Cardiovascular Disease and Functional Foods: The Effect of Milk Derived Peptides on Hypertension

Author: Clare Tilley
Supervisor: Dr Moira Taylor

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Cardiovascular Disease and Hypertension

Cardiovascular disease (CVD) encompasses many conditions including coronary heart disease, heart attack (myocardial infarction), stroke and hypertension. In 2003, CVD accounted for 16.7 million premature deaths worldwide (World Health Organisation (WHO), 2003), 238000 of which occurred in the UK (Sproston and Primatesta, 2003). In addition to this, CVD seriously affects physical fitness and impacts upon lifestyle resulting in restrictions upon diet, employment, recreation and travel.

Hypertension refers to blood pressures above those typical for an adult. Blood pressure is measured indirectly as the highest and lowest pressures in the large artery of the arm, via a pressurised cuff. Blood pressure is presented in the non-SI., units of millimetres of mercury (mmHg). Typically normal blood pressures are below 130 mmHg (the systolic or maximum value occurring when the heart beats) and 90 mmHg (the diastolic or minimum value occurring between heart beats) and are written as 130/90 mmHg. Values of 140/90 mmHg or more are considered hypertensive. Optimal blood pressure (one pertaining to good health) is classified as <120/80mmHg (see table 1).

The USA has defined a separate blood pressure category called prehypertension which reflects those at risk of developing hypertension and is classified as 120-139/80-89mmHg.

Hypertension (140/90mmHg) is a strong, yet controllable risk factor for CVD. For example, hypertension alone has been shown to increase the risk of a heart attack by 91% (Yusuf *et al.,* 2004). Currently, up to 40% of the English and Welsh

population have hypertension (Beyer *et al.,* 2006). Therefore, by preventing and treating high blood pressure, it should be possible to reduce the increasing mortality rates caused by CVD.

Category of blood pressure	Blood pressure (systolic blood pressure/diastolic blood pressure) (mmHg)
Optimal blood pressure	<120/80
Normal blood pressure	<130/85
High-normal blood pressure	130-139/85-89
Mild hypertension (grade one)	140-159/90-99
Moderate hypertension (grade two)	160-179/100-109
Severe hypertension (grade three)	≥180/110

TABLE 1: The classification of blood pressure according to the British Hypertension Society Guidelines (Williams *et al.,* 2004).

Functional foods

"A functional food is a branded food which claims explicitly or implicitly to improve health or well-being"
(Katan and De Roos, 2004).

Well known examples of functional foods include Benecol, Flora Pro-Activ and Danecol margarines, milk and yogurts which contain planet sterols shown to assist with the reduction of cholesterol. Other functional foods include pre-and pro-biotic yogurts which assist with gastrointestinal function. In both of these cases, an ingredient is added to the food to give it the health-enhancing properties.

Over recent years, research has been conducted to identify and develop a new functional food based upon certain peptides derived from milk, aimed at lowering blood pressure. Ordinary dairy products such as milk, yogurt, cheese, butter and buttermilk do not contain the active ingredient (milk derived peptides), necessary to assist with blood pressure reduction. However, Calpis® sour milk, Evolus® sour milk, Dahi fermented milk and a Flora Pro-Activ mini-drink are examples of functional foods containing milk derived peptides for blood pressure reduction. The availability of these products is currently limited in the UK. The only product

marketed in England Flora Pro-Activ. However, this product has now been discontinued.

This project evaluates the scientific research associating milk peptides with hypertension, in order to:

- Determine which, if any, milk peptides exhibit significant antihypertensive (blood pressure lowering) effects and how they have this effect,
- Evaluate whether milk peptides will have a significant impact on reducing CVD risk through lowering blood pressure,
- Indicate the potential of milk peptides as a functional food in preventing and treating hypertension,
- Highlight the need for any further research in this area.

Blood pressure and milk peptides

Over twenty years ago, epidemiological studies first noted that individuals with a higher milk intake were more likely to have an optimal blood pressure compared to those who drank less milk, who were more likely to have hypertension (Ackley *et al.,* 1983; Garcia-Palmieri *et al.,* 1984). This was found even for intakes of whole milk, which despite concerns contains only 3.9g fat per 100ml.

Milk contains a number of components which may have antihypertensive effects. This includes the minerals calcium, magnesium and potassium (Griffith *et al.,* 1999; Dickinson *et al.,* 2006a; Cappuccio and MacGregor, 1991 respectively). Calcium is thought to aid blood pressure reduction via its actions to assist weight loss, which includes an increase in fat metabolism. Potassium may help to lower blood pressure as it counters any blood pressure increase created by sodium (see figure 1). The antihypertensive effect of magnesium remains unclear.
The effect of milk derived peptides was discovered more recently. These active peptides are released from casein or whey proteins via bacterial fermentation (Miguel *et al.,* 2005). Thus, only sour/fermented milk, not fresh milk, contains these active peptides.

In 1990, Karaki *et al.,* discovered that a single dose of peptides derived from sour milk in powdered form (hydrolysate) reduced blood pressure in a species of normally hypertensive rats. Continuing the dose of these milk peptides reduced the rats' blood pressure further. A few years later, Nakamura *et al.,* (1995a) found that two specific milk peptides lowered blood pressure by inhibiting angiotensin-1-converting enzyme (ACE). This is the same mechanism by which medications such as Ramipril and Lisinopril act to lower blood pressure. The inhibition of ACE reduces the production of angiotensin II and thereby lowers blood pressure, protecting against subsequent CVD (see Figure 1).

The peptides identified by Nakamura *et al.,* (1995a) were Valine-Proline-Proline (VPP) and Isoleucine-Proline-Proline (IPP) which are just three amino acids long. Calpis® sour milk contains VPP and IPP peptides. In a further trial, administering a single 5ml/kg body weight dose of Calpis® sour milk to naturally hypertensive rats reduced blood pressure in a dose-dependent manner just 6-8 hours after being administered (Nakamura *et al.,* 1995b). Furthermore, long term feeding on this functional food prevented hypertension in these rats (Nakamura *et al.,* 1995b). Masuda *et al.,* (1996) discovered that VPP and IPP peptides survived enzymatic

digestion and were absorbed into the circulation of rats. Here, they were free to act as ACE inhibitors.

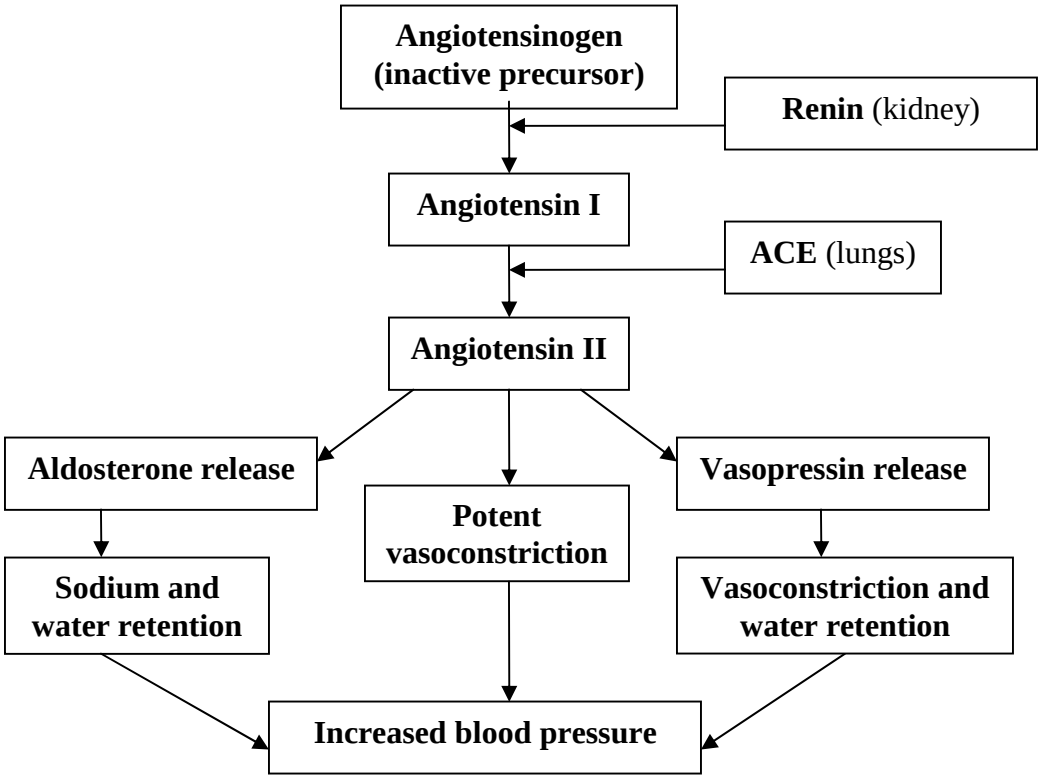

FIGURE 1: This diagram, adapted from Bray *et al.,* (1999) and FitzGerald *et al.,* (2004) shows the renin-angiotensin-aldosterone system (RAAS) and how angiotensin II increases blood pressure. ACE = angiotensin-I-converting enzyme.

The research in animals led to several clinical trials in humans to identify if milk peptides, delivered via fermented sour milk drinks or casein/whey hydrolysate tablets, could be used to prevent or treat hypertension.

Clinical Trials

The results of fourteen randomized, controlled trials in humans are discussed below. All studies included adult men and women (aged 18 and above) in general good health who had either prehypertension/high blood pressure (≥120/80mmHg) or optimal blood pressure (≤120/80mmHg). The antihypertensive effects of four different milk peptides were evaluated. The milk peptides included were: the combined tripeptides valine-proline-proline (VPP) and isoleucine-proline-proline (IPP) found in the products Calpis, Evolus and Flora Pro-Activ marketed by Calpis Co Ltd, Valio and Unilever respectively; C12 peptide; serine-lysine-valine-tyrosine-proline (SKVYP) peptide; and unidentified whey peptides. Currently, none of these products are available to purchase in UK supermarkets.

VPP and IPP: These combined peptides are the active ingredients in Calpis® and Evolus® sour milk and the recently discontinued Flora Pro-Activ mini-drink to help lower blood pressure. VPP and IPP peptides are derived from casein protein following fermentation with a variety of different bacteria including *Lactobacillus helveticus*

(LBK-16H)*, Saccharomyces cerevisiae* or *Aspergillus oryzae.* Nine studies assessed the antihypertensive effects of these peptides; six in a fermented sour milk drink, one in a fruit and vegetable juice based drink and two as tablets. All nine studies indicated a reduction in both systolic and diastolic blood pressure. Statistically significant reductions of 4.7-14.1mmHg ($P<0.05$-$P<0.01$) systolic and 4.2-6.6mmHg ($P<0.05$) diastolic blood pressure were observed.

C12 peptide: Derived from casein, the antihypertensive effect of this peptide contained in tablets, was evaluated in two clinical trials. Both studies noted a significant reduction in blood pressure of 9.2-10.7mmHg systolic ($P<0.05$), and 6.0-6.9mmHg diastolic ($P<0.05$). In one trial, 200mg C12 peptide did not significantly lower blood pressure. However, when 200mg of C12 peptide was combined with 3.5g of alginic acid, the significant blood pressure reduction of 9.2/6.0mmHg was observed (Townsend *et al.,* 2004). This suggests the alginic acid assisted with the blood pressure reduction. Alginic acid is derived from seaweed and has numerous uses within the pharmacological industry for example as a thickening or hydrating agent.

SKVYP peptide: This peptide originating from casein following fermentation of milk with *Lactobacillus delbrueckii* ssp*. bulgaricus, Streptococcus salivarius* ssp*. thermophilus and Lactococcus lactis* biovar*. diacetylactis*, is the active ingredient in the Dahi fermented milk functional food. SKVYP peptide was assessed in just one clinical trial and showed a significant reduction of 8.9mmHg ($p<0.05$) in systolic blood pressure only.

Whey peptides: Two trials assessed the antihypertensive effects of unidentified whey peptides from whey protein. One trial used a fermented milk whey powder dissolved into water whilst the other trial delivered the whey peptides via a skimmed milk drink. Only the former trial observed a significant decrease in blood pressure: systolic; 8.0mmHg ($P<0.05$) and diastolic; 5.5mmHg ($P<0.05$). The whey peptides in the skimmed milk drink did not cause a decrease in blood pressure. The authors of this paper expressed their surprise at this anomalous result. However, there were discrepancies between information in the text and tables of this paper, which may indicate that results were attributed to groups incorrectly.

Discussion

The evidence of several clinical trials appears to suggest that milk peptides exhibit antihypertensive effects in individuals with prehypertension and hypertension, though greater reductions were observed for those with a higher initial blood pressure. Potentially this means functional foods containing milk peptides as their active ingredient could be used to help prevent or treat high blood pressure.

The majority of studies found blood pressure reductions of between 5 and 10 mmHg in systolic and diastolic blood pressure following milk peptide intervention. Brunner *et al.,* (2007) suggests that a reduction of 5mmHg in diastolic blood pressure could reduce population coronary heart disease by 21% and stroke by 34%. Similarly, Lawes et al (2006) predict that a 10mmHg reduction in systolic blood pressure in all individuals with non-optimal blood pressure (>120/80mmHg) may lower stroke, ischaemic heart disease, hypertensive diseases and other CVD risks by 37%, 25%, 45% and 18% respectively.

To date in the UK, products containing milk peptides have not been advocated as preferable treatments for hypertension, despite the evidence of recent clinical trials. Similar reductions in blood pressure are obtained by a combination of well understood alternatives. It has long been known that weight loss, smoking cessation, increased physical activity and dietary modifications (reduced salt and alcohol intake and increased consumption of fruit, vegetables, fibre and low fat dairy products) significantly lowers blood pressure and protects against CVD. The question is whether milk peptide consumption would lower blood pressure further in addition to these remedies. Thus, additional research is necessary to determine if milk peptide functional foods could extend the benefits of current treatment regimes and improve the blood pressure profile of non-hypertensives.

Current Medications, Side Effects and Functional Foods

In contrast to many medications, a positive aspect of functional foods is the absence of serious side effects. Blood pressure lowering medications, such as the ACE inhibitors Ramipril and Captopril, are widely available and more effective at lowering blood pressure than milk peptides but often come with a number of unpleasant side effects. These include: impairment of renal function, a persistent dry cough, swelling, rashes, nausea, vomiting and diarrhoea. Milk peptides, acting via the same pathway as ACE inhibiting medications, do not exhibit the side effects of the commonly used drugs. Although this is likely to be due to a lower dosage of the active ingredient, milk peptide functional foods may be a more preferable way of controlling high blood pressure for many individuals.

Cost

There is also the cost of functional foods to consider. Flora Pro-Activ recently discontinued their milk peptide containing yogurt drink. If this was because the product was too expensive to produce or buy, it highlights a potential barrier to the use of milk peptides in controlling blood pressure nationally and internationally. A prescription for hypertensive medication now costs £7.10. The question is whether milk peptide functional foods, if available, would be cheaper to purchase yet have similar beneficial effects to prescribable products.

Conclusion

Milk peptide functional foods offer a new way of controlling high blood pressure and might be advocated as a component of CVD prevention and treatment globally. Further research is required to determine whether milk peptides have an additive antihypertensive effect when combined with increased exercise, dietary alterations, weight loss and smoking cessation.

Further reading

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Author Profile

Clare is 23 years old and following A levels went straight to the School of Biosciences, graduating in 2008 with a first class degree in Masters of Nutrition. Currently, Clare works as a dietitian at Leicester Royal Infirmary and hopes to expand her career into cardiothoracics, as she has a particularly interest in the dietary prevention and treatment of cardiovascular disease. Clare is also keen to participate in research within this area and hopes to study for a PhD in the future.