrast, chronic inflammation is typically triggered by damage-associated molecular patterns (DAMPs), in the absence of an infection or the activation of pathogen-associated patterns (PAMPs).[4,5] It has been observed that chronic inflammation increases with age, as older individuals appear to have higher circulating levels of cytokines, chemokines and acute-phase proteins, together with a greater expression of genes involved in inflammation.[4] Chronic inflammation is a key feature in obesity, atherosclerosis, cardiovascular disease, cancer, type 2 diabetes, and even neurodegenerative diseases.[4,6]

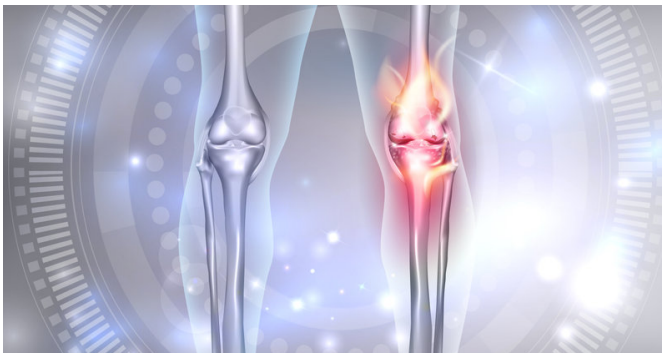

Table 1:
Characteristics of acute and chronic inflammation[4]

	Acute inflammation	Systemic chronic inflammation
Trigger	• PAMPs (infection) • DAMPs (cellular stress, trauma)	DAMPs ('exposome',* metabolic dysfunction, tissue damage)
Duration	Short, acute	Persistent, non-resolving
Magnitude	High grade (high level)	Low grade (low level)
Outcome(s)	Healing, trigger removal, tissue repair	Collateral damage, e.g. initiation of disease
Age related?	No	Yes
Biomarkers	IL-6, IL-1β, TNF-α, CRP	Silent; no standard biomarkers or hs-CRP

- *The 'exposome' represents the total exposure to environmental stimuli during life and how these exposures relate to health.
- PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns IL-6, interleukin-6; IL-1β, interleukin-1 beta, TNF-α, tumour necrosis factor alpha; CRP, C-reactive protein

Causes of inflammation

Inflammatory stimuli can include a combination of endogenous and exogenous triggers:

- Endogenous causes include DNA damage, dysfunctional telomeres (distinctive structures found at the ends of chromosomes), epigenomic disruption (epigenomes systematically control gene expression during development), disrupted mitogenic signals (mitogens are small proteins or peptides that induce cell division), and oxidative stress.
- Exogenous triggers include chronic infections, obesity, microbiome dysbiosis, diet, social and cultural changes, and environmental and industrial toxins, which all contribute to the systemic chronic inflammation, illustrated in Figure 1.

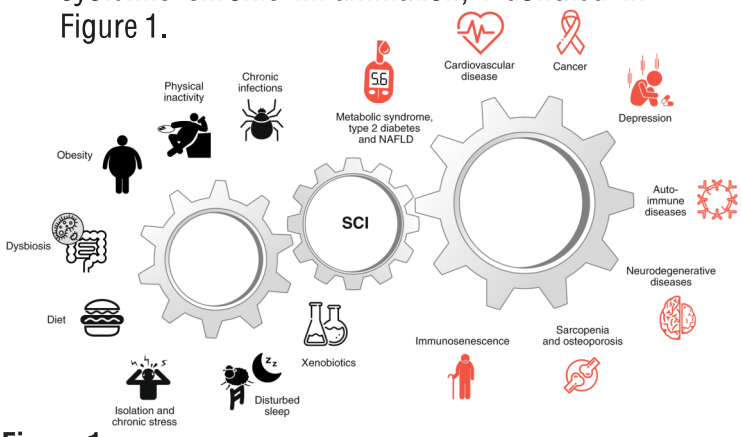

Figure 1:
Causes and consequences of low-grade systemic chronic inflammation (SCI) (Furman, 2019)[4]

A Westernised dietary pattern is typically characterised by high consumption of proteins (derived from fatty domesticated and processed meats), saturated fats, refined grains, sugar, alcohol, salt and corn-derived fructose syrup, and a low intake of fruits and vegetables.[7] Over time, this dietary pattern can lead to post-prandial hyperlipaemia and hyperglycaemia. Post-prandial lipaemia is an independent risk factor for cardiovascular disease, obesity, metabolic syndrome and type 2 diabetes. Spikes in the levels of triglycerides and glucose can also generate excess plasma reactive oxygen species that initiate pro-inflammatory reactions.[8] The inflammatory process therefore seems to be potentially modulated by dietary intake.[1]

How does dairy impact inflammation?

Recent reviews have found contrasting results regarding the effect of dairy products on inflammation. On the one hand, the consumption of dairy, particularly full-fat and non-fermented products such as butter and cream, appears to be associated with an increased risk for obesity and non-communicable diseases such as prediabetes and type 2 diabetes, or to contribute to the development of chronic inflammatory disorders and autoimmune diseases.[1] In contrast, full-cream dairy and fermented dairy products, including yoghurt or cheese, have been associated with a decreased or neutral effect on cardiovascular risk and mortality.[1,2]

Fermented dairy products may modulate the inflammatory and immune response via a number of mechanisms. These include effects due to the bacteria in fermented products, palmitic acid (16:0 saturated fatty acid) via toll-like receptors, and short-chain fatty acids produced after consumption of fermented dairy, which may reduce the secretion of pro-inflammatory cytokines and chemokines. Fermented dairy also contains unique *trans* and other odd-chain fatty acids (15:0 and 17:0), which may be associated with reduced cardiometabolic risk.[2,5] The composition of the gut microbiota may be altered by the intake of fermented dairy and the dairy matrix may modify the interactions between nutrients, which could explain differences in health effects from the intake of different dairy products.

Types of dairy products

Dairy products include liquid milk, fermented dairy products [e.g. yoghurt, kefir, maas, buttermilk and doogh (a fermented savoury yoghurt drink)], and butter. These products vary with regard to their food matrix and nutrient content, including fat, protein and calcium. As a result, the effects of different dairy products on fat absorption, gut microbiota, gene expression and blood metabolomics vary, influencing lipid metabolism and inflammation.[2,9] In light of this, it is essential to consider the type of dairy before making dietary recommendations associated with inflammation. Ice cream and fermented plain yoghurt are both considered dairy products, yet the health effect of these two products can be very different. For the purpose of the current review, the effects of milk, fermented products, dairy lipids and leucine on inflammation will be discussed.

Latest research on dairy consumption and effects on inflammatory markers

Dugan et al.[10] conducted a randomised controlled trial to assess the effect of the consumption of low-fat dairy on systemic inflammation in 37 participants with metabolic syndrome. The researchers found that female participants expressed significantly lower levels of TNF-α and monochemo attractant protein-1 (MCP-1), a key chemokine that regulates migration and infiltration of monocytes and macrophages, after six weeks of consuming low-fat dairy (three servings of dairy per day: 300 ml of 1% milk, 180 g fat-free yoghurt, 120 g 2% cheese) compared with the control group, who consumed a 45 g granola bar and 360 ml 100% juice every day. In addition, low-fat dairy consumption significantly lowered the hepatic steatosis index, a screening tool that, through calculating levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), is used to optimise the management of non-alcoholic fatty liver disease.

Van Meijl and Mensink[11] previously reported that overweight and obese research participants who consumed 500 ml low-fat milk and 150 g low-fat yoghurt daily demonstrated small decreases in TNF-α concentrations compared with participants who consumed carbohydrate-rich control products (600 ml fruit juice and three fruit biscuits). However, there were no significant effects on serum MCP-1, IL-6 and vascular cellular adhesion molecules (VCAMs) or intracellular adhesion molecules (ICAMs). VCAMs and ICAMs are endothelial cellular adhesion molecules of the immunoglobulin superfamily and have a critical role in mediating the firm adhesion of leukocytes to endothelial cells in various acute and chronic inflammatory diseases. No significant effects of milk consumption on markers of endothelial function and inflammatory response (TNF-α, IL-6, CRP, complement 3 and complement 4 – acute-phase proteins of the immune system) were reported.

More recently, a systematic review by Zhang et al.[12] showed that a higher milk intake was related to a reduced risk of type 2 diabetes, metabolic syndrome and obesity. A dose–response analysis suggested that a 193 ml increment of milk intake per day was related to a 13% lower risk of metabolic syndrome and a 16% lower risk of obesity. Obesity is characterised as a chronic, low-grade, systemic inflammatory state that predisposes the body to developing other chronic conditions such as metabolic syndrome or type 2 diabetes.

The effect of fermented dairy

Some of the randomised controlled studies included in the systemic reviews mentioned earlier are highlighted here:

- Burton et al.[13] reviewed a post-prandial response in healthy adults consuming yoghurt or acidified milk and found no significant difference in inflammatory biomarkers, including high-sensitive CRP, chemokines (MCP-1, MCP-1/CCL-2), IL-6, lipopolysaccharide (LPS), and TNF-α. Both yoghurt and acidified milk intake appeared to regulate inflammatory genes; in particular, a significant down regulation of the expression of inflammatory genes was reported after two hours in participants who drank milk and after four hours in the group who consumed yoghurt.
- Rundblad et al.[9] demonstrated that a high-fat meal composed of fermented dairy products, and specifically cheese, had a lesser pro-inflammatory effect than intake of non-fermented high-fat dairy products, including butter and whipped cream. The high protein and calcium content of cheese may explain some of these differences. Of interest, cell adhesion was also investigated, and between the four meals studied the researchers demonstrated that only the non-fermented dairy products including dairy fats, e.g. butter and whipped cream, increased circulating concentrations of adhesion molecules.
- Pei et al.[14] found that in premenopausal women daily consumption of 339 g low-fat yoghurt over nine weeks resulted in reduced concentrations of inflammatory biomarkers compared with intake of a non-dairy control food (soy pudding).
- The review of clinical trials by Bordoni et al.[1] concluded that fermented dairy products tend to have anti-inflammatory properties and that these effects are enhanced in participants with metabolic abnormalities.

Dairy lipids

Labonté et al.[15] reported on a randomised controlled trial among 112 participants with chronic low-grade inflammation and found that dairy consumption had no significant adverse effects on inflammatory markers. They concluded that despite the high saturated-fat content of dairy foods, consumption did not exert adverse effects on biomarkers of inflammation in overweight or obese adults.

Similarly, a meta-analysis of cohort studies[16] revealed no significant relationship between dairy consumption and the risk of cardiovascular disease,

despite the high saturated-fat content. It was suggested that milk intake might even be associated with an overall reduced risk of cardiovascular disease.

In a study by Rundblad et al.,[9] 47 healthy participants were randomly selected to consume one of four different high-fat meals that included butter, cheese, whipped cream or sour cream in a randomised controlled cross-over study. All the meals induced a post-prandial inflammatory response. However, no increase in post-prandial CRP concentrations was observed. The mechanism may involve an inflammatory response through liposaccharide toll-like receptor 4 binding, which likely activates nuclear factor kappa B and the expression of inflammation-related genes or altering the gut microbiota to overproduce liposaccharides, hence worsening the inflammatory response of a high-fat meal.

Meals containing cheese or sour cream (fermented dairy products) induced a lesser pro-inflammatory response than those containing butter and whipped cream, despite having the same amount of fat and the same fatty acid composition. The response after cheese intake differed the most from that of the non-fermented products. Cheese contains more protein than the other three products, and plasma concentrations of amino acids were shown to have increased after intake of cheese compared with consumption of the other products. Cheese is also rich in calcium, which has been shown to suppress the inflammatory response; by contributing to a more anti-inflammatory peripheral blood mononuclear cells (PBMC) gene expression response.[9]

Moosavian et al.[17] reviewed 11 randomsied controlled trials, which included 663 adult participants in total, and found that, compared with low or no dairy intake, high consumption of dairy products resulted in a decrease in CRP, TNF-α, IL-6, and MCP concentrations and increased adiponectin levels. These findings support the possible anti-inflammatory properties associated with dairy products. However, it must be kept in mind that between-study heterogeneity was considerable for CRP, TNF-α, IL-6, MCP and adiponectin, and moderate for leptin. Subgroup analysis showed that dairy consumption appeared to have no effect on inflammatory biomarkers and no differences were observed in these trials. The authors concluded that over the long term it appears that dairy products high in saturated fat do not promote inflammation because none of the studies reported an increase in circulating inflammatory markers in participants who received dairy.

Similarly, the review by Ulven et al.[2] indicated that no pro-inflammatory effect was elicited in response to milk or dairy intake in healthy adults or those who were overweight, obese or had been diagnosed with metabolic syndrome or type 2 diabetes. Over the long term, it appears that dairy supplementation may in fact produce a weak anti-inflammatory effect in both population groups.

Leucine

Moosavian et al.[17] suggest that the high concentration of the amino acid leucine in dairy contributes to its anti-inflammatory properties. Leucine appears to increase secretion of anti-inflammatory adiponectin and decrease secretion of pro-inflammatory cytokines. In addition, leucine reduces oxidative and inflammatory stress by stimulating mitochondrial biogenesis, increasing oxygen consumption and fatty acid oxidation in adipocytes and skeletal muscle cells, and by inducing protein synthesis and suppression of protein degradation. Leucine can also increase sirtuin 1 secretion, which increases mitochondrial biogenesis and oxidative capacity. In turn, this prevents oxidative and inflammatory stress. SIRT1 inhibits the inflammatory nuclear factor kappa B pathway.

Conclusion

Overall the scientific evidence of the effects of milk on inflammatory biomarkers demonstrates that consumption of milk does not appear to have a pro-inflammatory effect in healthy subjects or individuals with metabolic abnormalities (obesity, overweight, type 2 diabetes or metabolic syndrome). More evidence is needed to identify specific dairy foods as having anti-inflammatory potential. Fermented dairy products may modulate the inflammatory and immune response via a number of mechanisms. These include effects of the bacteria in fermented products, palmitic acid (16:0) via toll-like receptors, short-chain fatty acids produced after consumption of fermented dairy, which may reduce the secretion of pro-inflammatory cytokines and chemokines, and, finally, unique trans and other odd-chain fatty acids (15:0 and 17:0) that may be associated with a reduced cardiometabolic risk. A large body of evidence shows that, in addition to dairy containing a large number of nutrients important for growth and development, it does not appear to contribute to chronic inflammation and that fermented dairy products may, in fact, have anti-inflammatory properties.

REFERENCES

1. Bordoni A, Danesi F, Dardevet D, et al. Dairy products and inflammation: A review of the clinical evidence. Crit Rev Food Sci Nutr. 2017;57(12):2497-2525.
2. Ulven SM, Holven KB, Gil A, Rangel-Huerta OD. Milk and dairy product consumption and inflammatory biomarkers: An updated systematic review of randomized clinical trials. Adv Nutr. 2019;10(suppl_2):S239-S250.
3. Fullerton JN, Gilroy DW. Resolution of inflammation: A new therapeutic frontier. Nat Rev Drug Discov. 2016;15(8):551-567.
4. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25(12):1822-1832.
5. Hess JM, Stephensen CB, Kratz M, Bolling BW. Exploring the links between diet and inflammation: Dairy foods as case studies. Adv Nutr. 2021;12(Suppl 1):1S-13S.
6. Van Eldik LJ, Carrillob MC, Colec PE, et al. The roles of inflammation and immune mechanisms in Alzheimer's disease. Alzheimers Dement. 2016;2:99-109.
7. Statovci D, Aguilera M, MacSharry J, Melgar S. The impact of Western diet and nutrients on the microbiota and immune response at mucosal interfaces. Front Immunol. 2017;8:838.
8. Lordan R, Zabetakis I. Invited review: The anti-inflammatory properties of dairy lipids. J Dairy Sci. 2017;100(6):4197-4212.
9. Rundblad A, Holven KB, Øyri LKL, et al. Intake of fermented dairy products induces a less pro-inflammatory postprandial peripheral blood mononuclear cell gene expression response than non-fermented dairy products: A randomized controlled cross-over trial. Mol Nutr Food Res. 2020;64(21):e2000319.
10. Dugan CE, Aguila D, Park Y-K, Lee J-Y, Fernandez ML. Dairy consumption lowers systemic inflammation and liver enzymes in typically low-dairy consumers with clinical characteristics of metabolic syndrome. J Am Coll Nutr. 2016;35:255-261.
11. Van Meijl LEC, Mensink RP. Effects of low-fat dairy consumption on markers of low-grade systemic inflammation and endothelial function in overweight and obese subjects: An intervention study. Br J Nutr. 2010;104(10):1523-1527.
12. Zhang X, Chen X, Xu Y, et al. Milk consumption and multiple health outcomes: Umbrella review of systematic reviews and meta-analyses in humans. Nutr Metab. 2021;18(1):7.
13. Burton KJ, Pimentel G, Zangger N, et al. Modulation of the peripheral blood transcriptome by the ingestion of probiotic yoghurt and acidified milk in healthy, young men. PLoS One. 2018;13(2):e0192947.
14. Pei R, DiMarco DM, Putt KK, et al. Low-fat yogurt consumption reduces biomarkers of chronic inflammation and inhibits markers of endotoxin exposure in healthy premenopausal women: A randomised controlled trial. Br J Nutr. 2017;118:1043-1051.
15. Labonté ME, Cyr A, Abdullah MM, et al. Dairy product consumption has no impact on biomarkers of inflammation among men and women with low-grade systemic inflammation. J Nutr. 2014;144:1760–1767.
16. Alvarez-Bueno C, Cavero-Redondo I, Martinez-Vizcaino V, Sotos-Prieto M, Ruiz JR, Gil A. Effects of milk and dairy product consumption on type 2 diabetes: Overview of systematic reviews and meta-analyses. Adv Nutr. 2019;10:S154e63.
17. Moosavian SP, Rahimlou M, Saneei P, Esmaillzadeh A. Effects of dairy products consumption on inflammatory biomarkers among adults: A systematic review and meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2020;30(6):872-888.

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