

A1 Beta-casein, Type 1 Diabetes and Links to other Modern Illnesses

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Abstract

The role of milk and milk proteins in relation to human health remains controversial. However, there is a large body of evidence, reviewed in this paper, specifically linking A1 beta-casein to a range of illnesses.

A1 beta-casein is produced only by cattle of European origin. The proportion of European cattle producing A1 beta-casein varies by breed and country. High levels are found in many parts of northern Europe and also other parts of the world where particular breeds of European origin predominate. Cattle that produce A2 and not A1 beta-casein are known as A2 cattle. A2 beta-casein was the original variant.

A1 beta-casein releases bovine beta-casomorphin7 (BCM7) on digestion. The amount and stability of BCM7 that is cleaved from A1 beta-casein is linked to the presence and levels of various enzymes, in particular dipeptidyl peptidase 4. BCM7 is a strong opioid.

There are seven strands to the evidence linking A1 beta-casein and BCM7 to Type 1 diabetes. These include particularly strong correlations amongst developed countries between A1 beta-casein intake and Type 1 diabetes incidence ($r^2=0.84$, $p<0.00001$). Supporting evidence comes from biochemistry (structure of A1 beta-casein and cleavage of BCM7), pharmacology (opioid characteristics and binding affinities of BCM7), animal trials (NOD mice and BB rats), immunology (people with Type 1 diabetes have enhanced levels of antibodies to beta-casein and in particular A1 beta-casein), and human studies (high milk intake in children linked to high incidence of diabetes). A plausible auto immune mechanism relates to the homology between an amino acid sequence in both BCM7 and the GLUT2 glucose transporting molecule produced within the pancreas.

Countries with high levels of Type 1 diabetes are the same countries that have high levels of heart disease ($r^2=.74$, $p<0.001$). This strongly suggests linked factors of causation. A1 beta casein intake also correlates strongly with heart disease (r^2 up to 0.86, $p<0.001$). Supporting evidence includes an animal trial with rabbits, and LDL oxidation by BCM7.

BCM7 has also been linked to symptoms of autism and schizophrenia (animal and human trials) and BCM7 has been widely reported in urine of autistic people.

Intestinal and stomach permeability appears to be a common feature of all conditions where A1 beta-casein has been implicated. This permeability occurs in all babies and can occur for a range of health reasons in children and adults.

The debate about A1 and A2 beta-casein has largely been occurring in NZ and Australia. NZ has been typing all breeding bulls for A1/A2 status for approximately 10 years, and the national herd is drifting towards A2. However this is mainly because of a serendipitous association between A2 cattle and particular characteristics that are sought within the NZ breeding system (high protein production efficiency rather than milk production per cow). The national herd could convert to A2 over about a 10 year period. No other countries are routinely typing their bulls for A1/A2 status.

Although the scientific and medical evidence is published in peer reviewed journals it has not been widely reviewed as an integrated body of evidence. This paucity is linked to the breadth of encompassed disciplines. Further, much of the early research was undertaken from within the mainstream dairy industry, particularly in NZ. This industry has subsequently chosen to regard the A1 versus A2 issue as a threat rather than an opportunity, and has mounted a sophisticated public relations and political campaign that A1 versus A2 is a non issue.

Introduction

Mainstream medical opinion holds that milk is a nutritious food of benefit to most people. However, an extensive body of evidence now exists that one particular protein, called A1 beta-casein, which is present in the milk of some but not all cows, is linked to Type 1 diabetes, heart disease and symptoms of autism and schizophrenia. It may also be implicated in an additional range of auto-immune conditions. This protein is also linked to milk intolerance in some people.

Milk that does not contain A1 beta-casein, but contains the alternate A2 beta casein, is known as A2 milk. Cows that produce beta-casein that is solely of the A2 type are known as A2 cows.

If A1 beta-casein is indeed causally related to some or all of these conditions, then it does not mean that at-risk individuals need to avoid milk and milk products. But it does mean that the milk products should come from A2 cows.

The distinguishing amino-acid sequence that characterises A1 beta-casein is essentially unique to some European cattle.¹ African and Asian cattle, unless carrying some European genes, are A2. Goats, sheep, yaks and camels all produce milk that is of the A2 type. Human beta-casein is also of the A2 type as defined by the relevant amino-acid sequence.²

It is apparent that the A1 mutation in European cattle first appeared some thousands of years ago.³ The proportion of modern European cattle producing A1 beta-casein varies by breed and country. Currently, high levels are found in many parts of northern Europe, and also wherever particular northern European cattle breeds predominate. It is probable but not proven that the level of A1 beta-casein in milk has increased over the last century

as the Friesian/Holstein (black and white) breeds have become predominant in many countries. It is also relevant that milk itself has become a much more important part of human diets within the last 100 years

There are multiple strands to the evidence linking A1 beta-casein and BCM7 to Type 1 diabetes. These include epidemiology, biochemistry, pharmacology, immunology, animal trials, and human studies. This evidence will be reviewed within this paper.

The major focus within this paper will be on Type 1 diabetes. However, it is important that, both as contextual background and also in understanding the overall situation, there is recognition that A1 beta-casein is also implicated in other disease conditions. Also relevant is that intestinal and stomach permeability may be a common feature of all conditions where A1 beta-casein has been implicated. This permeability occurs in all newborn babies and can occur for a range of health reasons in children and adults.

To date, the debate about A1 and A2 beta-casein has largely been occurring in NZ and Australia. NZ has been typing all breeding bulls for A1/A2 status for approximately 10 years, and the national herd is now slowly drifting towards A2. However much of this drift is because of a serendipitous association between A2 cattle and particular characteristics that are sought within the NZ breeding system (high protein production efficiency rather than milk production per cow). There is no evidence that such a drift to A2 is occurring elsewhere in the world. In most countries the national herds could convert to A2 over about a 10 year period, or more rapidly using new technologies of sex-selected semen. However, no other countries apart from New Zealand are routinely typing their bulls for A1/A2 status.

Although the relevant scientific and medical evidence (more than 100 relevant papers) is published in peer reviewed journals, it has not been widely reviewed as an integrated body of evidence.⁴ This paucity is linked to the breadth of encompassed disciplines. Most scientists do not read across all of these disciplines and hence the richness of the overall evidence has been missed. Further, much of the early research was undertaken from within the mainstream dairy industry, particularly in NZ. This industry has subsequently chosen to regard the A1 versus A2 issue as a threat rather than an opportunity, and has mounted a sophisticated public relations and political campaign that A1 versus A2 is a non issue. This campaign has included non disclosure, misinformation, and obfuscation.

The issue of A1 beta-casein is therefore not only a story about the medical evidence. It is also very much a story about how that evidence has been and is being manipulated.

Where it all started

The scientist who deserves great credit for the initial work and key insights relating to A1 beta-casein and Type 1 diabetes is clearly Professor Bob Elliott, who is with us today as a commentator on this paper. Bob Elliott knew from his work in Samoa that there was a more than 10 fold difference in the incidence of Type 1 diabetes in Samoan children living in New Zealand compared to Samoan children living in Samoa. It was obvious that the factor had to be environmental. Bob Elliott also knew that Samoan children in Samoa drank very much less milk than Samoan children in New Zealand, and milk

therefore stood out as an obvious candidate. In addition, Bob Elliott also knew from his own previously published work that casein, or an unidentified component thereof, was diabetogenic in rodents.⁵ However, he also knew that the Masai people in Kenya drink large amounts of milk but that childhood diabetes is extremely rare amongst those who still live this traditional lifestyle. In 1993 he therefore approached the NZ Dairy Research Institute, asked to speak to a milk biochemist, and asked the key insightful question: *Are there any protein differences in the milk that the Masai people drink compared to the milk that is drunk in New Zealand?* The answer, from NZDRI scientist Dr Jeremy Hill, was that there is indeed a difference in the beta casein protein. The milk the Masai people were drinking contained beta casein that was totally A2 whereas that drunk in NZ contained major amounts of the A1 beta casein. It was that question and response that first led to the hypothesis that A1 beta-casein might be implicated in Type 1 diabetes, although at that stage the mechanisms by which it might be occurring were totally unclear. Indeed Jeremy Hill has subsequently said that he always saw it as a 'long shot'.⁶

One of the first steps in testing the hypothesis was to undertake trials with rodents (this time NOD mice). The trials were funded by the New Zealand Dairy Board and the National Children's Health Research Foundation (a Rotary Charity). The mice were fed a range of diets, including A1 beta-casein, A2 beta casein, or a combination of the two. The results showed that 47% of those fed A1 beta-casein developed Type 1 diabetes whereas none of those fed A2 beta-casein developed diabetes. In another group fed a milk formula containing both A1 and A2 casein there was an intermediate 19% level of diabetes. The differences between the A1 and A2 diets were very highly significant ($p < 0.001$). This indicates that the chance of falsely getting a result like this when there is no underlying cause is less than 1 in 1000. Supplying naloxone (an opioid antagonist) in the drinking water of another group of animals fed A1 beta-casein prevented development of diabetes.

These results were first reported in a patent specification (International Number PCT/NZ95/0014) by the two sponsoring organisations. They were also published in a special publication of the International Dairy Federation.⁷

There are two potential criticisms of these trials. The first is that the investigators were not 'blinded' as to which mice were receiving which treatment. Blinding is a means of protecting against either fraud or accidental bias, although the measures used to determine Type 1 diabetes leave minimal scope for subjective bias. The second criticism is that the results were not published in an international journal with wide readership.

These initial results have on occasions been described as 'preliminary' and they led to a much larger trial subsequently being set up. I will return to this subsequent trial later in this paper, but first I want to address some of the epidemiology and biochemistry of A1 beta-casein.

Epidemiology

One of the startling characteristics of Type 1 diabetes is the huge difference in incidence between different countries.⁸ Worldwide, the incidence varies by a factor of at least 300, with high levels being found in developed countries with western lifestyles and diets. But even between highly developed Western-type countries the incidence varies more than

tenfold.⁹ More than 65,000 new cases are recorded each year in children under the age of 14.

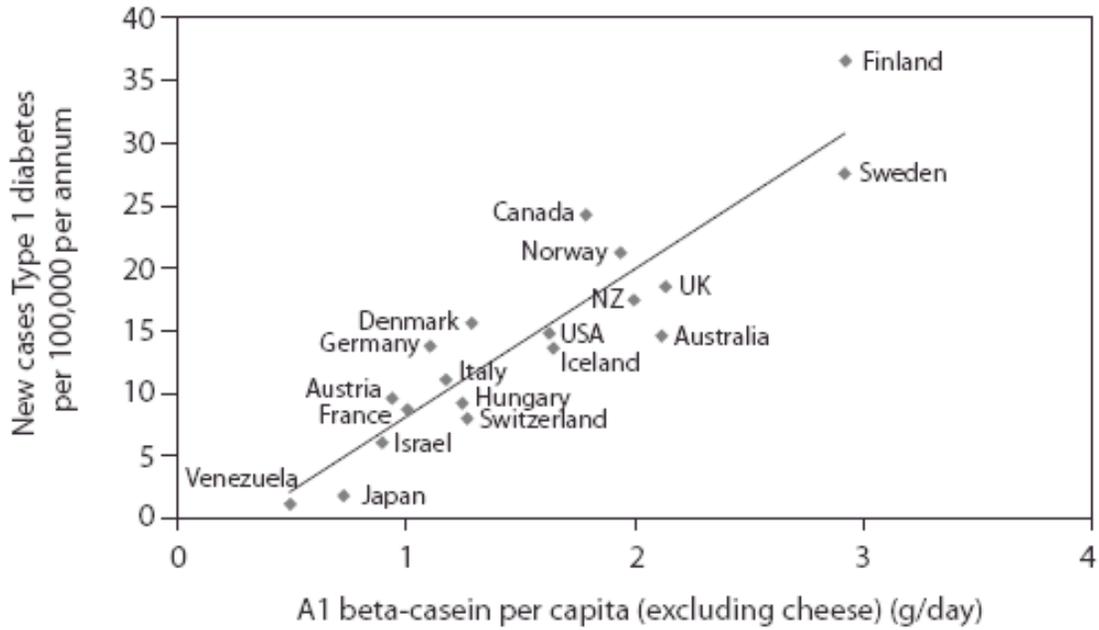
Analysing the relationship between diabetes incidence at the country level and intake of A1 beta-casein depends on both accurate ascertainment of diabetes incidence levels, and accurate knowledge not only of milk intake but of the A1 beta-casein level within that milk. Initially there were difficulties getting reliable data both on incidence level and intake of A1 beta-casein. But by 1999 Bob Elliott and colleagues had a paper published in the international journal *Diabetologia* showing remarkable correlation between Type 1 diabetes incidence and A1 beta-casein incidence for 10 developed countries.¹⁰ However, the most comprehensive paper came somewhat later when more information was available. Authored by Dr Murray Laugesen and Bob Elliott, it was published in the NZ Medical Journal in 2003.¹¹

Laugesen and Elliott found extremely strong relationships at the country level for 19 developed countries between A1 beta-casein and Type 1 diabetes incidence during the period 1990-1994 ($r=0.92$, $p<0.00001$) (Figure 1). They also compared Type 1 diabetes incidence with more than 100 other dietary and lifestyle factors but could find nothing that gave comparable correlations. By squaring the correlation coefficient (0.92^2) we can observe that A1 beta-casein can 'explain' some 84% of the variation between countries. This is a remarkably high figure.

Given that the intake of A1 beta casein is linked both to the intake of milk and the ratio of A1;A2 beta-casein, it is logical to expect that if the A1 beta-casein relationship is causal then there will also be a correlation between milk protein intake and Type 1 diabetes. This is indeed the case (Figure2) but the much lower r^2 value of 0.47 indicates that it is A1 beta –casein that is the important relationship, and that total protein is being dragged along by the cross correlation.. Similarly, given that A2 beta-casein intake is in part determined by total milk intake, and hence likely to be cross correlated to A1 beta-casein intake, one would expect to see a relationship between diabetes incidence and A2 beta-casein. This is indeed the case but with an r^2 of only 0.22.

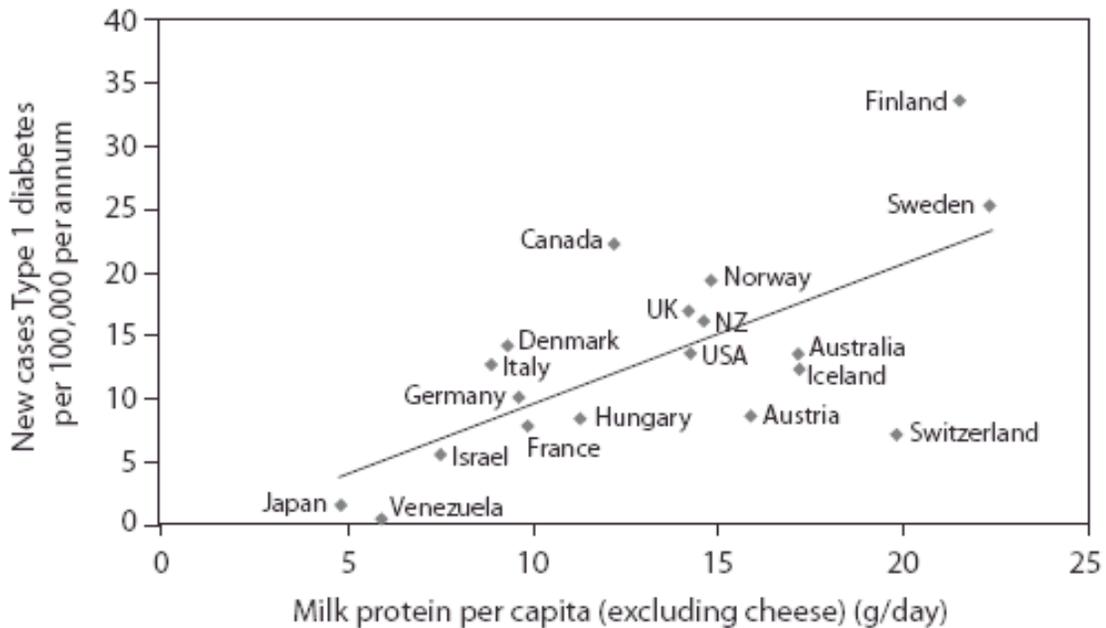
Within epidemiology there is ongoing debate as to the weight which should be placed on between-country analyses, which are sometimes called ecological studies. However, it is notable that many major health discoveries have their origins in ecological studies.¹² The potential problem is that it is possible for spurious correlations to occur. It could be that A1 beta-casein intake is strongly correlated to some other factor that is the causal factor. So a high correlation coefficient, even if statistically significant, is not usually regarded as 'proof' of causality. But if there is some other factor that is causing this between-country variation, and which is also linked to A1 beta –casein intake, then what could that be?

Figure 1. Incidence of Type 1 diabetes and intake of A1 beta-casein excluding cheese



(Data from Laugesen and Elliott 2003)

Figure 2. Incidence of Type 1 diabetes and intake of milk protein excluding cheese



(Data from Laugesen and Elliott 2003)

One of the key features of the Laugesen and Elliott analyses is that apart from Venezuela they restricted themselves to developed countries. This removed many of the potential confounding factors. (In fact removing Venezuela from the analysis –and this was tested by Laugesen and Elliott- does not change the story in any way). And they also tested for everything else they could possibly think of. It is indeed reasonable to dismiss a relationship that has modest statistical significance as being potentially spurious, but it is much more difficult to dismiss a relationship with a p-factor of less than 0.00001, and for which there is no alternative explanation.

Since the publication of my book in September 2007¹³ Dr Tony Merriman from Otago University has criticised me on radio and in the popular media for placing too much emphasis on this epidemiology. His argument goes along the lines that the between-country differences in Type 1 diabetes can be explained by latitudinal effects influencing exposure to UV light and subsequent impact on vitamin D synthesis. It is indeed true that there is a cross correlation between latitude and intake of A1 beta casein. This is because many of the countries with high intake of A1 beta-casein are also high latitude countries. But there are plenty of exceptions. And the Laugesen and Elliott evidence shows that the explanatory power of latitude ($r^2 = 0.65^2 = 0.42$) is only half that of A1 beta-casein. In the case of sunlight there was no meaningful relationship at all (M. Laugesen, pers comm). So it is possible that the modest latitude correlation is being dragged along by its association with A1 beta-casein but the evidence does not support the converse notion that the strong A1 beta casein relationship is being dragged along by the modest latitudinal relationship.

I would not want this debate about A1 beta-casein versus latitude to be taken as an inference that Vitamin D is not relevant to Type 1 diabetes. Almost certainly Type 1 diabetes is a multi-factorial disease, and I therefore remain very open to the notion that Vitamin D is an important part of the overall story. In particular, I note that there is evidence that Type 1 diabetes typically reaches the clinical stage during winter when UV radiation is lowest, and also that diabetics may have lower circulating levels of vitamin D in their bloodstream.¹⁴ But what I do say very strongly, is that neither latitude nor sunlight exposure can be used to explain away the relationships that we have between Type 1 diabetes incidence and intake of A1 beta-casein.

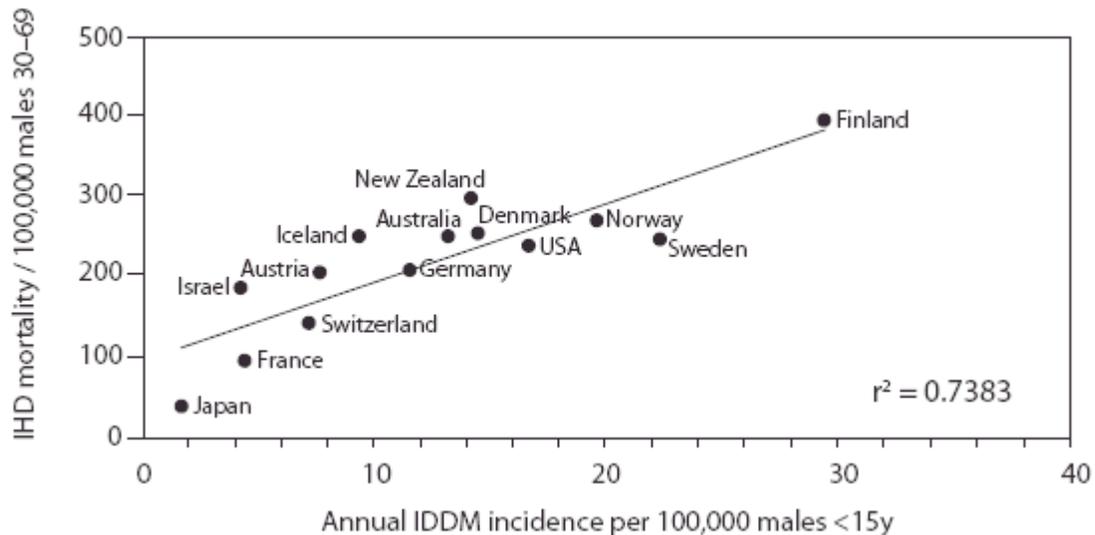
Epidemiological links to heart disease

At an early stage of Bob Elliott's work his proposals were forwarded to Dr Corran McLachlan for peer review. McLachlan's expertise was more in relation to heart disease than diabetes. What immediately struck McLachlan was that the countries with high Type 1 diabetes were also the countries that he knew from his own work to be countries with high levels of heart disease (Figure 3). This is a remarkable graph. It suggests from a public health perspective, and at a population level, that there are common factors that influence the level of both Type 1 diabetes and heart disease. Of course medical scientists and doctors have all known for a long time that at the level of individuals there are strong links between Type 2 diabetes and heart disease, but this graph is telling us something quite different. It is not saying at the individual level that people who have Type 1 diabetes will get heart disease or vice versa. But at the population level the two diseases occur together. Nor can we dismiss this relationship as simply being a collective

of many modern-world environmental factors, because we can see from this figure that it is only some developed countries that have a high incidence of these diseases. This graph was only published as a letter in the NZ Medical Journal¹⁵ and apart from in my book has received scant exposure in the medical community. It is a hugely important graph.

Figure 3 IHD death rate 1985 for males aged 30-69vs IDDM incidence for males aged <15

(Reproduced from NZ Medical Journal 116 (1170))



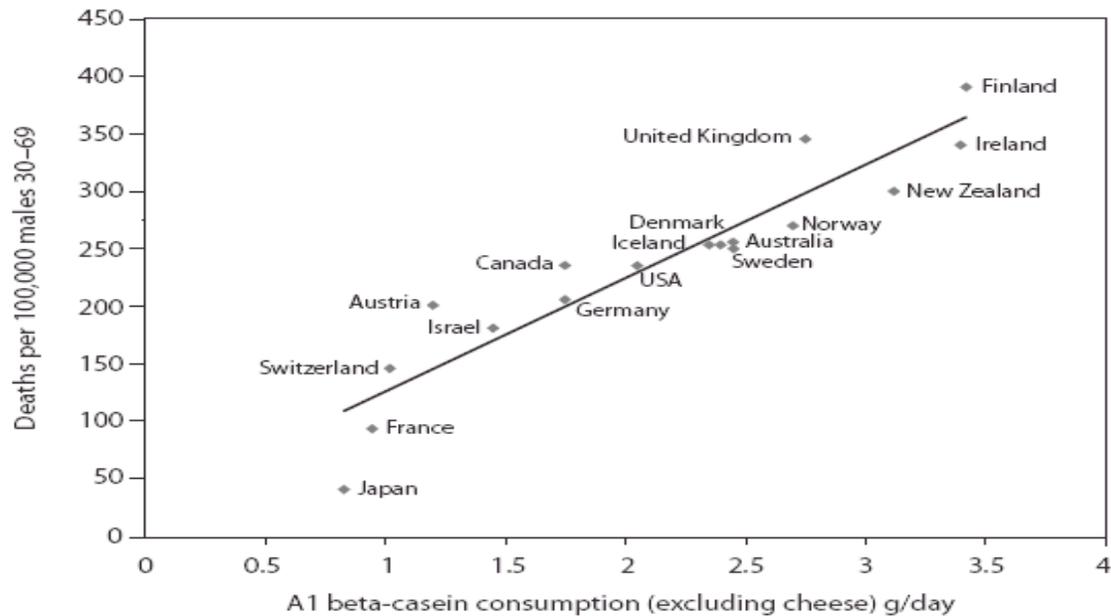
Subsequently McLachlan explored whether, given that heart disease and Type 1 diabetes occur in the same populations, and given that Type 1 diabetes is linked to A1 beta-casein, is there also a direct link between heart disease and intake of A1 beta-casein? The answer, at the population level is a very strong ‘yes’ (Figure 4).¹⁶ McLachlan’s work was subsequently confirmed by Laugesen and Elliott.¹⁷

I do not have time here to further develop the heart disease epidemiology in this paper, except to mention that for many in this audience who are working with Type 2 diabetes, there will be a very obvious question. Given that Type 2 diabetes and heart disease are very closely linked at the individual level through metabolic syndrome, does this suggest a potential link between Type 2 diabetes and A1 beta-casein. At this stage the answer has to be that we do not know. The work has not been done. But I do draw attention to a 2005 paper in the European Journal of Clinical Nutrition, authored by Danish scientists, and titled ‘High intakes of milk, but not meat, increase s-insulin and insulin resistance in 8-year-old boys’.¹⁸ They found that with high milk intakes both s-insulin and insulin resistance approximately doubled. Also, research with dairy cattle has shown that casomorphins injected into the digestive system reduce the subsequent insulin responses to glucose infusions.¹⁹

It is now time to move away from the epidemiology, because epidemiology is just one of the many strands of relevant evidence that build up the rich picture of Type 1 diabetes

and A1 beta casein. Some of those who argue against the A1/A2 hypothesis claim that the evidence is essentially limited to epidemiology. Do not believe it.

Figure 4. Death rates from ischaemic heart disease in males aged 30-69 in 1985
(Redrawn from McLachlan (2001) *Medical Hypotheses* 56(2):265



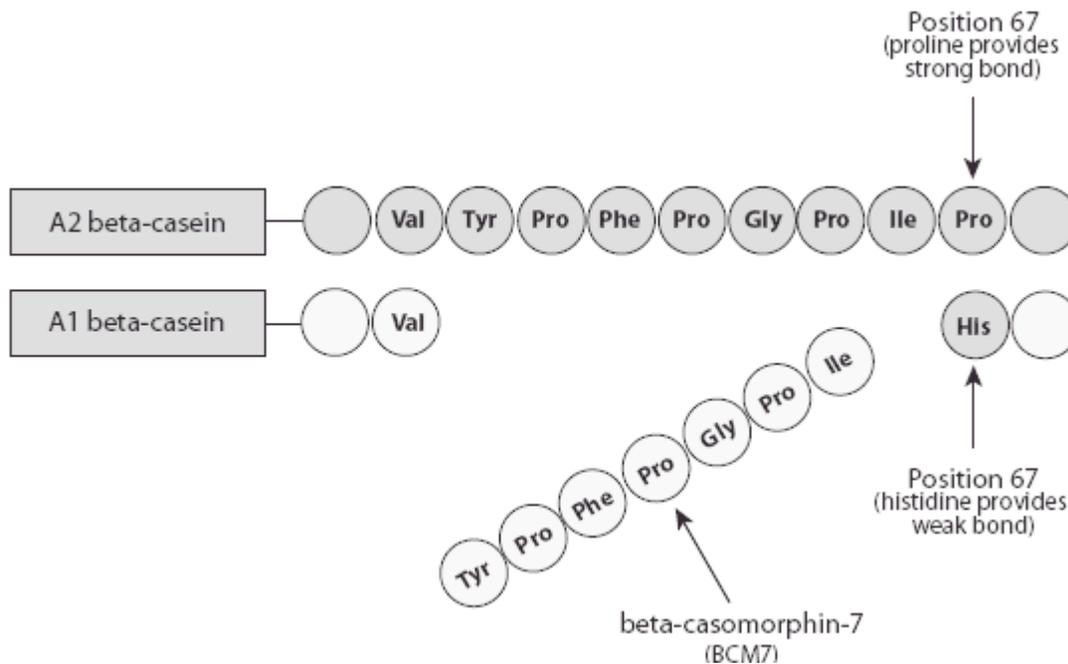
Biochemistry

The only difference between bovine A1 beta-casein and A2 beta casein is one amino acid out of 209. Whereas A2 beta-casein has a proline at position 67, A1 beta-casein has a histidine. However, this can have a profound effect on the release during digestion of a particular peptide (protein fragment). Specifically, the histidine at position 67 in A1 beta-casein facilitates the release of the opioid peptide beta-casomorphin7 (BCM7) upon digestion, whereas the proline acts as a major barrier to this release.^{20, 21}

BCM7 is particularly stable on account of three of its seven amino acids being prolines. However, it is evident that BCM7 can be degraded by the enzyme dipeptidyl peptidase 4 (DPP4) that is found on cell surfaces within mesenteric tissues.²² It is also apparent that in many people the intestinal lining combined with the presence of DPP4 is sufficient to prevent the BCM7 from passing through in to the bloodstream. However, there is also evidence that in people who for a range of reasons have 'leaky guts' it is possible for BCM7 to pass through.^{23, 24}

There are many reasons why individuals can suffer from leaky guts. Newborn babies have permeable intestines to allow macro molecules in colostrum to pass through. In later life, permeability can arise, either short term or long term, from a range of health conditions such as Coeliac disease, ulcerative colitis, Crohn's disease, and stomach ulcers. Of particular relevance in relation to stomach ulcers is that the historical treatment of ulcers with a high milk diet (such as the Sippy and similar diets) was shown to lead to a very high death rate from heart disease relative to other diets.²⁵

Figure 5. Formation of beta-casomorphin.



Scientists working on Type 2 diabetes will be aware that there are a several clinical trials underway looking at whether drugs that reduce DPP4 production might lead to reduced insulin levels in the blood. An unintended and potentially important side effect could be reduced ability to breakdown BCM7.

Pharmacology

Bovine BCM7 is a strong opioid.^{26, 27} It can be counteracted by administration of naloxone but BCM7 has very strong binding affinity and ten times more naloxone is required to counteract a molecule of BCM7 than is required to counteract a molecule of ordinary morphine. Animal trials have shown that in rodents BCM7 easily crosses the blood brain barrier and leads to bizarre behaviour patterns akin to those observed in autism and schizophrenia.^{28, 29, 30} Several groups have shown that autistic humans typically excrete BCM7 in their urine.^{31, 32, 33} This can only have come from milk. Humans milk can also release BCM7 but apparently only in small quantities. Also, human BCM7 is different to bovine BCM7 with the Pro-Gly sequence (positions 4 and 5) replaced by Val-Glu. Human BCM7 is a much weaker opioid than bovine BCM7.

Immunology

There is a broad range of evidence suggesting that persons with Type 1 diabetes have enhanced levels of antibodies to beta-casein.^{34, 35} How this should be interpreted is open to debate. It is possible that this is simply a manifestation of Type 1 diabetics being particularly sensitive to antibody reactions. However research by German scientists has shown that for persons with Type 1 diabetes the ratio of A1 to A2 beta-casein antibodies is higher than for case controls (p<0.001).³⁶ In addition to the literature published in scientific journals, the NZ Dairy Board (now Fonterra) has a patent linking Type 1 diabetes with A1 beta-casein (PCT/NZ95/0014) that presents evidence showing that

IgG(1+3) antibodies discriminate against A1 beta-casein relative to A2 beta-casein (p=0.003).

Finding the specific mechanism

Italian scientist Paulo Pozzilli has pointed out in a patent application (US patent 6,750,203) that there is a sequence of four amino acids at the end of the BCM7 molecule (Pro-Gly-Pro-Ile) that is identical to a sequence within the GLUT2 molecule, which is the glucose transporting molecule inside insulin-producing cells in the pancreas. He has hypothesised that antibodies to BCM7 are attacking through cross-reactivity the GLUT2 molecule and thereby destroying the insulin-producing cells. There is no proof that Pozzilli is correct, but it is a plausible hypothesis that brings together the known biochemistry, pharmacology and immunology into a coherent hypothesis. Other authors have pointed out that sequence homologies exist between beta-casein and several pancreatic beta-cell molecules.³⁷

Human trials

There have been no human trials specifically comparing the diabetogenic effects of A1 beta casein and A2 beta-casein. However, Finnish scientists led by Suvi Virtanen have monitored milk consumption by the siblings of diabetic children.³⁸ These siblings were non-diabetic at the start of the monitoring but were considered on account of specific genetic factors to be high risk. They found that those drinking more than 540ml of milk per day were more than five times as likely to become diabetic than those drinking less than this amount (p<0.01). There is further preliminary data from Finland as part of the TRIGR program that babies aged 6-8 months fed casein hydrolysate rather than standard infant formula are significantly less likely to develop 'positivity for islet cell antibodies (p=0.02) and at least one autoantibody (p=0.03)'.³⁹

More on animals

There is one paper that has been widely used to discredit the link between A1 beta-casein and Type 1 diabetes. It is a multi country trial using NOD mice in NZ and Britain, and BB rats in Canada. The diets were supplied by the NZ Dairy Research Institute (NZDRI) (then part of the NZ Dairy Board, subsequently part of Fonterra). The results were published in *Diabetologia*.⁴⁰

There is a huge problem with this trial that was never acknowledged in the published paper. It was known both to the supplier of the diets (NZDRI), and to at least four of the authors (one of whom was from NZDRI and remains a senior Fonterra employee) that half of the A2 diets were contaminated with large amounts of BCM7. And this was known well over a year before the paper was submitted for publication. The detailed documentation for the above statements is provided in my book.⁴¹ What is also remarkable is the way that three of the authors of this paper have subsequently argued in other forums that, given the results of this trial, a link between A1 beta-casein and Type 1 diabetes is unlikely.^{42, 43} In fact, the results of this trial, once the contaminated diets are removed, are broadly supportive of such a link with statistically significant results for the BB rats.

I regard the issue of scientific integrity involved in this saga as one which the diabetes research community has to take up. My own attempts to get *Diabetologia* to investigate

this issue have been unsuccessful. The documentation, both in regard to the contamination and the pre publication knowledge of the authors concerning this contamination, is irrefutable.

Some other health conditions linked to A1 beta-casein

The epidemiology of heart disease was introduced earlier in this paper. Other evidence relevant to heart disease includes Australian evidence that rodents fed A1 beta casein are susceptible to the development of arterial plaque whereas this does not occur with A2 beta-casein.⁴⁴ Also, European research has shown that BCM7 can act as a catalyst in the oxidation of LDL.⁴⁵

Key evidence linking BCM7 to symptoms of autism and schizophrenia (animal and human trials) has also been introduced earlier in this paper in relation to the biochemistry and pharmacology of BCM7. However, the detailed issues linking symptoms of autism and schizophrenia with BCM7 are far too broad to be covered here.

There are additional autoimmune diseases for which there is existing circumstantial evidence of a link with casein but for which the evidence remains at the hypothesis stage.^{46, 47, 48} The key issue linking many of these autoimmune conditions may be a leaky gut.

Recently it has also been shown that BCM7 stimulates production of mucins, which are the proteins found within mucus, and which make the mucus sticky.⁴⁹ This is consistent with the widely held belief that milk leads to mucus in the throat and nose. It is also apparent, although based on observational evidence and not tested in controlled clinical situations, that a considerable number of people who have previously considered themselves intolerant to milk with symptoms of nausea and diarrhoea, can however drink A2 milk. Indeed it is these experiences that have led many consumers to become A2 believers.

The counter attack

The New Zealand dairy industry had to make a decision early on as to how to deal with the beta-casein issue. Back in 1997 and thereabouts there was serious discussion both within the NZDRI and within NZ Dairy Group (NZDG), which was then the largest of the NZ dairy co-operatives, as to whether or not the national herd should, on precautionary grounds, be converted to A2. (I hold unpublished documentation relating to that discussion). A reliable source tells me it was a close decision for NZDG, but in the end, commercial pressures won out. It would have been a challenge during the transition phase to market milk containing A1 beta-casein. So a decision was made to do nothing overt, and presumably hope the issue would fade away. At that time there was of course much less evidence available than is currently the case, and so perhaps that decision was indeed reasonable. However, the evidence even then was sufficiently convincing that since that time the A1/A2 status of all of the artificial insemination bulls in New Zealand has been recorded.

From about the year 2000 and onwards, and apparently linked to the formation of A2 Corporation as a commercial entity hoping to exploit patents and trademarks associated with A2 beta-casein, the mainstream dairy industry decided to counter attack. This attack

included a number of poster papers authored and presented by Fonterra's scientists at the International Dairy Federation Conference in 2002. These were subsequently published, but only as non refereed poster papers, in the Australian Journal of Dairy Technology. The attack also included a conference review paper in the Proceedings of the NZ Society of Animal Production in 2002,⁵⁰ where supposedly new results were presented (but without supporting data) showing a lack of correlation between A1 beta-casein and heart disease. Although the dairy industry public relations machine has subsequently used these papers to claim that hypotheses associated with A1 beta-casein have been refuted, none of this work has ever been published as peer reviewed. None of these papers can be found through a search of the major electronic medical database 'PubMed' despite more than 16 million scientific citations being listed there. The supposed findings and major flaws in each of these papers are set out in my book.⁵¹

Then in 2004 Fonterra produced a 12 page document which they distributed widely to people who they thought might be influential. However, this document has not only never been published, but it would also seem to have never appeared on any website where it might be submitted to closer scrutiny. It included many erroneous statements, and a number of quotes taken seriously out of context. For anyone reading this document with no previous knowledge, it would have seemed a very convincing counter attack, and any reader could have been forgiven for thinking that the whole issue of A1 and A2 was commercial, non scientific, and a media beat up.

More recently, in August 2007, the overarching Australian dairy industry group called Dairy Australia produced a 17 page document along the same lines. Once again, this was sent to influential people but it appears to have never been placed in any public arena where it might be countered.

Back in 2005 Professor Truswell, presenting as a University of Sydney Professor of Nutrition, and without disclosure of industry associations, authored a paper published in the European Journal of Clinical Nutrition, which absolutely trashed the A1/A2 hypothesis.⁵² This then led to a series of correspondence within the journal but still without identification of Truswell's associations.^{53, 54, 55} Professor Truswell has subsequently admitted in writing that he was employed by Fonterra and received payment from them for reviewing issues surrounding A1 and A2, although not specifically for writing the paper for the EJCN.⁵⁶ He was also Fonterra's expert witness in unsuccessful Intellectual Property Office hearings relating to claims by Fonterra against an A2 Corporation patent. Clearly, it is not acceptable, and even more so in the case of a review publication where specific material to be included or excluded is dependent on author judgements, to not disclose industry associations. Other scientists have subsequently cited Truswell's supposedly independent findings without knowledge of his conflicts of interest.⁵⁷

Following the publication of the Laugesen and Elliott paper in 2003, the New Zealand Food Safety Authority (NZFSA) set up a review of issues associated with A1 and A2 beta casein. That review was undertaken by one of our commentators today, Professor Boyd Swinburn. A key message of that review, based on analysis of 38 published papers, was one of uncertainty, and that this uncertainty needed to be communicated to the public. However, the NZFSA chose to portray the findings of the review as being that all milk

was safe. Professor Swinburn privately remonstrated with the NZFSA for the way they reported his findings and referred to 'NZFSA spin'. I have obtained that correspondence through the Official Information Act. Professor Swinburn further explained to them his position in terms of risk management with the following analogy. . . *'...if I had a child with Type 1 diabetes and was due to have another and I could easily obtain and afford A2 milk or formula, I would certainly use it for the next child because the cost/benefit is low because of the potentially very large benefit of preventing Type 1 diabetes.'*

Professor Swinburn also remonstrated with the NZFSA for the way that they released his report at precisely the time when he had told them he would not be available for media comments. NZFSA official Carole Inkster apologised, but also opined: *'...we did not believe that [your unavailability] was a distraction in so far as the media were not able to engage on points of science unnecessarily and potentially beat up the issue.'*

The actions of the NZFSA in relation to A1 and A2 are currently under investigation in a review of NZFSA processes being undertaken by Dr Stuart Slorach from Sweden. However, NZFSA Director Andrew McKenzie, in publicly announcing the setting up of this review, emphasised its importance in terms of 'burying the issue once and for all', and also in relation to maintaining public perceptions relating to NZFSA integrity. I will await the outcome with great interest, but I do comment here that I would have liked to see much greater separation of NZFSA personnel from the Review. The Slorach review needed to be seen as independent. It should have been managed by the State Services Commission and not by the NZFSA itself. My own analysis of the NZFSA processes, based on published documents and information obtained under the Official Information Act, is available on the internet.^{58, 59}

A second international review has also been announced in relation to the science behind the A1/A2 hypothesis. This is to be undertaken by the European Food Safety Authority. At this stage there are no final terms of reference from the EFSA. It is essential that these terms of reference, unlike the Swinburn Review, ensure that not only clinical evidence but the underlying biochemistry, pharmacology and immunology are also considered. If clinical evidenced based on the 'gold standard' double blind trial were the only acceptable criteria, then we would still be saying there was no evidence linking smoking to lung cancer!

In relation to Type 1 diabetes there appears to be only one counter argument that is worthy of consideration. It is the fact that although the A1/A2 epidemiology provides a remarkable explanation for the between-country variations in Type 1 diabetes incidence, it does not explain why that incidence level has been increasing at approximately 3% per annum. However, there are several other factors that may explain this in the context of a disease which is widely accepted to be multi-factorial. One hypothesis is that of Bob Elliott, who believes that the answer may lie with glycated (AGE) products in general, and in particular glycated BCM7.⁶⁰ It is also important to recognise that in an autoimmune disease which requires multiple 'triggers' to line up together for the disease to occur, it may only require removal of any one of these triggers to create a very large impact on overall disease incidence.

Moving forward

There are two fronts on which there is a need for urgent movement. The first relates to dispassionate analysis and communication of the very extensive body of knowledge that does exist. As part of this communication, there is a need to bring into the open the way that industry politics have allowed the debate to be commandeered. This current paper is one part of this communication process which others now need to take up. There is a lot more that needs to be communicated, not only in relation to Type 1 diabetes but also in relation to heart disease, autism, schizophrenia, and a range of other autoimmune diseases.

Medical scientists and organisations working with diabetes and these other diseases in which A1 beta-casein is implicated have an important role in getting the message out to the public. An essential part of this message is that from a human health perspective there is only potential 'upside' and no 'downside' associated with a move to A2 milk, which is the original natural form. Once key health organisations communicate that message, then a comprehensive supply of A2 milk can be quickly organised. It is also important to understand that although there are key patents and trademarks owned by one particular organisation, no company or organisation owns the A2 gene. Anyone can produce milk that is free of A1 beta-casein.

The second front on which action is needed is in relation to additional research. This needs to be occurring at several levels. It is something that Professor Swinburn called for in his 2004 report to the NZFSA, but that message was ignored and effectively buried.

At a very simple level we need ongoing monitoring of the levels of A1 beta-casein in commercial milk supplies, and how that level is changing. This needs to be done internationally. In relation to Type 1 diabetes we also need improved ascertainment of diabetes incidence rates and how that too is changing.

Despite there being more than 230 papers in the PubMed database that can be found using the keyword of 'casomorphin' there is still much that we do not know about the biochemistry and pharmacology of this peptide.

It would be extremely valuable if a trial comparable to the current TRIGR trial⁶¹ was undertaken using specifically A1 and A2 beta-casein. However, given the existing body of knowledge, there may be ethical issues associated with subjecting babies to A1 beta-casein.

But finally, the question has to be addressed, both in relation to action and the precautionary principle, when is 'enough enough'. In the case of New Zealand, LIC, who are the major suppliers of semen to NZ dairy farmers, and who also supply semen internationally, have said the following⁶²:

LIC could, within 48 hours, respond to a market directive to move to A2 milk (i.e. only put A2 bulls forward for collection). This would mean that, within eight to ten years, virtually every cow in New Zealand would be A2. This shift – if directed by consumer demand – could be done without compromising other genetic qualities.

Why is it not happening?

Note: This version of the paper compared to an earlier website version contains a restatement of one sentence on the immunology (p9) to more accurately reflect the findings of German scientists re antibodies to A1 and A2 beta-casein. [Correction made 14/5/08]

Further Information.

More comprehensive information on issues discussed in this paper can be found in my book “Devil in the Milk” published September 2007 by Craig Potton Publishers and available for purchase internationally at:

www.devilinthemilk.co.nz

Disclosure of Interest

As Lincoln University’s Professor of Farm Management and Agribusiness I have close professional links with all issues affecting the New Zealand dairy industry, and I undertake significant media commentary on a range of agribusiness issues. I have undertaken no consultancies for A2 Corporation, Fonterra, or the former NZDRI in relation to either the issue of A1 and A2 beta-casein, or on any other topic. Prior to June 2007 I had family members who owned a very minor shareholding in A2 Corporation. I have never personally owned shares on A2 Corporation. The family shares were purchased on market under normal market conditions. The existence of these family-owned shares was acknowledged at the time in articles relating to A2 that I wrote. To avoid any perceptions of direct or indirect interest, and prior to the publication of my book, my family sold their shares in June 2007.

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