DN FORUM
DAIRY NUTRITION FORUM
PUBLICATION FOR INDUSTRY & HEALTH PROFESSIONALS

Inflammation & Metabolic Health

Exploring dairy related solutions

Volume 14, Issue 2 | November 2022

Summary Points

- Obesity is associated with a range of metabolic diseases including insulin resistance, non-alcoholic fatty liver disease, type 2 diabetes and cardiovascular disease. These conditions are all characterised by a state of chronic low-grade inflammation.
- This inflammatory phenotype has traditionally been characterized by the presence of innate immune cells called macrophages which can polarise from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype in obese adipose tissue.
- Diet is one of the strongest regulators of obesity induced inflammation. Saturated fats are known to activate inflammatory pathways while monounsaturated and long-chain omega-3 polyunsaturated fats can have a positive health impact indicating that the source of dietary fat is important for improving health outcomes.
- However, increasing focus has turned to the role of the food matrix in terms of overall health outcomes which considers not only the role of individual nutrients and other bioactives but all aspects of the food including its physical matrix. While dairy products contain saturated fat, the overall fatty acid profile may not have the detrimental effect on cardiovascular parameters that has been assumed.
- There are now a number of epidemiological and molecular studies which demonstrate that the dairy matrix itself, as opposed to the individual nutrients in dairy products may have neutral or indeed beneficial effects on cardiometabolic health outcomes. While this has been examined in healthy individuals, the role of the dairy matrix in mediating the resolution of obesity-induced inflammation has not been comprehensively studied.
- Even within dairy food, matrices differ and more work is required to identify the particular effects of different dairy food sources on metabolic health outcomes going forward.

Editorial

Back in 2013, we explored the topic of the effects of dairy and dairy components on various inflammatory biomarkers and their potential protective impact with regards to metabolic health. We revisit this topic again in 2022 to update you on developments in this area including evolving consideration of the health effects of the entire food matrix.

On page 4 we feature our updated Nutrition & You booklet for Children for those aged 1+ to 12 years.

We hope you find this an interesting edition of DN Forum. We would also encourage you to check out the Health Professional Area of the NDC website, where you can access other NDC resources. Your comments and feedback are very welcome via: nutrition@ndc.ie

Yvonne Finnegan

Dr. Yvonne Finnegan.
Registered Dietitian

Nutrition Consultant to the National Dairy Council (NDC)

Obesity, inflammation and diet

Michelle Kearns,

Postgraduate Research Student
UCD Institute of Food and Health &
School of Public Health, Physiotherapy
and Sports Science, University College
Dublin, Ireland

Clare Reynolds

Assistant Professor/Ad astra fellow,
UCD Institute of Food and Health & School
of Public Health, Physiotherapy and
Sports Science, Food for Health Ireland,
University College Dublin, Ireland

INTRODUCTION

Obesity and cardiometabolic disease remain one of the most significant health concerns globally. There has been a tripling of obesity rates over the last 35 years with almost 2 billion people world-wide now affected by overweight/obesity. In addition to those living with overweight/obesity, there is evidence that normal weight individuals can also experience metabolic dysregulation caused by a 'thin on the outside, fat on the inside' (TOFI) phenotype. This indicates that the distribution of excess fat is a major factor in metabolic dysfunction. Excess fat mass is linked to a state of chronic low-grade inflammation, in contrast to acute inflammation which is associated with pain, redness and swelling.

This type of inflammation is asymptomatic but when sustained over time disrupts metabolic homeostasis and results in a range of cardiometabolic complications such as insulin resistance, non-alcoholic fatty liver disease (NAFLD), atherosclerosis and type 2 diabetes[1]. In addition to increasing the risk for cardiometabolic diseases, overweight and obesity also increases susceptibility to infectious disease as well as a number of other inflammatory conditions[2]. This is of particular concern given the recent COVID-19 pandemic, where individuals are more likely to have increased disease severity, with worse outcomes as BMI increases outside the normal range[3]. While the metabolic conditions associated with overweight and obesity are potentially treatable through weight loss, maintenance of long term weight loss can be challenging and investigating other dietary or therapeutic strategies to target the metabolic dysfunction and which can sit independently or alongside lifestyle changes can be useful.

INFLAMMATION AND HEALTH

Inflammation is a hugely important process which is instrumental in mediating tissue repair and defence against harmful pathogens such as viruses and bacteria. However, a range of factors can cause inflammation to run unchecked, including autoimmune conditions or increased environmental inflammatory stimuli (diet, pollutants etc), which can be harmful and contribute to tissue damage and progression of conditions such as inflammatory bowel disease (IBD), insulin resistance, arthritis etc. Excess fat mass and cardiometabolic disease have also been associated with chronic low-grade inflammation.

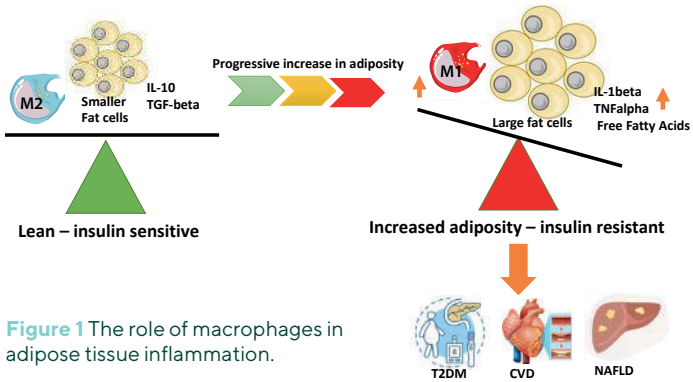

Figure 1 The role of macrophages in adipose tissue inflammation.

Under normal conditions, the adipose tissue (fatty tissue) contains small insulin sensitive adipocytes, or fat cells, as well as fat precursor cells and immune cells. While this immune fraction contains some B cells and T cells, macrophages make up the largest portion of immune cells in the adipose tissue[4]. Macrophages are a type of white blood cell that are present in almost all tissues and are critical for maintaining tissue homeostasis by repairing and restructuring aged or damaged cells. These cells are very dynamic and have the ability to sense and adapt quickly to their microenvironment. This often involves a process where by macrophages switch from an anti-inflammatory or M2 phenotype (production of anti-inflammatory proteins such as IL-10 and transforming growth factor-beta (TGF-beta) to a more pro-inflammatory or M1 output (potent pro-inflammatory proteins such as tumour necrosis factor-alpha (TNF-alpha) and Interleukin (IL)-1 beta). This polarisation gives them the ability to respond to injury or infection but can have detrimental effects when initiated out of context.

As adipose tissue mass increases two major events contribute to metabolic dysfunction. There is an increase in a) the size of the adipocyte (hypertrophy) and b) a shift in the balance of anti-inflammatory and pro-inflammatory macrophages in the adipose tissue. Both of these events are linked. When the size of the fat cells increases, this is accompanied by an increase in systemic free fatty acids (FFA) and the production of proteins called chemoattractants or chemokines. These proteins act as a signal which attract immune cells such as macrophages and recruit them into the adipose tissue[5]. These macrophages are then activated and adaptation occurs resulting in the production of cytokines which further increase inflammation and disrupts normal biological processes such as insulin signalling and lipid synthesis in the adipose tissue. This in turn increases insulin resistance resulting in further circulating FFA and heightened glucose concentrations impacting other organ systems[6,7] (Figure 1). This includes the liver, where increased FFA can increase the risk of NALFD[8] and the pancreas where increased glucose concentrations put excess stress on the pancreatic beta-cells resulting in the development of type 2 diabetes[9]. The size of the adipocyte is causally linked to cellular stress, decreased metabolic flexibility and metabolic disease. While this is correlated with overweight and obesity, some individuals living with obesity or overweight can have a healthy phenotype (metabolically healthy obese) if their adipocytes are smaller.

DIET AND LOW-GRADE METABOLIC INFLAMMATION

Diet is one of the strongest environmental regulators of inflammation. Fats are the most comprehensively explored macronutrient in relation to obesity induced inflammation. Work over the last 20 years has shown that saturated fatty acids (SFA), particularly stearate and palmitate, initiate immune reactions that result in the low-grade chronic inflammation that is associated with obesity. It does this through activation of the toll-like receptor (TLR)/Interleukin-1 (IL-1) and the NLRP3 inflammasome signalling pathways which promotes release[10] of pro-inflammatory cytokines[11–13]. These pathways then disrupt insulin signalling pathways promoting metabolic dysfunction and eventual type 2 diabetes. However, not all fats have this negative effect, mono- and omega-3 long-chain poly-unsaturated fats (MUFA and n-3 PUFA) are anti-inflammatory in nature and promote resolution of inflammation, providing a beneficial impact on metabolic health[14,15]. This occurs through down regulation of TLR4/IL-1 signalling and increased expression of peroxisome proliferator activated receptor gamma (PPAR) which promotes polarisation of macrophages to an anti-inflammatory phenotype. Indeed, preclinical studies have demonstrated that dietary substitution of saturated fat with mono-unsaturated fats has beneficial effects on insulin concentrations and inflammation resulting in an overall benefit to metabolic health[16].

Many other nutrients and bioactives have also been explored for their anti-inflammatory role including conjugated linoleic acid (CLA), a lipid found in the meat and dairy products of pasture fed cattle. While there has been some conflicting evidence in relation to its effects in humans, a recent systematic review and metaanalysis demonstrated that CLA has beneficial effects in relation to markers of oxidative stress, a biomarker associated with metabolic dysfunction[17]. The efficacy of lactoferrin, an iron binding glycoprotein also found in milk was described in a study supplementing young obese individuals with 250mg/day lactoferrin capsules for 3 months. Supplementation reduced pro-inflammatory cytokines (IL-1beta, IL-6 and TNF-A) and was accompanied by a reduction in glucose concentrations[18].

THE DAIRY MATRIX

(More than a sum of its parts)

In addition to effects of isolated bioactives it is important to consider the concept of the entire food matrix. Nutrition research is increasingly focused on the health effects of whole food products that cannot be predicted from their individual nutrients alone. Whole foods can have physically and nutritionally complex structures which can influence the digestion of the food product and the absorption of the nutrients. The dairy matrix is a good example of this. While dairy products contain saturated fat, the negative health effects that are traditionally associated with SFA are not observed in response to dairy consumption[19]. This is likely due to the diversity of fatty acids found in milk. Dairy foods can contain up to 400 different fatty acids and are rich in medium and odd-chain fatty acids, phospholipids, unsaturated and branched chain fatty acids as well as milk fat membrane globules (MFMG) which are known to reduce cardiometabolic disease and lower mortality[20, 21]. Research by Feeney et al., found that fat contained in the matrix of the cheese resulted in significantly lower total cholesterol and low-density lipoprotein cholesterol compared with the same constituents eaten in different matrices in a cohort of overweight adults. These results confirm that dairy fat in the cheese matrix does not appear to adversely affect blood lipid profiles in those at risk of metabolic disease[22]. (Figure 2). Depending on the individual product, milk, yogurt and cheese contains many vitamins and minerals (calcium, phosphorus, iodine, zinc, vitamin B2 and B12), and multiple bioactive components such as milk peptides. These peptides can be produced via breakdown in the gut or by bacteria present in fermented dairy. These confer anti-inflammatory health effects promoting beneficial effects on inflammatory conditions including cardiometabolic disease[23]. For this reason, it is important to consider the contribution of the whole dairy matrix rather than focusing on individual components like total saturated fat content, particularly in relation to disease risk. The physical structure of dairy is also an important factor in their overall health impact. This can affect gastric transit, appetite regulation and nutrition absorption, all of which can impact the metabolic response. It is therefore important to consider how these differences can affect the health impacts of dairy products beyond the sum of their means.

Figure 2 The Cheese Matrix
Research on the cheese matrix suggests components present interact with the overall structure to produce unexpected effects based on nutrient content alone

THE DAIRY MATRIX AND METABOLIC INFLAMMATION

It has become increasingly clear over the last decade that dairy products such as yogurt, milk and cheese supports cardiometabolic health[24]. A recent study from the PURE cohort which examined 136,384 individuals from 21 countries over 9 years has shown that milk and yogurt consumption reduces risk for cardiometabolic disease as well as all-cause mortality[25]. In terms of biomarkers of inflammation, a recent systematic review demonstrated that high vs low -dairy consumption results in reduced systemic C-reactive protein, IL-6, TNF-A and MCP-1 in overweight/obese individuals[26]. Similarly, in healthy adults there is evidence that overall inflammatory score (based on 98 biomarkers) was lower in high versus low consumers of dairy[27]. While these studies did not specifically examine the mechanistic underpinnings, in vitro studies demonstrate that treatment of macrophages with whole milk results in a shift in polarisation from an M1 pro-inflammatory phenotype to an anti-inflammatory M2 phenotype with reduction in the overall inflammatory cytokine output[28].

New innovations researched through FHI continue to identify novel dairy components which confer beneficial health effects. Addition of a novel casein hydrolysate, a bioactive component derived from milk, a high-fat diet in obese mice reduced glucose concentrations and NLRP3 inflammasome mediated inflammation, improving overall insulin resistance[29].

Further work is needed to tease out the effects of different dairy products. Fermented dairy products are known to provide additional benefits beyond their nutritional composition[30]. Addition of cultured bacterial strains may provide added health impacts through production of bioactive anti-inflammatory peptides and short chain fatty acids. These bioactives may have direct anti-inflammatory effects on immune cells or promote positive changes in relation to gut microbiota composition. A recent in vitro study demonstrated that milk and milk fermented with Lactobacillus rhamnosus R0011 reduced lipopolysaccharide (LPS) induced M1 cytokines in a macrophage cell line and increased cytokines associated with M2 macrophages compared to a no-milk control, notably the fermented milk had a more potent effect[31]. Further, a study examining dietary consumption of dairy foods in healthy individuals identified that fermented products such as cheese and sour cream had a less inflammatory profile compared to non-fermented dairy in human peripheral blood monocytes[32], further supporting the suggestion that reduced macrophage activation may represent a plausible mechanism.

Current studies within FHI (partners in UCD, DCU, UCC and Teagasc) are examining the role of dairy fermentates within the context of inflammation, gut health and metabolic health. These fermentates are being considered as potential post-biotics which are a new class of bioactives that include preparations of inanimate microorganisms and their components. This research will add to our understanding of the complexities of the dairy matrix.

CONCLUSION

Obesity continues to be a significant health concern on a global scale. The recent COVID-19 pandemic has highlighted the impact of obesity on inflammation and immunity and the vulnerability of individuals with compromised cardiometabolic health. It is therefore imperative that we understand the role of our nutritional environments on the pathogenesis of these conditions and indeed identify anti-inflammatory dietary components which improve obesity related comorbidities such as hyperglycaemia, insulin resistance and immune system impairment. While much experimental work has been carried out in relation to the mechanistic understanding of individual dietary components such as fatty acids (both pro- and anti-inflammatory), vitamins and minerals, consideration of the effects of food matrices are not as comprehensively examined. Dairy products with their complex nutritional and physical matrices continue to demonstrate beneficial effects in relation to overall cardiometabolic health with indications that both individual components as well as the entire dairy matrix may be involved. Research also suggests that both whole dairy products and individual components may dampen dysregulated metabolic inflammation, promoting a more favourable anti-inflammatory profile thereby improving metabolic health. Evolution of the dairy matrix continues, with current research in Ireland within FHI examining the potential of dairy fermentates as anti-inflammatory functional foods.

References

1. Zatterale F, Longo M, Naderi J, et al. (2020) Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. *Frontiers in Physiology* **10**.
2. Pugliese G, Liccardi A, Graziadio C, et al. (2022) Obesity and infectious diseases: pathophysiology and epidemiology of a double pandemic condition. *Int J Obes* **46**, 449–465. Nature Publishing Group.
3. Simonnet A, Chetboun M, Poissy J, et al. (2020) High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring)* **28**, 1195–1199.
4. Weisberg SP, McCann D, Desai M, et al. (2003) Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* **112**, 1796–1808. American Society for Clinical Investigation.
5. Kaplan JL, Marshall MA, C. McSkimming C, et al. (2015) Adipocyte progenitor cells initiate monocyte chemoattractant protein-1-mediated macrophage accumulation in visceral adipose tissue. *Mol Metab* **4**, 779–794.
6. Lee B-C & Lee J (2014) Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **1842**, 446–462.
7. Chakarov S, Blériot C & Ginhoux F (2022) Role of adipose tissue macrophages in obesity-related disorders. *Journal of Experimental Medicine* **219**, e20211948.
8. Qureshi K & Abrams GA (2007) Metabolic liver disease of obesity and role of adipose tissue in the pathogenesis of nonalcoholic fatty liver disease. *World J Gastroenterol* **13**, 3540–3553.
9. Gerst F, Wagner R, Oquendo MB, et al. (2019) What role do fat cells play in pancreatic tissue? *Mol Metab* **25**, 1–10.
10. Xiong L, Ren F, Lv J, et al. (2018) Lactoferrin attenuates high-fat diet–induced hepatic steatosis and lipid metabolic dysfunctions by suppressing hepatic lipogenesis and down-regulating inflammation in C57BL/6J mice. *Food Funct* **9**, 4328–4339.
11. Reynolds CM, McGillicuddy FC, Harford KA, et al. (2012) Dietary saturated fatty acids prime the NLRP3 inflammasome via TLR4 in dendritic cells–implications for diet-induced insulin resistance. *Mol Nutr Food Res* **56**, 1212–1222.
12. Huang S, Rutkowsky JM, Snodgrass RG, et al. (2012) Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. *J Lipid Res* **53**, 2002–2013.
13. McGillicuddy FC, Harford KA, Reynolds CM, et al. (2011) Lack of interleukin-1 receptor I (IL-1RI) protects mice from high-fat diet-induced adipose tissue inflammation coincident with improved glucose homeostasis. *Diabetes* **60**, 1688–1698.
14. Finucane OM, Lyons CL, Murphy AM, et al. (2015) Monounsaturated fatty acid-enriched high-fat diets impede adipose NLRP3 inflammasome-mediated IL-1 secretion and insulin resistance despite obesity. *Diabetes* **64**, 2116–2128.
15. Noureddine N, Hartling I, Wawrzyniak P, et al. (2022) Lipid emulsion rich in n-3 polyunsaturated fatty acids elicits a pro-resolution lipid mediator profile in mouse tissues and in human immune cells. *Am J Clin Nutr*, nqac131.
16. Ralston JC, Nguyen-Tu M-S, Lyons CL, et al. (2020) Dietary substitution of SFA with MUFA within high-fat diets attenuates hyperinsulinaemia and pancreatic islet dysfunction. *Br J Nutr* **124**, 247–255.
17. Suksatan W, Putera HD, Abdulkadhim AH, et al. (2022) The effect of conjugated linoleic acid supplementation on oxidative stress markers: A systematic review and meta-analysis of randomized controlled trials. *Clin Nutr ESPEN* **49**, 121–128.
18. Mohamed WA & Schaalan MF (2018) Antidiabetic efficacy of lactoferrin in type 2 diabetic pediatrics; controlling impact on PPAR-, SIRT-1, and TLR4 downstream signaling pathway. *Diabetol Metab Syndr* **10**, 89.
19. Givens DI (2017) Saturated fats, dairy foods and health: A curious paradox? *Nutrition Bulletin* **42**, 274–282.
20. Venn-Watson S, Lumpkin R & Dennis EA (2020) Efficacy of dietary odd-chain saturated fatty acid pentadecanoic acid parallels broad associated health benefits in humans: could it be essential? *Sci Rep* **10**, 8161. Nature Publishing Group.
21. Mollica MP, Trinchese G, Cimmino F, et al. (2021) Milk Fatty Acid Profiles in Different Animal Species: Focus on the Potential Effect of Selected PUFAs on Metabolism and Brain Functions. *Nutrients* **13**, 1111.
22. Feeney EL, et al., (2017). Dairy matrix effects: response to consumption of dairy fat differs when eaten within the cheese matrix – a randomized controlled trial. *Am J Clin Nutr*, **108**:1-8.
23. Perazza LR, Daniel N, Dubois M-J, et al. (2020) Distinct Effects of Milk-Derived and Fermented Dairy Protein on Gut Microbiota and Cardiometabolic Markers in Diet-Induced Obese Mice. *J Nutr* **150**, 2673–2686.
24. Soedamah-Muthu SS & de Goede J (2018) Dairy Consumption and Cardiometabolic Diseases: Systematic Review and Updated Meta-Analyses of Prospective Cohort Studies. *Curr Nutr Rep* **7**, 171–182.
25. Dehghan M, Mente A, Rangarajan S, et al. (2018) Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *The Lancet* **392**, 2288–2297.
26. Labonté M-È, Couture P, Richard C, et al. (2013) Impact of dairy products on biomarkers of inflammation: a systematic review of randomized controlled nutritional intervention studies in overweight and obese adults. *Am J Clin Nutr* **97**, 706–717.
27. Bordoni A, Danesi F, Dardevet D, et al. (2017) Dairy products and inflammation: A review of the clinical evidence. *Critical Reviews in Food Science and Nutrition* **57**, 2497–2525. Taylor & Francis.
28. Panahipour L, Kochergina E, Kreissl A, et al. (2019) Milk modulates macrophage polarization in vitro. *Cytokine X* **1**, 100009.
29. Healy NP, Kirwan AM, McArdle MA, et al. (2016) A casein hydrolysate protects mice against high fat diet induced hyperglycemia by attenuating NLRP3 inflammasome-mediated inflammation and improving insulin signaling. *Mol Nutr Food Res* **60**, 2421–2432.
30. García-Burgos M, Moreno-Fernández J, Alférez MJM, et al. (2020) New perspectives in fermented dairy products and their health relevance. *Journal of Functional Foods* **72**, 104059.
31. Jeffrey MP, Jones Taggart H, Strap JL, Edun G, Green-Johnson JM. (2020) Milk fermented with Lactobacillus rhamnosus R0011 induces a regulatory cytokine profile in LPS-challenged U937 and THP-1 macrophages. Current Research in Food Science. 1;3:51–8.30.
32. Rundblad A, Holven KB, Øyri LKL, et al. (2020) 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. *Molecular Nutrition & Food Research* **64**, 2000319.

UPDATED NUTRITION & YOU BOOKLETS

Developed by the National Dairy Council and endorsed by the Irish Nutrition and Dietetic Institute, the Nutrition & You booklet series highlights the importance of a balanced diet across the life stages. The series is currently being updated, with the latest edition for 'Children' now available. Free copies are available to download from www.ndc.ie or order by contacting nutrition@ndc.ie

Contact us

The National Dairy Council
The Studio, Maple Avenue
Stillorgan, Co. Dublin, Ireland

+353 (0)1 290 2451
info@ndc.ie

www.ndc.ie

Mission:
To deliver real and unique value to Irish dairy farmers by protecting and promoting the image, quality, taste and nutritional credentials of Irish dairy produce to a wide variety of audiences in a clearly defined, focused and effective manner.

@NDC_ie /NDCIreland

Food for Health Ireland
Science Centre South
University College Dublin

+ 353 (0)1 716 2391
fhi@ucd.ie

www.fhi.ie

Mission:
To leverage the world-class capabilities of the Irish academic partners, with the market expertise of the industry partners, into a pipeline of innovative, nutritional functional ingredients/ products for the global food industry.

@fhi_tweets /Food for Health Ireland