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Milk and consumer health: a review of the evidence for a relationship between the consumption of beta-casein A1 with heart disease and insulin-dependent diabetes mellitus.

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ABSTRACT

New developments in dairy foods, identifying health benefits from "functional foods" have a counterpart in claims of adverse health effects from milk components. A prime example is the present highly publicised claim of adverse effects of "A1 milk". Although there is some evidence that the consumption of beta-casein A1 may have an effect on the development of insulin dependent diabetes, other studies in this area have produced results that are inconsistent with such a claim. Some studies indicate that the removal of beta-casein A1 from the diet would have no influence on the incidence of insulin dependent diabetes. Epidemiological evidence for a relationship between the consumption of milk (and of beta-casein A1) with heart disease appears to have been a serendipitous correlation that occurred in the past (perhaps due to a common underlying factor) but now no longer holds. Elimination of beta-casein A1 from the diet will have no effect on the mortality rate due to heart disease. Evidence to support claims that the consumption of the A1 variant of the milk protein beta-casein is a causative factor in heart disease and insulin dependent diabetes is therefore not sufficient to promote a change in consumer milk consumption away from dairy products containing beta-casein A1.

Keywords: milk consumption; epidemiology; diabetes; heart disease.

INTRODUCTION

Milk has evolved to provide total nutrition to newborn mammals and for this reason contains a wider range of nutrients than most other foods. Milk is nutrient dense in certain essential components such as calcium, amino acids and other macro- and micro-nutrients important for healthy development, particularly of infants and children (Hamraeus, 1992; Flynn & Cashman, 1997). Milk components are an important ingredient in a number of formulated or processed foods and are often used to improve the nutritional value of such foods. Consumption of milk and dairy products is thus considered to be an important part of a healthy balanced diet, particularly in western societies.

There has been a strong international trend over recent years to identify beneficial activities in foods beyond their nutritional value, leading to so-called "functional foods" or "nutraceuticals". The dairy industry has been quick to explore this area, and a range of bioactive peptides from milk proteins was identified as early as the 1980's. There is also a strong history of probiotic dairy bacteria. A potential downside to this activity is the possible connection between the same bioactive species, and disease. Suggestions of a possible link between the development of type-1 diabetes and heart disease and the consumption of milk containing beta-casein A1 (Elliott *et al.*, 1997; 1999; Thorsdottir *et al.*, 2000; McLachlan, 2001) are examples of this. These suggestions have been highly publicised, and have the potential to damage the image of milk as a healthy source of nutrients. They must be scrutinised carefully.

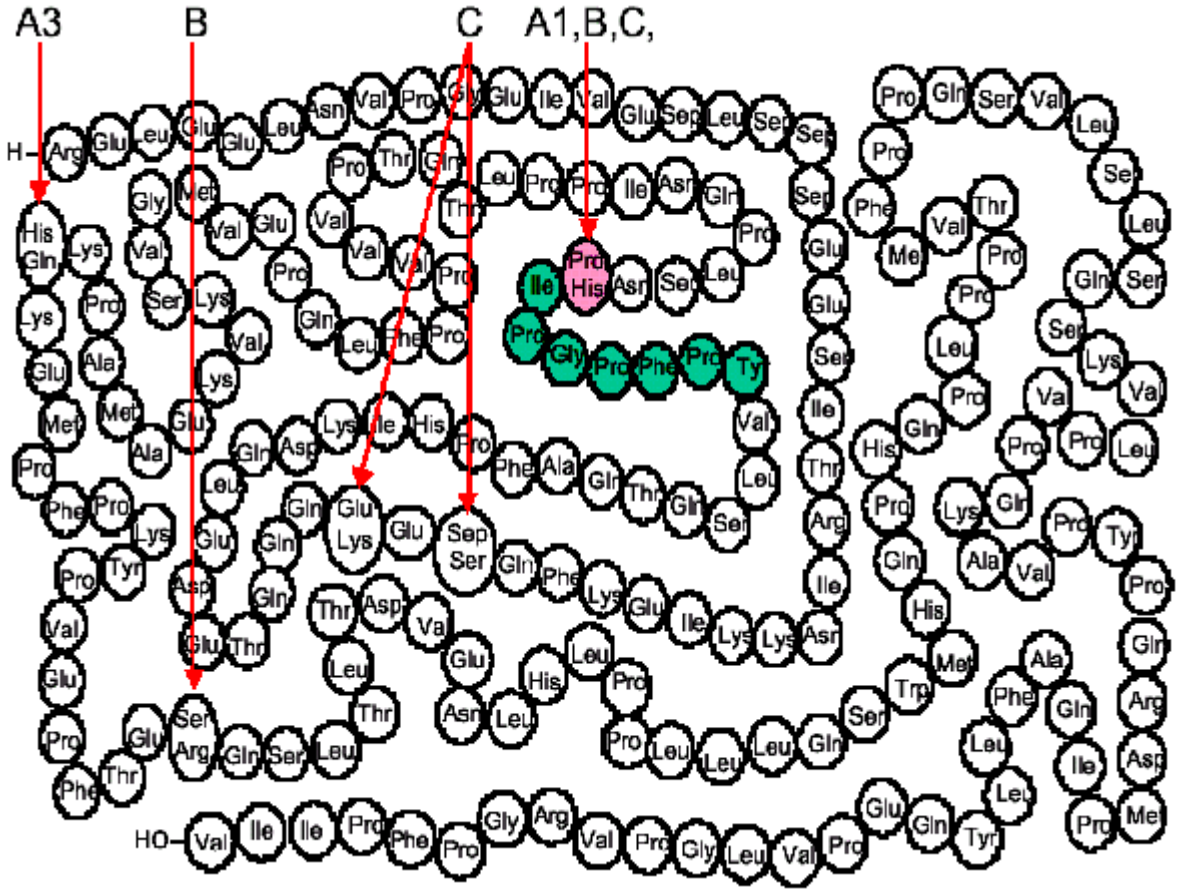
There are two common genetic variants of the milk protein beta-casein: A1 and A2, although a number of other variants can also be found (Figure 1). The B variant is more common in the brown breeds such as Jersey cattle, and the beta-casein A3 variant is found at low frequency in North European cattle breeds and in Channel Island breeds. The beta-casein C variant is found at low frequencies in some Mid- and Southern European cattle breeds and also in Channel Island breeds, with other variants being found only at very low frequencies or restricted to rare breeds of cattle (for review see Ng-Kwai-Hang & Grosclaude, 1992).

Relationship between beta-casein A1 consumption and IDDM

Type-1 diabetes or insulin-dependent diabetes mellitus (IDDM) is an autoimmune disease, which presents as a loss of insulin production, often in younger members of the population. IDDM affects less than one percent of the population, although the incidence of the disease varies considerably between countries and ethnic groupings. The exact cause of IDDM is currently unknown, however, the disease is known to be genetically linked: Those individuals with alleles that predispose them to diabetes may get the disease, but those individuals without such alleles will not get it. It is believed that for an individual to get diabetes they must be genetically predisposed to the disease and also be subjected to one or more environmental triggers. A number of triggers have been proposed, including virus and bacterial infections, exposure to chemicals and consumption of certain food types.

The non-obese diabetic mouse (NOD mouse) and the Biobreeding rat (BB rat) are the two animal models of choice for studying IDDM. Using these animal models, some studies have shown a significant effect of feeding milk protein on diabetes incidence, whereas other studies have found only a minor or no effect on diabetes incidence (for review see Wasmuth & Kolb, 2000). One study has reported a high incidence of diabetes in NOD mice when they were fed a diet containing beta-casein A1 but not when fed a diet containing beta-casein A2 (Elliott *et al.*, 1997), although the statistical significance of these results

FIGURE 1. Primary structure of bovine beta-casein A2 showing the amino acid substitutions present in the beta-casein A1, A3, B and C variants. Highlighted is the amino acid sequence of beta-casomorphin-7 (Tyr-60 to Ile-66) and the His – Pro substitution at position 67.



was not reported. However, multi-national inter-laboratory studies using BB rats and NOD mice found that there was a significantly higher incidence of diabetes in rodents fed a cereal-based diet containing no milk components than in rodents fed diets containing milk components (Food and Diabetes Study Group, 1999). With the exception of the cereal diet, where the incidence of diabetes was significantly higher ($P<0.05$, log rank test), individual laboratories did not produce consistent results, and matched casein-based diets containing only the A1 or A2 variant of beta casein showed no clear trends with either animal model.

There is epidemiological evidence that the consumption of beta-casein variants with a histidine in position 67 (A1 and B) is highly correlated with IDDM (Elliott *et al.*, 1999). The consumption of other common variants of beta-casein (A2 and A3) was not significantly correlated with IDDM (Boland *et al.*, 2001). It is important to note that only ten countries were included in the study and a number of unsubstantiated assumptions were made. The sample of cows phenotyped/genotyped for beta-casein variants in each country was assumed to be representative of that country's milk supply; and the *per capita* consumption of milk protein (inferred from disappearance data) was assumed to be representative of the consumption of milk protein by children within the countries examined. Many other countries were excluded from the study because of significant milk imports (which will distort derived consumption data), inadequate data on beta-casein variants in the national dairy herd, or inadequate data on diabetes incidence.

Experiments *in vitro* have shown that beta-caseins A1 and B release the seven amino acid bioactive peptide beta-casomophin-7 (BCM-7, see Figure 1) upon digestion with gut proteases, whereas beta-casein A2 and A3 variants do not release this peptide (Jinsmaa & Yoshikawa, 1999; Hartwig *et al.*, 1997). This is due to the change from histidine to proline at position 67 in the beta-casein sequence, which blocks activity of most proteolytic enzymes. BCM-7 has been observed to have a marked inhibitory effect on immune cell activity in NOD mice and extracted immune cells from NOD mice and pre-diabetic humans (Elliott *et al.*, 1997). In contrast, BCM-7 appeared to activate immune cell function in normal mice and normal humans. Although it is possible that BCM-7 somehow precipitates the onset of type 1 diabetes by altering immune cell activity, there is currently no mechanistic evidence to show how this might occur.

Relationship between beta-casein A1 consumption and heart disease

There are many general diseases that affect the heart and these are classified according to the part of the heart affected, or the nature of the changes produced (Havard, 1990). The most important heart disease, in terms of its lethality, is coronary artery disease, which is commonly referred to in the medical world as ischaemic heart disease (IHD). The underlying cause of IHD is the narrowing of

the coronary arteries, which supply blood and energy to the muscles of the heart. If the narrowing occurs suddenly, then a complete blockage of a coronary artery may occur thus cutting off the blood supply to the heart muscle resulting in what is commonly known as a heart attack. The ensuing damage to the heart muscle (known as myocardial infarction) may eventually result in death.

A number of animal studies by various authors have demonstrated a hypercholesterolemic effect of casein compared with cereal based diets when fed to certain laboratory animals (West *et al*., 1984; 1991; Terpstra *et al*., 1982; 1983; Huff & Carroll, 1980; Kritchevsky, 1979; 1983; Carroll & Hamilton, 1975). However, the hypercholesterolemic effect is not specific to casein and appears to reflect a difference between proteins of plant and animal origin (Carol & Hamilton, 1975).

A correlation between the consumption of milk protein and *per capita* deaths due to heart disease, based on across country comparisons, has been previously reported (Seely, 1981; 1984). These reports provide no evidence for cause and effect relationships between milk protein consumption and deaths due to heart disease. To observe strong correlations between milk protein consumption and heart disease, a lag period of 5 to 10 years was required between consumption data and data on deaths due to heart disease comparisons (Seely, 1981; 1984). McLachlan (2001) took a similar approach in the analysis of data on the consumption of beta-casein A1 and IHD mortality. Milk protein consumption data are an indicator of general dietary and/or lifestyle habits within a country and it may be that the nature of the whole diet/lifestyle, rather than consumption of milk protein as such, that influences the incidence of cardiovascular disease.

Using data from 40 countries, the relationship between the consumption of milk protein and heart disease over the period from 1969 to 1995 has been re-examined (Table 1). The correlations between milk protein consumption and heart disease become progressively weaker over the period examined, particularly after the mid 1970s. Thus, although it could be argued that there was a significant relationship between the consumption of milk protein and deaths due to heart disease in the late 1960s and 1970s, this relationship is no longer found for the 1990s.

McLachlan (2001) has proposed that the consumption of beta-casein A1 is a major risk factor for IHD based on per-capita consumption data for beta-casein A1 and deaths due to this disease. McLachlan (2001) found a positive correlation ($r^2 = 0.86$) between the per-capita consumption

TABLE 1: Correlation coefficients (r) between the occurrence of deaths from heart disease and consumption of milk protein, 1960-1995. IHD rates are correlated against *per capita* milk consumption for each previous year. N=40 (Countries), values >0.3 (bold) are significant at p<0.05. Data used to construct this table are from FAO (2001) and WHO (2001) databases.

	Year, deaths due to ischaemic heart disease																										
Year, Milk consumption	**1969**	**1970**	**1971**	**1972**	**1973**	**1974**	**1975**	**1976**	**1977**	**1978**	**1979**	**1980**	**1981**	**1982**	**1983**	**1984**	**1985**	**1986**	**1987**	**1988**	**1989**	**1990**	**1991**	1992	1993	1994	1995
1961	**0.77**	**0.78**	**0.76**	**0.79**	**0.76**	**0.77**	**0.76**	**0.75**	**0.71**	**0.72**	**0.73**	**0.73**	**0.76**	**0.71**	**0.70**	**0.67**	**0.65**	**0.58**	**0.56**	**0.52**	**0.41**	**0.39**	**0.39**	0.27	0.23	0.20	0.04
1962	**0.78**	**0.78**	**0.75**	**0.77**	**0.73**	**0.75**	**0.74**	**0.73**	**0.68**	**0.70**	**0.71**	**0.71**	**0.74**	**0.69**	**0.68**	**0.65**	**0.63**	**0.55**	**0.54**	**0.50**	**0.39**	**0.37**	**0.37**	0.25	0.21	0.18	0.02
1963	**0.78**	**0.78**	**0.75**	**0.77**	**0.73**	**0.75**	**0.74**	**0.73**	**0.68**	**0.70**	**0.71**	**0.71**	**0.74**	**0.69**	**0.68**	**0.65**	**0.63**	**0.55**	**0.54**	**0.50**	**0.39**	**0.37**	**0.37**	0.25	0.21	0.18	0.02
1964	**0.76**	**0.76**	**0.74**	**0.76**	**0.73**	**0.75**	**0.73**	**0.73**	**0.68**	**0.71**	**0.71**	**0.71**	**0.74**	**0.68**	**0.68**	**0.65**	**0.64**	**0.56**	**0.55**	**0.50**	**0.39**	**0.37**	**0.37**	0.24	0.21	0.18	0.01
1965	**0.76**	**0.76**	**0.74**	**0.76**	**0.74**	**0.76**	**0.74**	**0.74**	**0.69**	**0.71**	**0.72**	**0.71**	**0.74**	**0.68**	**0.68**	**0.65**	**0.64**	**0.56**	**0.55**	**0.50**	**0.39**	**0.37**	**0.37**	0.23	0.20	0.17	0.01
1966	**0.76**	**0.76**	**0.73**	**0.76**	**0.74**	**0.76**	**0.74**	**0.73**	**0.69**	**0.71**	**0.72**	**0.71**	**0.74**	**0.68**	**0.67**	**0.65**	**0.64**	**0.55**	**0.55**	**0.50**	**0.38**	**0.36**	**0.36**	0.23	0.20	0.17	0.01
1967	**0.72**	**0.72**	**0.70**	**0.73**	**0.70**	**0.73**	**0.71**	**0.71**	**0.67**	**0.69**	**0.69**	**0.69**	**0.73**	**0.67**	**0.66**	**0.64**	**0.64**	**0.56**	**0.55**	**0.50**	**0.39**	**0.38**	**0.37**	0.23	0.21	0.18	0.02
1968	**0.75**	**0.75**	**0.72**	**0.75**	**0.72**	**0.75**	**0.72**	**0.72**	**0.68**	**0.70**	**0.71**	**0.71**	**0.74**	**0.68**	**0.66**	**0.65**	**0.64**	**0.56**	**0.55**	**0.50**	**0.39**	**0.37**	**0.37**	0.23	0.20	0.17	-0.01
1969	**0.74**	**0.74**	**0.72**	**0.75**	**0.72**	**0.75**	**0.72**	**0.72**	**0.68**	**0.70**	**0.71**	**0.70**	**0.74**	**0.68**	**0.67**	**0.65**	**0.64**	**0.56**	**0.56**	**0.51**	**0.39**	**0.38**	**0.38**	0.24	0.20	0.17	0.00
1970		**0.73**	**0.71**	**0.72**	**0.70**	**0.73**	**0.71**	**0.71**	**0.67**	**0.70**	**0.71**	**0.71**	**0.74**	**0.68**	**0.67**	**0.65**	**0.65**	**0.57**	**0.57**	**0.52**	**0.40**	**0.38**	**0.39**	0.25	0.21	0.17	0.00
1971			**0.71**	**0.73**	**0.71**	**0.73**	**0.71**	**0.71**	**0.68**	**0.70**	**0.71**	**0.70**	**0.73**	**0.67**	**0.65**	**0.64**	**0.64**	**0.56**	**0.55**	**0.50**	**0.38**	**0.37**	**0.36**	0.22	0.18	0.15	-0.03
1972				**0.73**	**0.71**	**0.74**	**0.72**	**0.72**	**0.68**	**0.70**	**0.70**	**0.71**	**0.74**	**0.68**	**0.66**	**0.65**	**0.64**	**0.56**	**0.56**	**0.50**	**0.38**	**0.37**	**0.37**	0.24	0.20	0.17	-0.01
1973					**0.72**	**0.74**	**0.71**	**0.71**	**0.68**	**0.70**	**0.71**	**0.70**	**0.73**	**0.66**	**0.65**	**0.64**	**0.63**	**0.55**	**0.55**	**0.49**	**0.37**	**0.35**	**0.35**	0.22	0.17	0.14	-0.04
1974						**0.74**	**0.71**	**0.71**	**0.69**	**0.70**	**0.72**	**0.70**	**0.73**	**0.67**	**0.66**	**0.64**	**0.64**	**0.56**	**0.56**	**0.50**	**0.37**	**0.35**	**0.35**	0.22	0.17	0.14	-0.05
1975							**0.72**	**0.73**	**0.69**	**0.71**	**0.72**	**0.72**	**0.75**	**0.69**	**0.68**	**0.67**	**0.65**	**0.59**	**0.58**	**0.53**	**0.40**	**0.39**	**0.39**	0.26	0.22	0.19	0.02
1976								**0.74**	**0.70**	**0.73**	**0.73**	**0.73**	**0.76**	**0.70**	**0.69**	**0.67**	**0.66**	**0.60**	**0.59**	**0.54**	**0.41**	**0.40**	**0.41**	0.28	0.24	0.21	0.03
1977									**0.69**	**0.72**	**0.72**	**0.72**	**0.74**	**0.69**	**0.69**	**0.66**	**0.65**	**0.60**	**0.58**	**0.52**	**0.40**	**0.38**	**0.39**	0.26	0.24	0.20	0.03
1978										**0.69**	**0.69**	**0.69**	**0.71**	**0.66**	**0.66**	**0.64**	**0.63**	**0.58**	**0.57**	**0.50**	**0.38**	**0.37**	**0.38**	0.24	0.23	0.20	0.03
1979											**0.69**	**0.69**	**0.72**	**0.66**	**0.65**	**0.63**	**0.62**	**0.57**	**0.56**	**0.48**	**0.35**	**0.35**	**0.36**	0.23	0.22	0.19	0.02
1980												**0.68**	**0.70**	**0.64**	**0.63**	**0.62**	**0.61**	**0.56**	**0.54**	**0.46**	**0.33**	**0.32**	**0.34**	0.19	0.19	0.16	-0.01
1981													**0.72**	**0.67**	**0.66**	**0.64**	**0.63**	**0.58**	**0.57**	**0.49**	**0.36**	**0.35**	**0.37**	0.22	0.21	0.18	0.02
1982														**0.67**	**0.63**	**0.63**	**0.61**	**0.56**	**0.54**	**0.45**	**0.31**	0.29	**0.31**	0.16	0.14	0.11	-0.06
1983															**0.63**	**0.62**	**0.60**	**0.55**	**0.53**	**0.44**	**0.30**	0.29	**0.31**	0.17	0.15	0.12	-0.07
1984																**0.61**	**0.59**	**0.53**	**0.52**	**0.43**	0.28	0.27	**0.30**	0.15	0.14	0.12	-0.08
1985																	**0.62**	**0.57**	**0.56**	**0.48**	**0.34**	**0.33**	**0.36**	0.23	0.21	0.18	0.00
1986																		**0.56**	**0.55**	**0.46**	**0.33**	**0.33**	**0.36**	0.21	0.20	0.17	-0.01
1987																			**0.59**	**0.51**	**0.38**	**0.37**	**0.40**	0.25	0.24	0.21	0.03
1988																				**0.53**	**0.41**	**0.40**	**0.42**	0.28	0.27	0.23	0.07
1989																					**0.41**	**0.38**	**0.40**	0.26	0.23	0.19	0.03
1990																						**0.31**	**0.33**	0.17	0.14	0.10	-0.06
1991																							**0.32**	0.17	0.14	0.10	-0.05
1992																								0.11	0.09	0.06	-0.04
1993																									0.21	0.19	0.10
1994																										0.11	-0.01
1995																											0.00

of beta-casein A1 and IHD mortality. In contrast to the findings of Elliott *et al*. (1999), where the inclusion of the beta-casein B variant (beta-casein A1 + B) produced a stronger correlation with IDDM than beta-casein A1 alone, this was not found by McLachlan (2001), where the inclusion of beta-casein B weakened the correlation with IHD. This result is difficult to explain, because the only difference between beta-casein B and beta-casein A1 is at position 122 in the protein sequence, where a serine in beta-casein A1 is replaced by an arginine in beta-casein B. Both beta-casein A1 and B have a histidine at position 67, thought to be important for the release of BCM-7.

McLachlan (2001) found that excluding cheese consumption from the analysis improved the correlation of IHD with beta-casein A1 consumption ($r^2 = 0.71$ increased to $r^2 = 0.86$). The argument for the exclusion of cheese was based on the observation that BCM-7 was not reported to be found in some cheese varieties and that perhaps intact beta-casein is important for biological activity. However, substantial amounts of intact beta-casein or large fragments of the protein are to be found in most cheese varieties (Fox *et al*., 2000) .

There is at present no evidence outside these correlations to support a link between consumption of milk and heart disease, and since even the milk protein-based correlations have disappeared over time, there is no reason to suppose that selection of single variant milks would have any effect at all on heart disease.

CONCLUSION

There is currently no compelling evidence to indicate that the consumption of beta-casein A1 contributes to the development of diabetes. The initial speculative evidence for a correlation between the occurrence of heart disease and the consumption of beta-casein A1 does not hold upon more detailed analysis. Consumption of milk protein, and therefore beta casein A1, has no effect on mortality due to heart disease.

Although there is the potential for a small minority of the population to have an adverse reaction to the consumption of milk protein in general and its constituents (as is the case with all foods), it is dangerous to make generalisations that relate to the population as a whole. Milk protein continues to be an important nutritional component in a healthy diet.

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