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A1/A2 grading of milk: An enigma or reality

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Abstract

India is a leading milk producing country in the world. The requirement of milk and its products start from the first day till the last day of our life. Milk is always associated with prevention of diseases or as cure for diseases in India. Association of specific breeds of cow (A1) milk with non communicable diseases is very intriguing. The concept of A1 A2 milk has created a buzz in the world. A1 milk beta casein protein has a bioactive peptide BCM-7 which is associated with these diseases. The concept has great commercial opportunity as well as important for the planning of new strategies for increase milk production in the world.

Keywords: A1/A2, milk, enigma, reality

Introduction

India is the world's largest producer of milk having an output of about 165 million tonnes. Milk and milk products are essential component of our food. It is the base of all forms of dairy products consumed by majority of people. Its importance in the diet is well documented in our old scriptures. It is a rich source of energy, fat and micronutrients like calcium, magnesium, phosphorus, selenium, riboflavin, vitamin B₁₂ and pantothenic acid (vitamin B₅). It helps in prevention of various disorders such as obesity, osteoporosis, poor gastrointestinal health, cardiovascular diseases, hypertension, colorectal cancer, bone ailments, ageing and others (Nagpal *et al*, 2012) [19]. Although, India is leading the world in milk production but quality check for clean milk production is a challenge for the developing country. Besides clean milk a new concept is arising yet not new for other countries (New Zealand, USA, Australia, and other developed countries) i.e., A1 and A2 milk. Various non communicable diseases (NCD) like type 1 diabetes mellitus (DM-1), ischemic heart disease (IHD), schizophrenia, and autism are being associated with a mutant gene that leads to production of A1 milk (Bell *et al*; 2006) [2]. New diseases entries in this list are milk intolerance, along with lactose intolerance and milk allergy (Mei *et al*; 2017; Pal *et al*; 2015) [13, 21]. These associations of diseases with milk are contrasting to earlier views on therapeutic effects of milk against them.

Globally, cow milk consists 83 percent of total production and at least 80 percent of total production in all regions except South Asia. Here its share is less than half (42 percent) due to milk production of buffaloes (Muehlhoff, 2013) [18]. Holstein-Friesian is the most popular breed for milk production across the world, approximately accounts for 35 percent of dairy cows (about 70 million head). The popularity of this breed is largely because of its high average milk production and superior ability to convert feed into protein. A1 is the most frequent in Holstein-Friesian (0.310–0.660), Ayrshire (0.432–0.720) and Red (0.710) cattle. In contrast, a high frequency of A2 is observed in Guernsey (0.880–0.970) and Jersey (0.490–0.721) cattle (Kaminski *et al*, 2007) [9]. The A2 allele gene in Indian milk breeds of cows (Sahiwal, Red Sindhi, Tharparkar, Gir, Kangayam, Rathi) and buffaloes (Murrah, Mehsana, Marathwada, South Kanara, Manipuri, Assamese Swamp, Nilli-Ravi, Pandharpuri) are 100%. Only two breeds of cattle Malnad Gidda and Kherigarh have A1 allele variant in their germplasm. It shows near desirable fixation of A2 β casein allele in zebu cattle as well as Indian riverine buffaloes (Mishra, *et al*. 2009) [16]. So, our indigenous cows and buffaloes are producing only A2 milk. India has 122.9 million cattle; there are 19.42 million crossbred cattle (livestock census 2012). Crossbred cattle are producing nearly 48% of total cow milk (Singh, 2016) [22].

The major proteins found in cow's milk are casein and whey proteins, with casein accounting for approximately 78 percent of the protein. The most common and famous forms of beta-casein in dairy cattle breeds are A1 and A2 (Farrell *et al*. 2004) [5]. It is believed that around 5000 - 10,000 years ago, a mutation occurred due to which proline at position 67 was replaced

by histidine in β casein protein and spreading widely throughout in the world through cross breeding. The former (wild) one is known as A2 β casein and the latter (mutant) one infamous as A1 β casein milk (Truswell, 2005) [25]. The amino acid difference between the two variants is CAT in A2 genotype and CCT in A1 genotype.

When milk proteins are digested or processed, number of peptides are released inside the gastrointestinal tract or in the processed product, some of these peptides which are inactive in the parent molecule when released become active and communicate with selected receptors and regulate the body's physiological functions, such fragments of peptides are known as bioactive peptides (BAP) (Korhonen, Pihlanto, 2003) [10]. Once these bioactive peptides are liberated, they act as ligand and bind with their specific receptors and influence numerous physiological responses including cardiovascular, digestive, endocrine, immune and neurological activity etc. Because of such physiological versatility, milk-derived BAPs have drawn the attention of many researchers worldwide in order to formulate several potential drugs, health promoting functional foods or other pharmaceutical products.

Several bioactive peptides (viz., antibacterial, immunomodulatory, anti-hypertensive and opioid peptides) are known to be released from casein and/or whey proteins by gastrointestinal digestion (Mohanty *et al.*, 2016) [17]. It is hypothesised that on digestion, the presence of histidine in β casein facilitates the release of a seven-amino-acid bio active peptide (BAP) called beta-casomorphin 7 (BCM7), which is released in relatively in very less concentration in A2 milk (Truswell, 2004) [25]. BCM7 is recognized to show a potent opioid activity and high affinity for opioid μ -receptors. BCM 7 is the implicated peptide that is believed to be associated with a number of diseases in humans (Swinburn, 2004) [23]. If it is true that BCM-7 is harming humans, this would be an important public health issue, as well as a commercial opportunity (Ivano *et al.*, 2009) [8]. BCM-7 (Tyr-Pro-Phe-Pro-Gly-Pro-Ile) was first isolated as a peptide having morphine-like activity in 1979 (Brantl *et al.* 1979) [4]. This BAP exhibits a strong opioid activity and has been shown to stimulate human lymphocyte T proliferation *in vitro* (Gill *et al.* 2000) [6]. In human milk, caseins comprise nearly less than 40 percent in human milk and comprised of primarily β and κ . There is also evidence of release of BCM-7 in the cheese- and yoghurt-making processes. [Nguyen *et al.*, 2015] [20]. Opioid receptors are found to be present in the endocrine, nervous and immune systems and the gastrointestinal tract of mammals. Newborn infants have more permeable gastrointestinal tracts and immature nervous systems, making them more prone to BAPs effects. Adults, on the other hand, appear to reap the biological activity locally on intestinal brush boarder. We here are interested in BAPs called, Casomorphines and more precisely β -casomorphins. They interact with opiate receptors in the serosal side of the intestinal epithelium and play a crucial role in certain activities like regulation of electrolyte transport, insulin secretion and food absorption (Tome and Debabbi, 1998) [24]. The natural casomorphins of importance are BCM-5, BCM-7 and BCM-9. Bovine BCM-7 has been identified in human jejunal contents following milk-protein feeding at levels consistent with pharmacological effects, with 4 mg BCM-7 released from 30 g of casein after 2 h of digestion, with further release thereafter [Boutrou, 2013] [3]. It has also been identified in the blood of human infants [Kost, 2009: Wasilewska, 2011] [11, 26].

A number of studies had been done in the past to establish the role of A1 milk in human diseases. Most of the studies were done *in vitro* and on lab animals. So their credibility in respect to human beings is always doubtful. In this article more emphasis is given on the studies related to human trials with A1/A2 milk. The ideal calcium to magnesium ratio for the human body should be 2:1. The A1 milk's ratio is said to be 10:1. So, by consuming only A1 cow's milk for calcium, magnesium deficiency and imbalance is known to occur, on the other hand, A2 milk does not cause such imbalances. The inflammation from A1 casein is known to cause lymphatic congestion and metabolic suppression. It worsens acne, eczema, upper respiratory infections and allergies. It is said that the digestive problems from the consumption of A1 milk is not due to lactose but because of the massive histamine release from casomorphin. In addition to this, bronchitis, ear infections, tonsillitis are driven by A1 casein. In 2004 New Zealand Food Safety Authority (Swinburn, 2004) [23] concluded that a high intake of milk containing A1 β -casein promoted conditions as heterogeneous as DM-1, IHD, schizophrenia and autism was intriguing and potentially important. That there were some very suggestive evidence from ecological studies for DM-1 and IHD, and there was certainly a possibility that the A1/A2 composition of milk is a factor in the etiology of these conditions. However, this hypothesis had yet to be backed by good human trials. After five years in 2009, the European Food Safety Authority (EFSA) reviewed the scientific literature and published a review (Ivano *et al.*, 2009) [8]. They found that experiments in cells and animals had shown that BCM-7 can act as a weak opioid receptor agonist, but that in most of the animal studies, BCM-7 was not administered orally, as humans would be exposed to it, but rather was given to animals by injection into the peritoneal cavity or even directly into the spinal cord or brain, which makes these studies not useful for understanding how BCM-7 might affect humans. The EFSA found no relationship between chronic diseases and drinking milk with the A1 protein. The EFSA study emphasized the dangers of drawing conclusions from correlations identified in epidemiological studies and the dangers of not reviewing all the evidence at hand. EFSA could not establish a cause-effect relationship between the oral intake of BCM7 or related peptides, and the development of any suggested non communicable diseases. In 2013 FAO report also mentioned the potential role of bioactive peptides on human health and on role of BCM 7, its conclusion consent with the EFSA. A 2014 review (Lacroix, 2014) [12] exploring the relationship between consumption of dairy products (including A1 and A2 proteins) and the incidence of diabetes found that while there appeared to be a positive correlation between consumption of dairy products by babies and the incidence of type 1 diabetes in some people, and an inverse relationship between the consumption of dairy products and the development of type 2 diabetes in some people, these correlations were tentative, it was impossible to determine what component or components of milk might be responsible for these effects, and it was unlikely that the expensive and complex research to determine the answers to these questions will ever be conducted. Now new researches more emphasised on effects of A1 milk on gastrointestinal track (Pal, 2015) [23]. A report from China in 2017 (Mei *et al.*, 2017) [13] showed that consumption of milk containing A2 β -casein attenuated the acute gastrointestinal symptoms following milk intake relative to conventional milk containing A1 and A2 β -casein. Gastrointestinal symptoms

after consuming milk containing A2 β -casein were consistently reduced in both lactose absorbers and lactose malabsorbers. These findings suggest that, in some individuals with self-reported lactose intolerance, the adverse gastrointestinal symptoms following milk intake might be related to the presence of A1 β -casein in milk rather than lactose itself.

Another study on the β casein digestion from Norway (Asledottir *et al.*, 2017) ^[1] has specifically emphasized on the need to use human enzymes for the digestion of milk. They found different genetic variants of β -casein can affect the hydrolysis by gastrointestinal proteases, thus affecting peptides formed in the gut. It has also been established that *ex vivo* digestion of β -caseins leads to generation of several BAPs; however, the release of BCM7 is potentially not solely dependent on the genetic variants with residue histidine at position 67 in the aminoacids sequence of β -casein. Moreover, there is a need for evaluating the bioavailability of generated BAPs, as their function after release in the intestines is rather ambiguous. However, recent research is now considering that physiological pH values of infant's stomach are quite different from the optimum for pepsin. A recent report claiming production of beta – casein A1 free infant formula (IF) observed that A2 β casein IF was submitted to simulated gastrointestinal digestion (SGID) to evaluate the release of BCM7 and compared with commercially available IFs. The results showed that A2 β casein IF produced the lowest level of BCM7 upon SGID at a pH peculiar of infant's stomach in comparison to other commercially available IFs (Miguel *et al.*, 2017) ^[15]. These bring additional insight into the field of infant nutrition and provide further evidence for the development of improved food technologies in the manufacturing of IFs.

Conclusion

In the conclusion of all the above mentioned reports a thorough human trial based studies are required on the role of BAPs on human health especially BCM7. Also, it is very difficult to evaluate which component of milk is causing / facilitating these correlation with the diseases. The epidemiological studies are needed to be backed with substainal lab reports to establish a cause effect relation between diseases and A1 milk. In India the requirement of quantity as well as quality of milk is increasing day by day. The cross breeding programme in cattle for increased milk production had been started by the government in the 1970s. Such studies could help us to plan better breeding policies for cattle Bioactive peptides have attracted the interest of researchers as a health promoting functional food There is an urgent need to focus on developing novel facilities including advanced proteomics approaches, recombinant enzyme technologies and microbial fermentation, to study the various impacts of bioactive peptides on expression of genes and also to optimize the nutritional and health effects of these compounds.

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