Beta-casein Variants
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Beta-casein protein makes up around 30% of the protein contained in cows’ milk, which is around 2.5 grams per glass. Owing to natural genetic variation, beta-casein may be present as one of two major types, the progenitor A2 type or the mutated A1 type. Cows’ milk which is free of A1 beta-casein is produced by cows specially selected for their genes to produce only the A2 type of beta-casein protein (e.g. a2 Milk™ in Australia). In contrast, A1 beta-casein is present in milk produced by most cows of European breed. Epidemiological evidence suggests that A1 beta-casein is a risk factor in the development of type 1 diabetes in children and ischemic heart disease in adults (Figures 1 and 2). The original variant, A2 beta-casein, has not been linked to these conditions\textsuperscript{1,2}.

**Figure 1:** A1 beta-casein per capita (excluding cheese) in grams/day and new cases of type 1 diabetes in 0 to 14-year olds between 1990–94 ($r=0.92$, 95% CI: 0.72–0.97) ($p<0.0001$). Dotted lines represent the 95% confidence limits of the regression line [adapted from reference (2)].

**Figure 2:** 1990 A1 beta-casein per capita (excluding cheese) in grams/day and 1995 ischemic heart disease death rates in 30–60 year old males ($r=0.76$, 95% CI: 0.48–0.90). Dotted lines represent the 95% confidence limits of the regression line [adapted from reference (2)].
The reported correlation coefficient ($r$) for the relationship between the consumption of A1 beta-casein and type 1 diabetes is 0.92, and for A1 beta-casein and heart disease is 0.76\(^{(1,2)}\). This is significant when compared with other epidemiological relationships such as smoking and lung cancer death rate, where $r=0.73^{(3)}$.

The difference between the A1 and A2 type beta-casein variants is a single amino acid substitution at the 67th residue of the 209-amino acid protein chain. This difference in structure results in A1 beta-casein and the rare variants related to A1 releasing the opioid peptide known as beta-casomorphin-7 (BCM-7) on digestion\(^{(4)}\) (Figure 3). A recent study in humans has confirmed that BCM-7 is produced in the digestive system following the intake of milk casein protein\(^{(5)}\). In this study, bovine BCM-7 was detected in the small intestinal effluents of adults fed 30 grams of milk casein protein, in amounts compatible with a "biological action"\(^{(5)}\). BCM-7 has the demonstrated potential to elicit opioid activity via its affinity to mu-opioid receptors, on a range of tissues and organs including the digestive tract, neurological and immune systems\(^{(6-10)}\). In addition, in vitro research has shown that BCM-7 promotes the oxidation of LDL-cholesterol\(^{(11)}\), which is implicated in the development of heart disease. BCM-7 can also be hydrolysed further to produce the shorter exorphin with greater opioid receptor binding affinity, beta-casomorphin-5\(^{(12)}\).

Research studies in animals show that A1 beta-casein feeding affects gastrointestinal function. Two recent animal studies have investigated A1 versus A2 beta-casein on gastrointestinal effects directly\(^{(14,15)}\). Barnett et al. (2014) showed that feeding rodents milk containing A1 beta-casein compared with A2 beta-casein protein delayed gastrointestinal transit time significantly\(^{(15)}\), which may lead to constipation and stimulate symptoms of digestive discomfort. In addition, Haq et al. (2013) showed in mice fed a milk free basal diet supplemented with A1 relative to A2 beta-casein that gut inflammation markers were increased significantly with A1 beta-casein whereas A2 beta-casein had no effect relative to control animals\(^{(10)}\), effects which a follow up study by the same research group show to be mediated by BCM-7\(^{(16)}\).

In humans, recent studies have identified that bovine immunoreactive BCM-7 (irBCM-7) is absorbed into the circulation of formula-fed human babies\(^{(17,18)}\), where there appears to be variation in the irBCM-7 elimination rate between babies and that this could be due to variable activity of the enzyme needed to break down BCM-7\(^{(16)}\). Furthermore, one of these infant studies reported a negative correlation between irBCM-7 levels and aspects of infant development\(^{(17)}\) and the other suggested that higher blood levels of bovine irBCM-7 may be a risk factor for apnoea in some infants and that bovine irBCM-7 from milk ingested by lactating mothers may be transferred directly to the mothers’ milk\(^{(18)}\). More recently, Sokolov et al. (2014) have detected irBCM-7 in the urine of children with autism spectrum disorders (ASD) and control children\(^{(19)}\). They reported significantly increased urinary irBCM-7 in children with ASD compared with control children and that urinary irBCM-7 concentration in children with ASD was strongly associated with clinical severity as scored by the Childhood Autism Rating Scale ($r=0.85$, $p<0.01$)\(^{(19)}\).
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Science relating to beta-casein variants has been the focus of two regulatory body reviews: by the New Zealand Food Safety Authority (NZFSA) in 2004[1][2], which focused primarily on epidemiological analyses and feeding trials, and by the European Food Safety Authority (EFSA) in 2009[3][4], which examined potential links between BCM-7 and non-communicable diseases. The EFSA report acknowledged that BCM-7 is an A1 beta-casein derived opioid that could affect a range of cells and tissues, including the digestive and immune systems, but that there was a need for further research to determine a causal link between A1 beta-casein consumption and disease. Similarly, the author of the New Zealand Food Safety Authority report, Professor Boyd Swinburn stated in his report entitled ‘Beta casein A1 and A2 in milk and human health’ (2004) that:

“…The appropriate government agencies have several important responsibilities in this matter: to support further research in the area (especially clinical research); to clearly communicate the state of knowledge and judged risks to the public, and; to take specific actions to promote and protect the health of the public, where appropriate”.

and

“As a matter of individual choice, people may wish to reduce or remove A1 beta-casein from their diet (or their children’s diet) as a precautionary measure. This may be particularly relevant for those individuals who have or are at risk of the diseases mentioned (type 1 diabetes, coronary heart disease, autism and schizophrenia). However, they should do so knowing that there is substantial uncertainty about the benefits of such an approach”.

While further research is needed to establish a cause-effect relationship between exposure to BCM-7 and non-communicable disease conditions, there is evidence to suggest that BCM-7 is linked to various unwanted physiological effects in susceptible individuals.

References