



A1 and A2 Bovine Milk, the Risk of Beta-casomorphin-7 and Its Possible Effects on Human Health: (II) Possible Effects of Beta-casomorphin-7 on Human Health

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ABSTRACT

Beta-casomorphin-7 (BCM-7) which is an opioid peptide during digestion of A1 milk, has been claimed as a possible cause of some health problems. There are some studies about the role of β -casomorphin-7 in some diseases such as type 1 diabetes, cardiovascular diseases, autism, schizophrenia, sudden infant death syndrome, apnea, constipation. For example, β -casomorphin-7 destroys pancreatic β cells, leading to the emergence of type 1 diabetes. It effects T and B cells related to immunity and negatively effects the autoimmune system.

The aim of this study is to reveal the diseases that can caused by β -casomorphin-7 in terms of both animal and human health, in this way to contribute to the reduction of the costs of animal and human health and to create an awareness.

1. Introduction¹

A1 β -casein, a variant of bovine β -casein, is composed of β -casomorphin-7 (BCM-7), a bioactive peptide during digestion. A1 β casein is enzymatically broken down in the intestine to produce BCM-7, and may exhibit an immune effect against antigens such as enteroviruses or endogenous retroviruses with morphine-like activity according to A2 Corporation (Kaminski et al 2007). BCM-7 is known certain that it is an opioid (Brantl et al 1979). While A1 casomorphin casein causes; (1) type 1 diabetes, (2) autism, (3) schizophrenia and (4) heart disease, A2 β casein does not cause such diseases (Woodford 2007; Mishra et al 2009; Sun et al 1999; Sodhi et al., 2012). The effects of BCM7 were clearly demonstrated when injected into rats, and Sun & Cade (1999) and Woolford (2007) stated that these effects could be eliminated by the use of naloxone (addiction inhibitor), an opioid antagonist. In addition, these opioid peptides play a negative role in a variety of events in humans (1) including breathing, (2) analgesia, (3) constipation and (4) behavior (Ng-Kwai-Hang & Grosclaude 2003). Several researchers have reported that A2 β -casein milk is better for human health for these reasons (Hartwig et al 1997; McLachlan 2001; Woodford 2007; Mishra et al 2009). In bovine and human BCM-7 differ by 2 amino acids at position 4 and 5 of the

peptide: the structure of the human derived BCM-7 is H-Tyr51-Pro52-Phe53-Val54-Glu55-Pro56-Ile57-OH while that of bovine origin is H-Tyr60Pro61-Phe62-Pro63-Gly64-Pro65-Ile66-OH. These structural differences affect the opioid activity of BCM-7 with bovine milk beta-casomorphins shown to be at least 10 times more potent (i.e. greater binding affinity to mu-opioid receptors) than human betacasomorphins. This may have consequences on the function of each variant. For instance, elevated circulating human BCM-7 has been correlated with beneficial developmental outcomes in breast fed infants, while the opposite has been observed in their bovine milk containing formula-fed counterparts with similarly elevated levels of bovine BCM-7 (Jaiswal et al 2014).

Empirical evidence obtained from some laboratory confirms that in the presence of in vitro and digestive enzymes, A1 β -casein milk releases large amounts of β casomorphin-7 (BCM-7), whereas the milk of A2 does not secrete it (Hartwig et al 1997; Jinsmaa & Yoshikawa 1999). Many investigations have been made with A1 and A2 milk, some of them are epidemiological and empirical studies.

The aim of this study is to reveal the diseases caused by β -casomorphin-7, to contribute to the prevention of diseases that may occur in this way and to create a social awareness.

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2. Some Diseases Related to BCM-7

2.1. Ischemic (or coronary) heart disease (IHD or CHD)

Ischemic or coronary heart disease (IHD or CHD) is one of the major cardiovascular diseases. This disease leads to constriction and vascular occlusion. Variations in the frequency of heart disease were found to be related to A1 β -casein consumption in developed countries (McLachlan 2001; Laugesen & Elliott 2003). McLachlan (2001) reported the correlation between A1 β -casein consumption and ischemic heart disease (r), 0.842 in men, A1 β -casein consumption (except cheese) correlation (r) as 0.927 in his study to determine the association between A1 β -casein consumption and A1 β -casein consumption (excluding cheese) with ischemic heart disease death rate (data from 1985) in 30-69 year old men (Figures 1, 2, 3, and 4) in 16 countries. The same investigator, using mortality rates for ischemic heart disease in 1990, found the correlation (r) between A1 β -casein consumption (except cheese) in men and women aged 65 and over and heart diseases as 0.916 and 0.854 respectively. In addition, pointing out the relationship between this

milk variant and mortality rates, the investigator stated that A1 β -casein was worth considering seriously as a potential source of cardiovascular disease when Northern Irish people are estimated to consume 3.23 times more cheese (A1 β -casein) than French. In conclusion, McLachlan (2001), basing on his studies, suggests that β -casein A1 or possibly peptide (BCM-7) has a significant effect on cardiovascular disease. Tailford et al (2003) reported in their studies by feeding the rabbits with A1 β -casein milk and A2 β -casein milk that, the rabbits fed with A1 β -casein milk had higher cholesterol level and more plaques on the aorta (the main artery in the heart) covered with oily veins than those fed with A2 β -casein. In other words, researchers stated that A2 β -casein milk consumption may be protective against ischemic heart disease because of low density lipoprotein (LDL) along with high density lipoprotein (HDL). Similarly, Elliott et al (1999) reported that physiological effect of BCM-7 on the oxidation of LDL or the effect of lipid component of LDL on peroxidation (degradation) is a determinant factor in the development of heart disease.

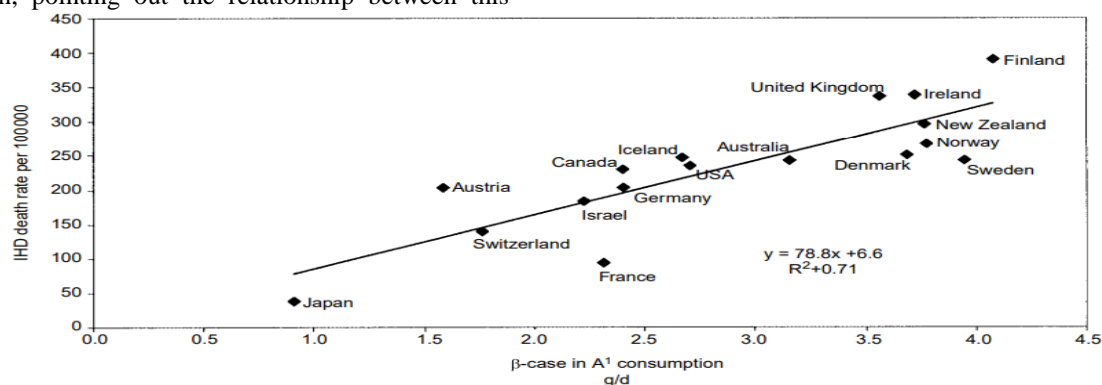


Figure 1
 β -casein A1 consumption and IHD death rate (1985) in males aged 30–69 (McLachlan 2001)

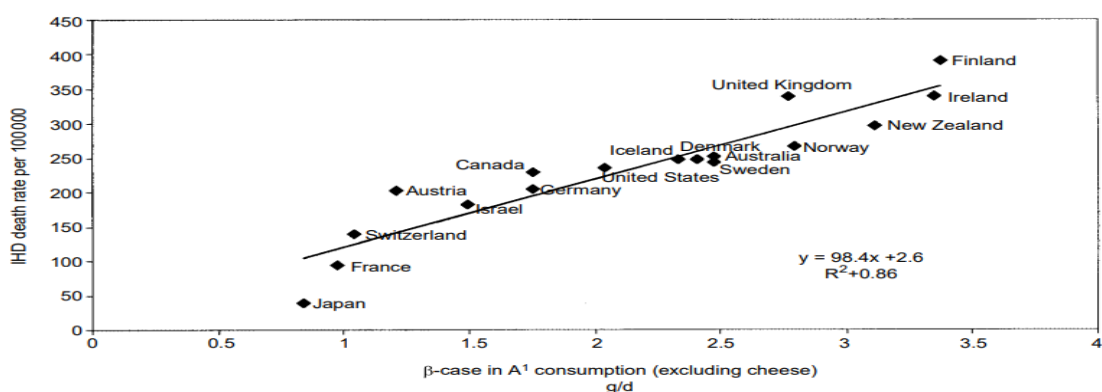


Figure 2
 β -casein A1 consumption (excluding cheese) and IHD death rate (1985) in males aged 30–69 (McLachlan 2001)

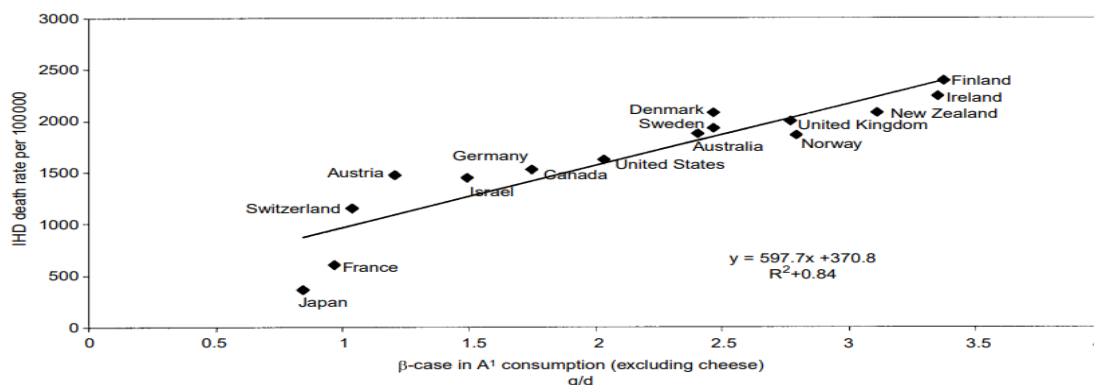


Figure 3
 β -casein A1 consumption (excluding cheese) and IHD death rate (1990) in males aged 65 and over (McLachlan 2001)

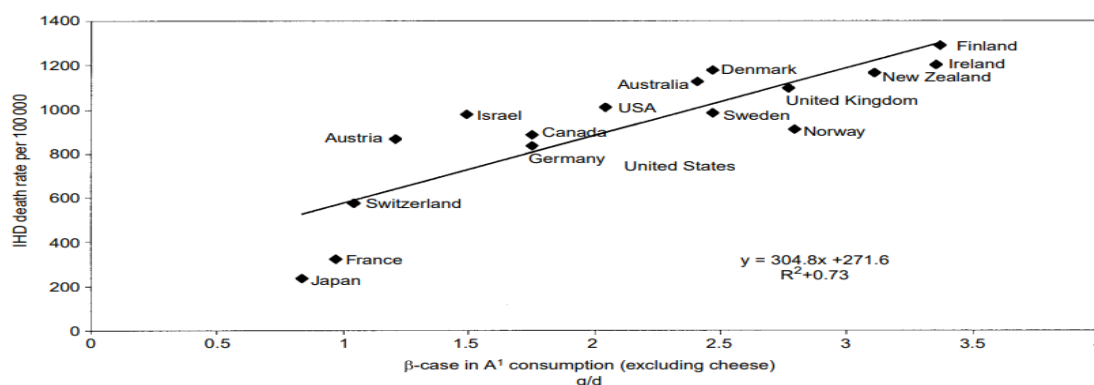


Figure 4.
 β -casein A1 consumption (excluding cheese) and IHD death rate (1990) in females aged 65 and over (McLachlan 2001)

2. 2. Diabetes mellitus type 1 (DM-1)

Type 1 diabetes (DM-1) is an autoimmune disease in which the pancreas loses its ability to produce insulin. Autoimmunity is the immune system's ability to produce antibodies against body cells, that is, to try to eradicate as a result of hypersensitivity. Genetic factors play an important role in the development of Type 1 diabetes (DM1). However, NIH (2010) stated that environmental and nutritional factors have been confirmed to be more effective because the disease have developed in only 5% or less people with a genetic predisposition to DM-1 (Jaiswal et al 2014). The prevalence of diabetes mellitus type 1 (DM-1) increases by 3% per year worldwide (Laugesen & Elliott, 2003).

Diabetes or diabetes mellitus type 1 (DM-1) develops as a result of insulin-secreting pancreatic cell lysis. This is guided by an autoimmune process during which T cells are thought to play an important role. T cells are a type of white blood cell that controls cellular abnormalities and infections and plays an important role in the protection of our immune system. B cells are like guards constantly looking for germs. When they encounter any invader, they begin to produce antibodies by dividing rapidly (Swinburn 2004). Pancreatic beta cells detect the sugar in the blood and provide the secretion of insulin hormone when the sugar content is high. There is a consensus that there is

one or more environmental triggers which destroy insulin-secreting pancreatic β cells in individuals genetically susceptible to type 1 diabetes (DM-1). The evidence that A1 β -casein is such a trigger is mainly understood from studies related to the disease (Swinburn 2004).

The first relationship between Type 1 diabetes and A1 β -casein milk was researched by Professor Bob Elliott at University of Auckland and stated that the Samoa children living in Samoa did not have diabetes, it was observed in Samoa children living in New Zealand. (Woodford 2007). Although studies on the disease showed a significant relationship between A1 milk consumption and the prevalence of Type 1 diabetes, there was no relation between A2 milk consumption (Elliott et al 1999; McLachlan 2001; Laugesen & Elliott 2003).

Elliott et al (1999) compared the frequency of DM-1 in children aged 0-14 years from 10 countries, including Australia, Canada, Denmark, Finland, Germany, Iceland, New Zealand, Norway, Sweden and USA - San Diego, taking into account the race composition and milk protein polymorphism. The researchers found that total protein consumption had low correlation ($r = 0.402$) with DM-1 frequency, the consumption of β -casein A1 variant had high correlation ($= 0.726$), and the relation between DM-1 and β -casein

A1 + B consumption was higher ($r = 0.982$). The same researchers reported that cows in Iceland have predominantly A2 allele, and therefore few cases of diabetes and heart diseases have occurred.

McLachlan (2001) showed that the consumption of A1 beta-casein across 16 countries is correlated strongly with the incidence of DM-1 in children under 15 years old. Laugesen & Elliott (2003) added nine more countries between the years 1990-94 to the study carried out by Elliott et al (1999) and confirmed the

study of Elliott et al (1999). They determined the correlation coefficient as $r = 0.90$ ($P < 0.001$) for the nine countries. Although the combination of A1 and B-casein consumption per capita was found to correlate better with DM-1 in the study of Elliott et al 1999, Laugesen & Elliott (2003) reported that when B (or C) β -casein was added, the correlation decreased and B or C was not separately associated with DM-1 (Figure 5; Table 1).

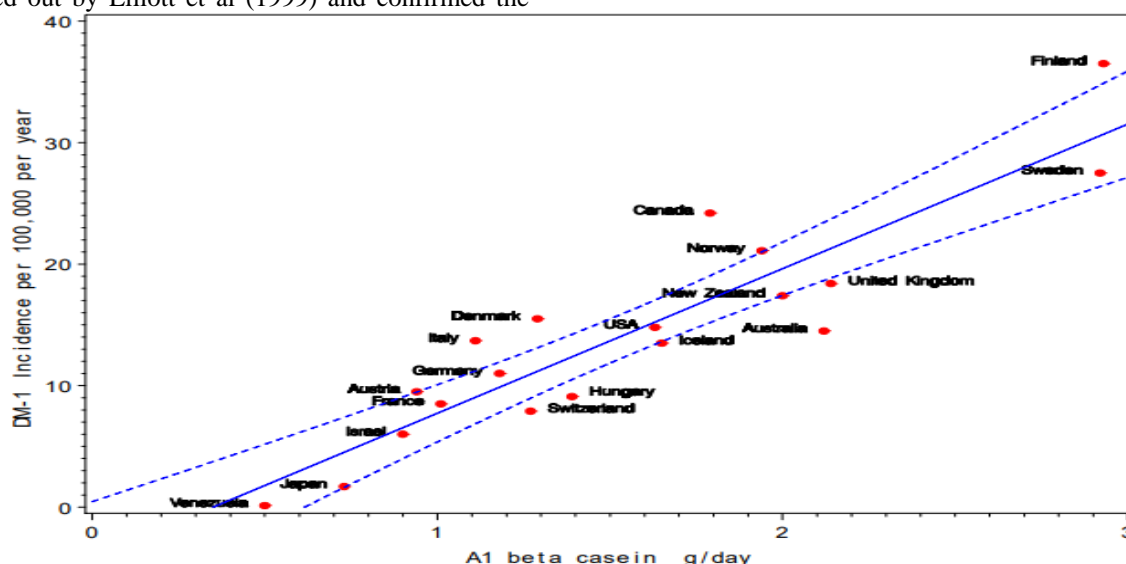


Figure 5

Correlation of A1/capita (A1 b-casein in the per capita milk and cream supply) with the incidence of diabetes mellitus Type 1 at age 0–14 years of age, 1990-94, 19 countries (Laugesen & Elliott 2003)

Table 1

Correlations of cow proteins per capita supply with the incidence of diabetes mellitus Type 1, age 0–14 years, across 19 countries, 1990–1994 (Laugesen & Elliott 2003)

Cow protein variables, 1990-94 averaged	Correlation (r) with DM-1 incidence	P values
A1 β -casein /capita, in milk & cream	0.92	<0.001
A1+B casein/capita, in milk & cream	0.86	<0.001
A1+B+C casein/capita, in milk & cream	0.84	<0.001
A kappa-casein/capita, in milk & cream	0.72	<0.001
Protein/capita in milk & cream	0.68	<0.01
A1/ β -casein fraction, in cheese	0.50	<0.05
A1/ β -casein fraction, in milk & cream	0.47	<0.05
A2 β -casein /capita, milk & cream	0.47	<0.05
A1 β -casein /capita, in cheese	0.46	<0.05
Protein/capita, in cheese	0.23	>0.05
B β -casein/capita, in milk & cream	-0.14	>0.05
C β -casein/capita, in milk & cream	-0.22	>0.05

Many mechanisms have been introduced to explain the milk consumption and the risk of DM-1, but all are based on the BCM-7. Studies have shown that BCM-7 inhibits the growth of intestinal lymphocyte cells and that BCM-7 affects the development of bowel-related immunity tolerance (Elliott et al 1999; Laugesen & Elliott 2003). Briefly, the decrease in intestinal lymphocyte cells weakens the intestinal permeability and thus toxic substances pass into the blood. In response to this, the immune system is activated and tries to

prevent this situation, resulting in inflammation and allergic reactions.

2. 3. Sudden Infant Death Syndrome (SIDS) and Child Development

Sudden infant death syndrome (SIDS) is the cause of death between the end of the first month and the 12th month of infants (Brooks 1982). BCM-7 has been thought to be a risk factor for SIDS for more than 20 years (Hedner & Hedner 1987). Milk is referred as the only common nutrient source for all children develop-

ing SIDS and it is claimed that BCM-7 from the immature gastrointestinal tract of the infant passes into the blood. In infants with abnormal respiratory control and vagal nerve development, the milk-induced opioid peptides can lead to death causing depression in the brainstem respiratory centers. Thus, the BCM-7 immune response has been reported to be in the brainstem of the human brain (Sun et al. 2003). Transfer of BCMs and related peptides from the central nervous system has also been demonstrated in rats and mice. These results clearly indicate that BCM-7 can cross the blood-brain barrier (Sun et al 2003; Whiteley et al 2010). Likewise, Bell et al (2006) reported that BCM-7 could potentially affect many opioid receptors in nerve, endocrine and immune systems. Moreover, Wasilewska et al (2011) have reported that BCM-7 causes respiratory depression in humans, and that babies whose life is threatened with apnea are characterized by three times higher BCM-7 levels than normal children. Researchers reported that DPPIV (BCM-7 degrading enzyme) levels were $58 \pm 3\%$ in normal children compared to these children. Basing on this research, Woodford (2011) states that even when infants are breastfed, bovine BCM-7 can be found in the blood of babies and the bovine BCM-7 is transferred to the infant with milk consumed by the mother.

Russian scientists have stated that BCM-7 is present in the blood of babies fed with milk diets and some babies can metabolize BCM-7 rapidly while others metabolize slowly. The risk of delayed mental development was also found higher in babies with high levels of BCM-7 in blood through food consumption and consumption (Kost et al. 2009).

2. 4. Neurological Disorders

A1 β -casein consumption has been associated with some neurological disorders such as autism and schizophrenia. Reichelt et al 1991, Cade et al (1990); Cade et al (2000) and Lindstrom et al. (1984); Reichelt et al (1990) reported a significant increase of BCM-7 level in the urine and blood of schizophrenia, autism and postpartum psychosis patients. Genetically, in individuals with neurological disorders such as schizophrenia and autism, peptide fragments with opioid properties are produced from proteins such as casein and gluten in the intestine. This bioactive peptide can significantly pass through the gastrointestinal tract mucosa and mix with blood in some individuals. These compounds have been reported to enter the circulation, cross the blood-brain barrier and affect neurological functions (Sun & Cade 1999). In addition, it is stated that a marker of diet sensitivity is abnormal urine peptide excretion (Knivsberg et al 2002). They have reported that absorption of food-derived exo-morphines such as BCM-7 could increase symptoms associated with autistic spectral disorder or schizophrenia, and a decrease in symptoms associated with autistic spectral disorder in the absence of milk A1, but also that genetic factors play an important role. The data obtained from the study of

192 identical and dizygotic twins showed that environmental factors accounted for 58% of the autistic spectral disorder (different levels of autistic symptoms in each individual), whereas genetic factors accounted for only 38% (Jaiswal et al 2014). Knivsberg et al (2002). A autistic spectral disorder, a neurological disorder, and schizophrenia have been stated to increase with the consumption of A1 milk. Swinburn (2004) reported that the autistic behavior of the individuals may be improved by reducing casein and gluten in the diets of people with autism.

2. 5. Other illnesses

Ho et al (2014) determined that FC values had higher correlation with digestive disorders in A1 diet, but lower in A2 diet. They also stated that the A1 diet was associated with abdominal pain and softer stool. In addition, some individuals may be susceptible to beta-casein A1 as was proved by higher FC values and associated intolerance measurements (*FC: is a protein present in calprotectin neutrophils. Calprotectin is present in high concentration stool in inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis disease*).

The ideal calcium and magnesium ratio for the human body should be 2: 1 (magnesium only half as much as calcium). The proportion of A1 milk is 10: 1 (the magnesium ratio decreases to one-tenth of calcium). That is to say, the calcium deficiency and imbalance of A1 cow milk, but A2 milk does not have this imbalance (Boro et al 2016; Priyadarshini et al 2018). Magnesium has a relaxing effect on the body's relaxation, ease of digestion, the function of nerve and muscles, it is de-toxicizing, and increases the alkalinity of blood and the flexibility of tissues. Magnesium is required for the body to produce and store energy. Without magnesium, it means there is no energy, no movement, no life (Boro et al 2016). A1 milk; causes inflammation, lymphatic obstruction and metabolic suppression. A1 milk; may cause acne, eczema, upper respiratory tract infections, asthma and allergies. It can induce digestive problems due to not lactose but the release of mass histidine from beta-casomorphin-7. Ear infection, bronchitis, tonsillitis can be seen with the consumption of casein A1 (Boro et al 2016; Priyadarshini et al 2018). A1 milk causes endometriosis due to its inflammatory and immune destructive effect. Endometriosis is a gynecological condition in which the cells from the lining of the uterus (endometrium) appear and develop on the membrane that usually depicts the abdominal cavity, outside the uterine cavity. Many women with infertility may suffer from endometriosis and other reproductive complications (Boro et al 2016).

3. Conclusion and Recommendations

While proline does not allow the degradation of β -casein, histidine causes it, and in this way a block of

seven amino acid blocks (prior to histidine) leads to the formation of β casomorphin-7, which causes various dangerous diseases. In today's modern world, deaths are observed due to various diseases. A1 and A2 milk are becoming more and more important to inhibit the diseases/diseases that may be caused by β casomorphin-7 and to prevent permanent diseases and deaths. Some recommendations for the prevention of diseases can be listed as follows:

- The relation between diseases and A1 should be further investigated.
- The therapeutic and beneficial properties of the A2 milk should be demonstrated more.
- Consumption of milk of other species such as sheep, goat and buffalo should be encouraged.
- The consumption of β -casomorphin-7 milk or A1 milk should be prevented by creating social awareness.
- The farmers producing A2 milk should be sponsored and the national economy should be contributed by reducing the additional costs of beta-casomorphin-7 induced diseases.

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