A1 & A2 Beta-casein and gastrointestinal effects
A1 & A2 Beta-casein and gastrointestinal effects... where do lactose intolerance and a2 Milk® fit in?

Lactose intolerance

Lactose intolerance has been described as one of the most common intolerance responses to cows’ milk(1), with an estimated prevalence of around 10% in Caucasian populations(2). However, for a proportion of adults who report intolerance symptoms following milk intake, lactose intolerance is not the cause, as cases of perceived lactose intolerance are more common than its prevalence in adults(3,4). For instance, in a group of 406 randomly recruited men and women (mean age 27 years), 20.2% reported abdominal discomfort following dairy intake, but only 6.4% had lactose intolerance diagnosed by a physician(5).

Other natural components in milk may be responsible for stimulating some of the remaining gastrointestinal intolerance responses and indeed there is recent evidence to support that cows’ milk A1 beta-casein protein type may also be involved in some people(6).

A1 and A2 Beta-casein milk proteins

Beta-casein is a cows’ milk protein that makes up around 30% of the total protein contained in cows’ milk and may stimulate effects beyond nutrition, due to the release of biologically active peptides on digestion(7).

Beta-casein may be present as one of two major genetic variants: A1 and A2(8). A2 is recognised as the original beta-casein variant because it existed before a mutation caused the appearance of A1 beta-casein in some European herds a few thousand years ago(9,10). In the U.S., regular cows’ milk contains a mix of A1 and A2 beta-casein types. In contrast, cows’ milk known as a2 Milk® comes from cows with the genes to produce only the A2 beta-casein type (Figure 1).

Cows’ milk A1 beta-casein is different to cows’ milk A2 beta-casein and other mammalian beta-caseins. A1 beta-casein has a histidine at position 67 on the 209 amino acid protein chain. Cows’ milk A2 beta-casein, human milk, goat milk, sheep milk and other species’ milk have a proline at their equivalent positions on their beta-casein protein chains, making them ‘A2 like’(11-13). Due to this amino acid variation, A1 beta-casein releases the bioactive opioid peptide beta-casomorphin-7 (BCM-7) upon normal enzymatic digestion(14-19) (Figure 2).

A1 beta-casein content in ordinary cows’ milk

In the U.S., where dairy cows are of northern European ancestry, the relative proportions of the co-dominant A1 to A2 beta-casein genes in cows are typically 1:1, which then produce the same ratio of A1 to A2 beta-casein in their milk (Figure 1A). This tends to be lower in breeds from Southern Europe and this ratio depends on the specific breeding history of the dominant breeds. In the U.S., most cows’ milk available commercially contains a mix of A1 and A2 beta-casein. The exception to this is milk produced by dairy cows genotyped and identified to carry only the unmutated A2 beta-casein expressing gene on both sides of the chromosome (i.e. a2 Milk®). These dairy cows produce milk containing only the A2 beta-casein type and not the A1 (Figure 1B).

A1 Beta-casein and gastrointestinal effects

Two recent animal studies have investigated cows’ milk A1 versus A2 beta-casein proteins on gastrointestinal effects directly(20,21). Feeding rodents milk containing A1 beta-casein resulted in significant delays in GI transit time and increased colonic activity of the inflammatory marker myeloperoxidase (MPO), compared to milk containing A2 beta-casein(22).

Similarly, feeding mice a milk free basal diet supplemented with A1 relative to A2 beta-casein also resulted in significant MPO level increases (by 204%), whereas A2 beta-casein had no effect relative to controls(23).

Cows’ milk proteins(24,25) and more specifically the casein milk protein(26,27) have been shown previously to be associated with various effects on the gastrointestinal tract, including the inhibition of motility(28,29), with evidence implicating exogenous opioids like BCM-7 as a mediator(30-33).

In dogs, a comparison of casein and soy protein on various GI motility measures (e.g. force and contraction frequency) showed that casein reduced these parameters significantly and that pretreatment with naloxone (an opioid antagonist) blocked this effect(34), suggesting a role for exogenous opioids like BCM-7.

Such BCM-7 effects on GI motility are physiologically plausible, since BCM-7 is a mu-receptor ligand and mu-receptor activation is known to affect the mechanics of intestinal propulsion(35).
**BCM-7 release**

BCM-7 has been detected following the simulated gastrointestinal digestion of a variety of infant formula and milk products\(^{16, 26}\). BCM-7 has also been detected in the jejunal effluents of humans fed 30 grams of casein in amounts compatible with a biological action\(^{27}\). This confirmed the identification around 30 years earlier of BCM-7 materials in the aspirated small intestinal contents of healthy male adults following milk intake using the ELISA assay technique\(^{28}\). Following the incomplete digestion of A1 beta-casein, the maximal theoretical release of BCM-7 from 1 cup of milk containing 2–3 grams of A1 beta-casein is between 66 to 100 mg\(^{15, 20}\) (Figure 3).

**Figure 3: Beta-casein content and potential BCM-7 release per 250mL of milk. Figure adapted from reference\(^{20}\).**

**a2 Milk® may assist some people with milk mediated digestion symptoms**

A human randomised crossover study comparing the effects of A1 versus A2 beta-casein milk proteins (A1 protein type milk vs a2 Milk\(^{®}\)) on gastrointestinal (GI) outcomes has shown significant differences in stool consistency, with stools on A1 being overall looser\(^{7}\). For people with looser stools on the A1 protein type milk, there was very strong evidence that this was associated with more abdominal pain (P=0.001). This relationship was absent when the same people consumed a2 Milk\(^{®}\). The difference between these two correlations was highly significant (Figure 4). As the A1 protein type milk and a2 Milk\(^{®}\) both contained lactose, the GI effects of the A1 protein type milk can be attributed to the A1 beta-casein protein rather than lactose, so a2 Milk\(^{®}\) may assist some with digestive wellbeing.

![Figure 4: Significant correlation between stool consistency and abdominal pain with A1 beta-casein milk (P=0.001).](image)

Forty-one people were recruited into this doubleblinded, randomised crossover study. Most participants at study entry considered themselves not to have problems digesting ordinary milk. Participants underwent a 2-week dairy washout (rice milk replaced all dairy), followed by two weeks of 750mL/milk/day containing beta-casein of either the A1 protein type milk or a2 Milk\(^{®}\), before undergoing a second washout followed by a final two weeks of the alternative A1 or a2 Milk\(^{®}\).

In addition to the above results, this study identified that while on the A1 protein type milk, higher gut inflammation (faecal calprotectin) correlated with higher abdominal pain (r=0.46, P=0.005) and higher bloating (r=0.36, P=0.03) scores but that on the a2 Milk\(^{®}\) and in the same people, these relationships were absent. Again, the difference in the correlation measures was significant for: 1) gut inflammation and abdominal pain (A1, 0.46 vs A2, 0.03; P=0.02); and 2) gut inflammation and bloating (A1, 0.36 vs A2, −0.02; P=0.05).

A sub-group analysis of study participants with self reported intolerance to ordinary A1 containing milk (n=8) showed further that the A1 protein type milk resulted in more GI symptoms than the a2 Milk\(^{®}\) (Figure 5), and while it was not possible to demonstrate statistically significant differences, the magnitude of these differences between A1 protein type milk versus a2 Milk\(^{®}\) may be clinically significant. Future studies examining this in different population groups with gastrointestinal conditions, such as irritable bowel syndrome, are needed.

![Figure 5: The mean A1 scores were considerably higher for abdominal pain (38% higher), bloating (61% higher) and voiding difficulty (83% higher) versus the mean A2 scores.](image)

Given the previous animal research that shows A1 protein type milk feeding delays gut transit via an opioid pathway\(^{29}\) and that A1 compared with A2 beta-casein feeding significantly increases gut inflammation as evidenced by MPO levels\(^{29, 30}\), these studies collectively suggest the softer stools observed by people consuming A1 compared with A2 beta-casein milk\(^{®}\) are caused by proinflammatory factors coupled with GI transit time effects.
While further clinical trials are needed to confirm these preliminary results in humans relating to GI response differences between A1 and A2 beta-casein proteins in milk, the following has been established:

- Digestion of A1 beta-casein yields BCM-7, while A2 beta-casein does not or it does, at a very low rate[39, 40].
- BCM-7 is an exogenous opioid that can bind mu-receptor opioid receptors expressed in cells throughout the body, including those found in digestive tissue[34, 35].
- Opioid mediated regulation of gastrointestinal motility is well documented[25], with mu-receptor activation producing effects on the mechanics of intestinal propulsion[26, 27].
- BCM-7 has the potential to be produced, absorbed and circulated in humans, particularly infants[28, 29].
- BCM-7 induces rapid secretion of intestinal mucus (in the first 30 min. of stimulation) in rodents via activation of the enteric nervous system and opioid receptors[30, 31].

References