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THIS ISSUE

Inflammation and Metabolic Health: Exploring Dairy-Related Solutions

The natural nutrient-richness of milk and the importance of milk and milk products within a balanced diet are well recognised. Milk, yogurt and cheese provide a natural source of a number of nutrients, with many health benefits and functions of such nutrients also well established: for example, the importance of calcium in relation to bone health and the role of vitamins B2 and B12 in energy metabolism. However, research continues to reveal the potential of dairy and dairy constituents beyond these somewhat established benefits – therefore, in this edition of *DN Forum* we review the effects of dairy and dairy components on the inflammatory profile with a view to exploring the potential impact in relation to metabolic health.

Although research on dairy and immune function is not a new concept, there is increased interest specifically in the relationship between dairy and inflammatory biomarkers, low-grade systemic inflammation and associated health conditions. Low-grade systemic inflammation is now thought to play a role in the development and progression of a number of multifactorial disorders such as the metabolic syndrome, type 2 diabetes and cardiovascular diseases. Hence, interest in how various foods, dietary components and dietary patterns influence low-grade systemic inflammation is growing.

In relation to dairy, there are a number of studies indicating beneficial effects with regards to certain inflammatory biomarkers. Indeed, a number of specific dairy components have been identified and are being explored with regards to potential immunoregulatory and anti-inflammatory effects. Such components include conjugated linoleic acid (CLA) and lactoferrin.

It is important to note, however, that such research is still in the early stages, with further studies required before conclusions can be drawn. Nevertheless, future work is, indeed, warranted to confirm the effects of dairy intake and patterns of consumption on inflammatory biomarkers implicated in the development of the aforementioned conditions; to identify and confirm mechanisms in relation to specific dairy components; and to evaluate possible applications for functional foods and ingredients.

EDITORIAL

In this July edition of *DN Forum* we explore a topic that is perhaps less well recognised in relation to dairy – the effects of dairy and dairy components on various inflammatory biomarkers and the potential protective impact with regards to metabolic health.

Accompanying the increasing research and knowledge regarding the links between obesity, low-grade systemic inflammation and a number of multifactorial disorders (such as the metabolic syndrome and type 2 diabetes), is the desire to identify specific dietary components and patterns that may influence inflammatory biomarkers. Dairy and bioactive components within the dairy matrix are revealing interesting findings in relation to this area of research; and the Expert Review article (pages 2-3) – prepared by Niamh Healy, Aoibheann McMorrow and Helen Roche, University College Dublin and Food for Health Ireland – provides an excellent overview of research to-date.

We hope you find this an interesting edition of *DN Forum*, and that it will help you in keeping up-to-date on dairy nutrition research. 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, both specifically on NDC resources and any other suggestions you wish to share: nutrition@ndc.ie

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Metabolism, Inflammation and Diabetes Risk – Looking to Milk for Novel Bioactives to Promote Metabolic Health

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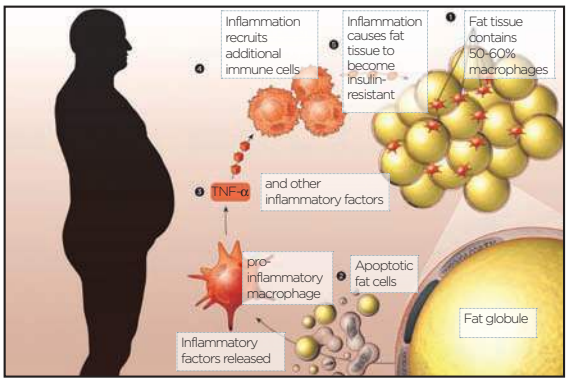
Introduction

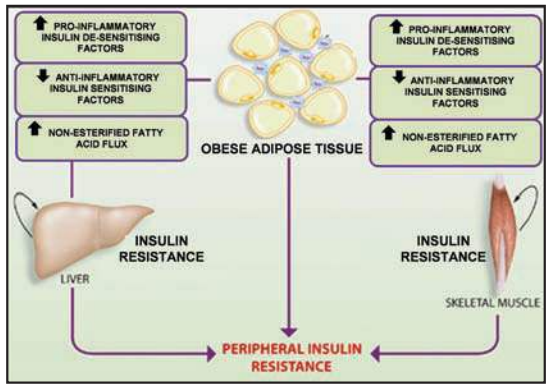
The prevalence of type 2 diabetes (T2D) is rising rapidly in parallel with the ongoing obesity epidemic[1]. In comparison with their lean counterparts, the risk of T2D for men and women with a body mass index of ≥ 35 kg/m² increases 42-fold[2] and 93-fold[3], respectively. Once regarded as a passive energy storage depot, adipose tissue is now recognised as an active endocrine organ that secretes a host of bioactive molecules known as adipokines[4]. In lean individuals, normal adipokine production plays a key role in maintaining metabolic homeostasis. However, chronic nutrient excess and adipose tissue expansion interrupts this milieu, triggering a low-grade inflammatory response in adipose tissue[5].

Inflammation: the link between obesity and insulin resistance

Obesity is accompanied by the infiltration of immune cells into adipose tissue and increased secretion of pro-inflammatory cytokines including TNF-α and IL-6[6]. It is probable that this inflammatory response represents an attempt to resolve the metabolic 'injury' associated with hypercaloric, obeseogenic diets with a view to restoring normal adipose tissue metabolism. Nevertheless, once this immune response is initiated in the form of T-cell and macrophage recruitment into the adipose tissue, this, in turn, instigates insulin resistance, which is an early biomarker of T2D[7] (see **figure 1**). This process is similar to foam cell formation, one of the earliest events in atherogenesis when the body sends macrophages to the location of a fatty deposit on blood vessel walls[8]. Similarly to atherogenesis, the chronic nature of obesity impedes resolution by recruited immune cells. Instead, obese adipose tissue acts as a constant immune stimulus, resulting in a long-term low grade inflammatory state. These inflammatory mediators generated in adipose tissue impair intracellular insulin signalling, promoting insulin resistance in fat, liver and muscle cells, culminating in whole body insulin resistance[9] (see **figure 2**).



▲ Figure 1: Low-grade chronic inflammatory state in response to obesity (Adapted from 'The Scientist', December 2012[10]).
Adipose tissue expansion promotes secretion of pro-inflammatory factors from fat cells and macrophages leading to local and systemic inflammation. These inflammatory mediators impair intracellular insulin signalling.



▲ Figure 2: Interplay between adipose tissue, skeletal muscle and the liver leads to peripheral insulin resistance in obesity (Adapted from Clària *et al.*, 2011, Frontiers in Immunology[11]).
The altered inflammatory profile in response to adipose tissue expansion gives rise to insulin resistance in the liver and skeletal muscle. Additionally, non-esterified fatty acids leak from adipose tissue to these insulin sensitive tissues, further reducing their glucose uptake ability.

Nutritional impact on low-grade inflammation

With the growing prevalence of obesity, research is focusing on strategies to attenuate the modifiable risk factors that link obesity and T2D. There is no doubt that weight loss will reduce progression to T2D: nevertheless, the success of long-term weight loss interventions can be limited [12]. Therefore, there is a crucial need to identify alternative nutritional approaches independent of weight loss to attenuate obesity induced inflammation and insulin resistance. In recent years, there has been a surge of interest in specific nutrients that may modulate inflammation. While long chain n-3 polyunsaturated fatty acids (PUFA), vitamin E, vitamin C, β-carotene and protein have been shown to be inversely associated with markers of chronic inflammation, saturated fatty acids and n-6 PUFA have been positively associated with inflammatory markers[13] (see **table 1**).

Dairy products and inflammation

A recent cross-sectional study proposed that increased consumption of dairy products is inversely associated with inflammatory markers[14]. The ATTICA study revealed that healthy adults consuming >14 servings of dairy per week (>2 servings/day) had a significant reduction in circulating inflammatory markers compared to those consuming <8 servings of dairy per week (≤1 serving/day)[14]. However, limitations within existing nutritional intervention studies means that evidence for a cause and effect relationship between inflammatory biomarkers and dairy consumption is inconclusive[15]. The potential of dairy and of milk-derived bioactives to reduce inflammation is to be explored in more detail.
Milk contains approximately 3.3% protein, of which 80% is casein and the remaining 20% is whey. The ability of whey and casein derived peptides to inhibit angiotensin I-converting enzyme (ACE)[16] sparked an interest for investigating the anti-inflammatory properties

Pro-inflammatory nutrients	Anti-inflammatory nutrients
Total fat	n-3 polyunsaturated fatty acids
Saturated fat	Conjugated linoleic acid
n-6 polyunsaturated fatty acids	Protein
Dietary cholesterol	Fibre
Carbohydrate	Magnesium
	Vitamin C
	Vitamin E
	β-carotene

▲ Table 1: Nutrients demonstrated to have either pro- or anti-inflammatory potential in cell culture, animal or human studies (adapted from Cavicchia *et al.*, 2009[13])

of milk proteins as inhibiting ACE is an established treatment for hypertension. Indeed, whey has immunoregulatory effects, stimulating the host defences in human cells[17] and during wound healing in diabetic mice[18]. Supplementation with either whey or casein isolates for 12 weeks had blood pressure lowering effects in overweight and obese individuals, however, there were no changes in pro-inflammatory markers (CRP, IL-6 and TNF-α)[19].

Conjugated linoleic acid (CLA) represents the positional and geometric isomers of linoleic acid and is found naturally in meat and dairy produce in numerous isoforms. CLA and its individual isoforms have been identified as beneficial for cardiovascular and bone health in cell lines and animal studies[20]. Although the anti-inflammatory potential of CLA has been demonstrated at a cellular and systemic level[21,22], the beneficial effects have not been reflected in human studies[23,24].

Lactoferrin is an iron-binding glycoprotein found in most biological fluids of mammals[25]. Lactoferrin has recognised anti-microbial effects and is, therefore, a key element in the immune defense system[25]. At a cellular level, lactoferrin has immunosuppressive effects by impairing immune cell differentiation when stimulated[26]. Administration of lactoferrin to mice also reduced the pro-inflammatory cytokines responsible for lung cancer cell growth: VEGF, TNF-α, IL-4, IL-6 and IL-10[27]. Subsequently, supplementation with milk-ribonuclease-enriched lactoferrin for 6 months improved the inflammatory status of post-menopausal women[28]. Lactoferrin may be a potential therapeutic agent in inflammatory diseases but further support is necessary.

The large research consortium, Food for Health Ireland (www.FHI.ie), aims to improve our knowledge of milk by delivering milk bioactives with anti-inflammatory potential, that in turn will improve glycaemic control and overall human health[29]. Through milk mining and using extensive screening processes our team at UCD – in collaboration with partners at UL, UCC and Teagasc – is completing a multi-disciplinary research approach in defining potential milk derived bioactives that promote metabolic health.

Conclusion

Obesity is associated with a state of chronic low-grade inflammation. Considerable evidence has now emerged to support the role of anti-inflammatory nutrients in attenuating obesity-induced inflammation and insulin resistance, independent of energy balance. Dairy products are a rich source of protein, CLA and lactoferrin, all of which have been suggested to attenuate the inflammatory response. Ongoing research in Ireland within FHI aims to investigate the anti-inflammatory potential of milk-derived bioactives – the objective being to generate interesting elements of milk that could be manipulated within a functional food context to attenuate the impact of obesity on subsequent risk of diabetes and heart disease.

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Key Points

- Chronic nutrient excess and adipose tissue expansion interrupts metabolic homeostasis, triggering a low-grade inflammatory response in adipose tissue. Inflammatory mediators generated in adipose tissue impair intracellular insulin signalling, promoting insulin resistance in fat, liver and muscle cells, culminating in whole body insulin resistance.
- While weight loss will reduce progression to type 2 diabetes, the success of long-term weight loss can be limited. Therefore, there is a crucial need to identify alternative nutritional approaches independent of weight loss to attenuate obesity-induced inflammation and insulin resistance.
- An inverse association between increased consumption of dairy products and inflammatory markers has been proposed. However, limitations within existing nutritional intervention studies mean that evidence for a 'cause and effect' relationship between inflammatory biomarkers and dairy consumption is inconclusive. Indeed, the potential of dairy and of milk-derived bioactive components to reduce inflammation merits further exploration.
- Specific dairy components that are currently under evaluation with regards to inflammation and associated health conditions include whey and casein-derived peptides, CLA and lactoferrin. Food for Health Ireland (FHI), the Irish research consortium, provides a platform to advance the knowledge and application of dairy/dairy components in this area.

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The Health Professional Area of the NDC website has been developed specifically with health professionals in mind. The aim of this online facility is to:

- House and provide access to NDC publications written specifically for professionals;
- Present the role and activities of the NDC in relation to dairy nutrition research;
- Provide information on NDC nutrition-related events; and,
- Allow you to have your say via the Dairy Dialogue!

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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, unique and effective manner.

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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.