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Review Article

The Science of A1 & A2 Milk: Decoding the Enigma

Bagavan Reddy[1]* and Athidi Lokavya Reddy[2]

[1]Ph.D. Scholar, Division of Animal Nutrition, Indian Veterinary Research Institute, Bareilly, India

[2]Senior Research Fellow, ET-IVF Lab, College of Veterinary Sciences, Korutla, P. V. Narsimha Rao Telangana State Veterinary University, Hyderabad, India

***Corresponding Author:** Bagavan Reddy, Ph.D. Scholar, Animal Nutrition Division, Indian Veterinary Research Institute, Bareilly, India.

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Abstract

An increase in metabolic diseases globally associated with changing lifestyles mandates continuous research on the food we consume. Though many of the conditions are multifactorial, identifying those risk factors poses a real challenge. One such risk factor currently in limelight is the myth and facts revolving around milk consumption. Milk and dairy products are said to be one of the most common essential commodities relished by people irrespective of age. But there always exists many misconceptions considering milk consumption among both literate and ignorant sectors. Observational, epidemiological, and clinical studies in humans and laboratory animals revealed potential health hazards concerned with the intake of A1 milk. However, such harmful effects are minimal with that of A2 milk. On the other hand, profound health benefits and medicinal importance were believed to be encrypted behind the consumption of indigenous dairy products. Irrespective of all these discussions conclusions on milk consumption is yet to be established. Hence, considering existing facts and beliefs, studies should be encouraged, and efforts are to be streamlined in the conservation and propagation of our indigenous breeds which are the prime source of A2 milk. This review summarised the importance of A2 milk in comparison with that of A1 milk and emphasized the necessity of protecting our natural resources within our Indian subcontinent.

Keywords: A1 Milk; A2 Milk; Epidemiological; Health Hazards

Introduction

Milk is said to be nature's perfect diet. But to Indians, Milk goes beyond dietary and nutritional outlook. The association of milk with the Indians remains to be connected not just in terms of economic backgrounds but also intertwines with the socio-cultural aspects. It's very hard to find a home in India that does start their day without it. Milk wasn't the same after Kurien came (Anonymous). Pioneer behind transforming our statistics from stage of "Cup of Tea" to the largest producer in the world. India is a land of milk puddles with the production reaching 198.4 million tonnes [21] in the year 2019-2020 and per capita, availability being 406 gm/day (DAHD and F, GoI). Apart from its emotional relationship, milk remains to play an important role in human nutrition and development throughout life. Milk is complex food containing different types of nutrients which help to meet the requirement of body protein, fat, sugar, minerals, and vitamins. In the present scenario, dairy cows are the major source of milk in the world. Milk from other animals is also consumed but the major contribution is from cows. Milk consumption brings in a controversial debate between its benefits and hazards. According to ancient ayurvedic literature,

cow milk is considered to possess medicinal properties along with its healthy nutritive value with bio-protective action and tissue regeneration effect [6]. While western studies say consumption of milk causes gastrointestinal disorders, digestive discomfort, and bloat with an increased risk of metabolic disorders. This controversy continues to remain with many turning to alternative diets i.e., veganism. What actually holds well is still unclear.

Milk is an abundant source of proteins and biologically active peptides. Milk mainly contains two types of proteins namely, casein and whey protein. Casein making up 80% of total protein content is the largest group of milk proteins and is responsible for the white colour of milk. This casein protein is subdivided into αs1-, αs2-, β-, and κ-casein families. Among these families, beta-casein is the 2nd most abundant protein. Mutation in the beta-casein in cow milk led to the formation of 13 different genetic variants of beta-casein and among them, A1 and A2 beta-casein are the most common. Based on the type of casein protein, milk is named A1 and A2 milk. Several studies are suggesting that A2 milk is safer than A1 milk. Cow milk that contains A1 type β- casein, is considered A1 milk, and A2 type β- casein then it is called A2 milk.

A1 and A2 milk

Milk proteins are heterogeneous polymorphic compounds having different molecular structures and properties. Milk proteins include caseins, whey proteins, enzymes, minor proteins, and other non-protein nitrogen compounds. Casein proteins form the majority portion (80%) of the milk protein. There are different forms of caseins present in the milk among them β- caseins are the primary and 2nd most prevalent form that exists in 13 different forms. Among these subtypes, A1 and A2 β- caseins are the most common and considered important. Based on existing literature the type of caseins that a cow produces in its milk depends on the kind of genes it carries for the same. This expression can be homozygous for either A1 or A2 or it can exist together as heterozygous co-dominance. Hence the animal-producing milk that contains A1 β- casein is called A1 milk and A2 β- casein is called A2 milk. Originally, all milk was A2, but due to genetic mutation in the A2 beta-casein gene at some point about 3000 years ago in Europe, the A1 form appeared [16]. Several studies and literature suggest that A1 milk is a potential etiological factor for human diseases such as type-I diabetes, coronary heart disease, autism, sudden infant death, and GI discomfort.

Does β- casein demarcation present only in cow's milk?

A1 milk has been exclusively found in the cattle of European origin. Not only milk contain A1 β- casein but also dairy products like yogurt, and cheese are likely to produce this A1 β- casein. Heat processing methods used in yogurt and cheese preparation also result in the release of BCM-7 [22]. Unlike bovine milk, human milk contains exclusively proline making it an A2 type [11]. Casomorphins released upon digestion of human milk differ from that BCM-7 in its amino acid sequence [38]. On the other hand, milk from the less popular dairy animals such as sheep and goats were also found to be of the A2 type [26]. Casein allergies associated with A1 milk are negligible with the dairy products made from the A2 milk.

What makes A1 and A2 β- caseins differ

Presence of histidine in A1 β- casein makes it susceptible to proteolytic degradation by enzymes of GIT. The matter of concern is when this peptide bond is digested by the enzymes like pepsin, aminopeptidase, and elastase, it leads to the formation of seven amino acid opioids like an intermediary digested product named β- casomorphin-7 (BCM-7). This active BCM-7 is found to pass through the intestinal barrier and is responsible for all the adverse effects of A1 milk consumption. While A2 milk is resistant to such digestion.

Cow breeds concerned with A1 and A2 milk

As discussed earlier due to genetic mutation at the 67th position, changes in the amino acids from proline (A2) to histidine (A1) lead to the most prevalent form of β- casein. The percentage of A1 and A2 β- casein production in the milch animals differ greatly among species, breeds, and at different geographical locations. This variation witnessed is more area-specific than breed-specific. Thus, the modern-day dairy breeds produce either A1 or A2, when both A1 and A2 are expressed, then the percentage varies between the breeds. Milk of northern European breeds contains a high amount of A1β- casein (A1 milk). A1 milk-producing breeds include Holstein, Friesians, Ayrshire, and British shorthorn. A2 milk-producing breeds are located in the Channel Islands and southern France such as Jersey, Guernsey, Charolais, and Limousine cows and also the zebu cattle of Asia and Africa. To increase milk production in India extensive cross-breeding has been encouraged which resulted in an increase in the Holstein and jersey population in our national herd. Both of which produce a varied amount of A1 and A2 milk across the world, but comparatively Jersey was found to produce

A2 type milk. As per the 20th Livestock census, 73.5% of cattle are indigenous with 41 recognized breeds distributed in different agro-climatic regions of India. However, Screening of milch animals was done in a few breeds i.e., Buffaloes, Sahiwal, Tharparkar, Karan Fries, Karan Swiss. All were found to be of A2 type. Among different indigenous breeds, the Badri breed of the cow was found to have the highest percentage of A2 β- casein almost 90% [13].

Screening of animals for a type of milk protein has to be done using DNA analysis, many countries have their commercial kits available today.

Health concerns associated with A1 and A2 milk

Proteins present in bovine milk are a common source of bioactive peptides. Components in the milk show various constructive actions but some studies found that its metabolites show a severe threat to human health. BCM-7 is one such bioactive peptide that is released when A1 β- casein is digested in the gastrointestinal tract by the proteolytic enzymes however proline in A2 β- casein minimizes such proteolysis [15].

BCM-7 possesses a deleterious effect on human health through its action on opioid receptors located in neural, immune, and endocrine systems [35]. Many epidemiological observational suggest that consumption of A1 β- casein is associated with higher mortality rates from ischemic heart disease, cardiovascular diseases, type 1 diabetes, and even neurological disorders such as autism and schizophrenia.

Type 1 Diabetes (DM-1)

It is a common chronic autoimmune disease up surging globally at the rate of 3% per annum [18]. This condition is developed mainly due to a lack of insulin resulting in insulin-secreting β cells destruction in the islets of Langerhans of the pancreas by some autoimmune processes. Though genetic susceptibility is the underlying cause environmental factors play potentiating effect on the phenotypic manifestation of DM-1 [27]. The contribution of A1 cow milk to the development of DM-1 has been controversial for decades. The hypothesis behind the controversy is that A1 beta-casein may increase the risk of DM-1 in genetically susceptible children with the release of opioid peptide, BCM-7, which affects the immune system and produces autoantibodies against β-cells of the pancreas. Also, BCM-7 through epigenetic modulation found to be differentially methylated genes that predispose DM-1 [17]. In a case-control study in Finland, the early introduction of bovine milk resulted in an increased risk of DM-1 by 2 times [37].

Many animal studies on rats and mice concluded the diabetogenic effect of milk protein and A1 β casein along with its mediating action via opioid receptors while such effect was negligible when A2 β casein was fed [7]. However, the release of BCM-7 has not yet been demonstrated in human subjects. To comprehend, the onset of DM-1 is multifactorial, there exists numerous evidence pointing that A1 β casein could be a prime environmental trigger and casual factor potentiating its development [3].

Coronary heart disease (CHD)

Coronary heart disease or ischemic heart disease is one of the major cardiovascular diseases. Foam cells play a crucial mediative role in the pathogenesis of atherosclerosis. These cells are formed as a result of fat infiltration in macrophages [41]. Several studies reported the incidence of cardiovascular disease with the consumption of A1 beta-casein. McLachlan [20] suggested that more intake of A1 beta-casein could pose a risk of developing CHD and he also proved it with epidemiological evidence showing the association between A1 beta-casein and CHD in 30-69 years old age group males across 16 countries. He also postulated that BCM-7 is a possible etiological factor for cardiovascular disease. The possible hypothetical reason behind the effect of milk protein on CHD is the plasma cholesterol rising effect of casein. Tyrosyl is a protein oxidation product seen in atherosclerotic lesions, and BCM-7 is a possible source [42] that is believed to be involved in process of oxidation of low-density lipoproteins. Oxidized LDL is further engulfed by macrophages leading to the initiation of atherosclerosis [12].

On the contrary, research including 15 asymptomatic adults (6Male and 9Female) who are at high risk of developing cardiovascular disease found that supplementing A1 milk had no adverse effect on cardiovascular health when compared to the A2 milk consumption. Similarly, Venn., *et al*. [36] showed that consumption of A1/A2 beta-casein did not affect plasma cholesterol concentration in humans. On the other hand, rabbits fed with A1 milk had higher cholesterol levels and showed a greater percentage of the aorta surface area covered by fatty streaks than A2 milk-fed rabbits [33]. Though there is no direct practical evidence to prove this adverse

effect of milk protein on cardiovascular health the correlation studies displayed a value of 0.79- 0.81 with coronary heart disease.

Sudden infant death syndrome (SIDS)

According to Brooks [2], the death of infants between the first month to the first year of life is sudden infant death syndrome (SIDS). Respiratory infections, brain anomalies, environmental factors, and low birth weight which causes difficulty in breathing in a baby are some of the potential causes of infant death. Some researchers suggested that BCM-7 is also one of the potential causes of SIDS [32,19]. It is believed that BCM-7, gets absorbed into the blood through the immature juvenile GI tract and can cross the blood-brain barrier due to the immature central nervous system in infants. Then it induces depression of the respiratory center in the brain stem causing the death of the infants with abnormal respiratory control and vagal nerve development. In support of this hypothesis, Wasilewska., *et al*. [39] observed a higher level of BCM-7 in the sera of infants after an apnoea than the healthy infants of the same age. There is no strong practical evidence for this hypothesis and further investigations are needed to prove this association between the opioid-derived milk protein and SIDS.

Neurological disorders (Autism and Schizophrenia)

It has been reported that consumption of bovine milk containing A1 beta-casein is associated with neurological disorders such as autism and schizophrenia [31]. Autism is a neurological disorder characterized by social deficit and repetitive behaviours, whereas schizophrenia is a mental disorder that affects a person's ability to think, feel and behave clearly. Some studies are reporting that milk casein-derived peptide, BCM-7 might play role in the development of autism and schizophrenia. Some researchers are reported that milk peptides can show toxic effects at the level of the central nervous system by interacting with the neurotransmitters.

According to a hypothesis, at an early age, genetic deposition and environmental stress cause changes in intestinal mucosa and increases the permeability of intestinal mucosa, and also cause a decrease in proteolytic activity. Reduced proteolytic activity and increased blood-brain barrier permeability lead to the accumulation of opioid peptides like BCM-7 in the brain and also in blood, which in turn results in hyperpeptidemia. An increased number of opioid peptides may affect the neurotransmitter systems in the brain and can cause disorders like autism and schizophrenia [28]. When such patients were fed a diet completely off gluten and casein, symptoms were got to reduced but the same did not completely cure the disorders [9]. Kost., *et al.* [10] observed delayed motor and muscular development in babies fed with a diet containing cow milk than in those fed with breastfeeding.

Gastrointestinal discomfort

There is an increasing trend of people exhibiting milk intolerance syndrome upon consumption of milk and dairy products. This could be attributed to the following reasons firstly, inability to digest lactose, falling under the lactose intolerant category, and secondly, A1 protein intolerance. Thirdly BCM-7 released from A1 β casein is known to slow down food passage that provides a longer time for lactose fermentation [40].

Many researchers have also reported that increased consumption of bovine milk (especially A1 milk) is related to an increased incidence of gastrointestinal disorders. BCM-7, a milk-derived bioactive peptide is thought to be a potential cause of gastrointestinal tract-associated disorders in humans consuming dairy products. This bioactive peptide is known to activate μ-receptors of the GIT and alter GI motility in adults and neonates [1]. A1 β casein has been known to trigger a local inflammatory reaction which was evident by the release of pro-inflammatory markers such as myeloperoxidase in the laboratory animals, as such results though not replicated in the humans, subclinical inflammatory response to the A1 β casein cannot be ruled out. BCM-7 disrupts gastrointestinal function and disturbs the niche of commensal bacteria through mucus production [43]. Clinical trials in humans revealed a strong correlation in the study group who consumed A1 milk exhibited gut inflammation, abdominal pain, and higher bloating [14].

What makes A2 milk healthy

Dairy products are revered and chosen considering their calcium content. Calcium is the major inorganic element in the animal kingdom and is known to reduce the risk of colon cancer and prevent osteoporosis [24]. The calcium to magnesium ratio of milk does alter its beneficial effects. A high Ca to Mg ratio increases the risk of colorectal cancer along with multiple chronic conditions such as cardiovascular disease, calcification, osteoporosis, and bone fractures [5]. The ideal calcium to magnesium ratio suggested would range from 1.70 to 2.60. The same of A1 milk is 10:1, which is far higher than that of A2 milk i.e., 2:1. Thus indirectly in-

dicating the health benefits of A2 milk. [25]. In few clinical studies conducted on humans proved, that no subjects witnessed neither classical digestive disturbances such as abdominal pain, bloat, and inflammation [14], nor signs of milk allergies [23]. To some extent to a few reports, it is now clear that the adverse effects caused by A1 milk are not replicated with the consumption of A2 milk. In the light of Vedic literature, Indian cow milk has got huge importance in terms of its unique beneficial effects. This area is less explored by the scientific community. Cow's milk is believed to possess anti-aging properties [29], antifungal properties [8] anti-cancer properties with a tonic effect on the heart and brain. Such effects are more pronounced in value-added products such as curd, ghee, buttermilk, etc. That is the reason why milk and milk products have always been part of a conventional traditional Indian family. Though huge oral evidence is present on the exceptional benefits of A2 milk, scientific evidence has to be supplemented to make it established globally.

Conclusion

To conclude India has been gifted with unique cattle breeds that are so evolved and adapted, by mere mimicking western ideology considering economic benefits, much of our true gene pool was diluted and germplasm has been on verge of vanish. A lot of scopes still exist for its conservation and propagation. Interdisciplinary research involving universities, industries, and farmers considering our environmental conditions to find the true potential and worth of our resources will certainly yield some beneficial information. Strict implementation of breeding policies must be considered which otherwise leads to irreplaceable losses that humankind would never bring back.

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