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Accepted Version

Can milk proteins be a useful tool in the management of cardiometabolic health? An updated review of human intervention trials

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Key words: dairy protein, metabolic health, blood pressure, vascular function

Running head: Milk proteins and cardiometabolic health

Abbreviation: ABPM: ambulatory blood pressure monitor; BP: blood pressure; CVD: cardiovascular diseases; DBP: diastolic blood pressure; FMD: flow mediated dilatation; LTP: lactotripeptides; RCT: randomised controlled trial; SBP: systolic blood pressure;

Abstract:

The prevalence of cardiometabolic diseases is a significant public health burden worldwide. Emerging evidence supports the inverse association between greater dairy consumption and reduced risk of cardiometabolic diseases. Dairy proteins may have in important role in the favourable impact of dairy on human health such as blood pressure (BP) control, blood lipid and glucose control. The purpose of this review is to update and critically evaluate the evidence on the impacts of casein and whey protein in relation to metabolic function. Evidence from acute clinical studies assessing postprandial responses to milk protein ingestion suggests benefits on vascular function independent of BP, as well as improvement in glycaemic homeostasis. Chronic interventions have been less conclusive, with some showing benefits and others indicating a lack of improvement in vascular function. During chronic consumption BP appears to be lowered and both dyslipidaemia and hyperglacaemia seems to be controlled. Limited number of trials investigated the effects of dairy proteins on oxidative stress and inflammation. The beneficial changes in cardiometabolic homeostasis are likely mediated through improvements in insulin resistance, however to gain more detailed understanding on the underlying mechanism of milk proteins warrants further research. The incorporation of meals enriched with dairy protein in the habitual diet may result in the beneficial effects on cardiometabolic health. Nevertheless, future well-designed, controlled studies are needed to investigate the relative effects of both casein and whey protein on BP, vascular function, glucose homeostasis and inflammation.

Introduction

Milk and dairy products are widely consumed around the world on a daily basis. They are not only an important source of nutrients in the human diet, but also represent important value in the food chain providing opportunities for farmers, food processors, and retailers to contribute to increased food security and poverty alleviation poverty[(1)]. Therefore any change in milk and dairy consumption will have multiple impacts on human and animal health, environment, food security, and economics. Indeed, according to an OECD-FAO report, milk production is projected to increase by 180 million tonnes in the next decade, predominantly in developing countries[(2)]. Moreover, the inclusion of animal-derived products adds diversity to plant-based diets, providing an important source of many essential nutrients, the dietary requirements of which would be more difficult to meet by plant-based diets. However the potential health impacts of animal-derived foods, and more specifically milk and dairy consumption, have been questioned owing to their high saturated fat content, (for review, see:[(3)]). Yet, emerging epidemiological evidence supports the beneficial effects of milk and dairy consumption on health, particularly cardiometabolic health[(4-6)].

Milk is a complex food, a unique package of many nutrients such as calcium, magnesium, iodine, phosphorus, vitamin B_{12}, pantothenic acid, riboflavin, high quality protein, peptides, and oligosaccharides. In the human body these bioactive components may interact with each other and exert synergistic effects, making it difficult to assign the specific health effect of a single component. Bovine milk, which is widely consumed around the world, contains approximately 32-34 g/L protein of which 80% (w/w) is casein and 20% (w/w) is whey protein. Both milk proteins consist of smaller protein fractions such as casein - alpha-s1, alpha-s2, beta and kappa-casein, and whey - beta-lactoglobulin, alpha-lactalbumin, lactoferrin, immunoglobulins, serum albumin, glycomacropeptide, enzymes and growth factors. Milk proteins are considered to be high quality proteins. Whey protein is rich in branched-chain amino acids (BCAA) such as leucine, isoleucine and valine, whilst casein contains more histidine, methionine, phenylalanine, proline, serine, tyrosine and valine. It is well established that casein and whey have differential effects on gastric emptying and kinetics of digestion and absorption[(7)]. Intact micellar casein clots in the stomach due to the low pH, and is, therefore, digested more slowly, which results in a prolonged and more sustained AA release. In contrast, intact whey (which is acid soluble) or hydrolysed whey and casein are absorbed more rapidly, with a slower AA release and half-life [(7)]. It is, however, of note that micellar casein is different from Ca or Na caseinate (micellar casein is acidified and

neutralised with alkali e.g. NaOH or $Ca(OH)_2$ in order to form caseinate), as the latter are soluble and thus may show similarities to whey in terms of digestion rates[8, 9]. As a result of their different inherent AA compositions leading to distinct absorption and kinetic behaviour, they may also have differential effects on human health.

The aim of this review is to update and critically evaluate the existing evidence on the effects of casein and whey on metabolic function, including blood pressure, vascular function, glucose and lipid metabolism, and inflammation.

Comprehensive literature search

A comprehensive literature search was conducted using the electronic databases MEDLINE, the Cochrane Library, EMBASE and Web of Science using the following terms: intervention, randomised controlled trials (RCT), clinical trials, high blood pressure, hypertension, anti-hypert*, vascular function, endothelial function, vascular stiffness, milk protein, milk peptide*, casein, hydrolysate, humans, lipids, insulin, glucose, inflammation. Furthermore, hand-searching was performed on the reference lists of both studies and review articles. In addition, Google and Google Scholar were used to confirm that the search was complete. The search period covered studies published until September 2015.

Blood pressure

Cardiovascular diseases (CVD) remain the leading cause of death in most countries worldwide. In the UK there has been a significant decrease in death rates since 1961, and due to a combination of better healthcare and preventative strategies, in 2012 CVD became the second main cause of death (CVD caused 28% of all death and cancer 29%)[10]. Approximately seven million people live with CVD in the UK which costs £19 billion each year (including premature death, lost productivity, hospital treatment, prescriptions) resulting in a significant economic burden[10]. Premature death from CVD can be prevented by improving modifiable risk factors. For example, it has been estimated that in the general population increasing physical activity, smoking cessation and dietary changes can lead to 50%, 20-30% and 15-40% mortality risk reduction, respectively[11].

High BP (hypertension) is the key modifiable risk factor of CVD and of stroke in particular. Nearly 30% of adults in the UK have high BP, however only half of them are aware of it and even less receive treatment[10]. High BP is present when systolic blood pressure (SBP) is ≥140 mmHg and/or diastolic blood pressure (DBP) is ≥90 mmHg[12]. It is important to treat hypertension and maintain BP in the normal range as elevated BP can cause irreversible damage to different organs such as kidneys, heart and eyes[12].

Long-term studies on blood pressure

We have recently reviewed the evidence from RCTs on the antihypertensive effects of milk proteins and peptides[13]. For that review we systematically searched and reviewed the literature until December 2012. There was an imbalance in the literature as more RCTs were conducted using mainly one type of casein-derived peptides, called lactotripeptides (LTP). We, therefore conducted an updated meta-analysis on the impact of LTP on BP[14], which included all available and relevant RCTs and detailed subgroup and regression analyses which were somewhat limited in previous meta-analyses in this area[15-18]. We found a small, but significant reduction in both SBP (−2.95 mmHg (95% CI: −4.17, −1.73; $p < 0.001$)) and DBP (−1.51 mmHg (95% CI: −2.21, −0.80; $p < 0.001$)) after four weeks of LTP supplementation in pre- and hypertensive populations. Since there was a statistically significant heterogeneity of treatment effects across studies, sub-group analyses were performed. These analyses suggested differences in countries where RCTs were conducted: Japanese studies reported significantly greater BP-lowering effect of LTP (-5.54 mmHg for SBP; and -3.01 mmHg for DBP), compared with European studies (-1.36 mmHg for SBP; and -0.83 mmHg for DBP; p=0.002 for SBP and <0.001 for DBP). This was confirmed in a recent meta-analysis which focused on Asian RCT only. However it only assessed SBP and the authors reported a very similar reduction of -5.63 mmHg in SBP as we found[19]. There may be several explanations for this observation. Firstly Japanese diets contains less milk and dairy products than European diets, therefore consumption of milk proteins may have a greater overall impact when compared to population that consume these proteins more regularly and in higher quantities[20]. Furthermore there are reported ethnic differences in the response to drug administration, BP-lowering in particular[21] which could impact on the response to these bioactive proteins and finally differences in response may have resulted from different spatial conformations (cis/trans) of LTP used in the studies, due to production

processes[22]. Intriguingly, we also found a "small-study effect", and when all bias was considered it shifted the treatment effect towards a less significant SBP and non-significant DBP reduction in response to LTP supplementation. We concluded that with potential bias considered, LTP consumption may still be effective in lowering blood pressure in mildly hypertensive or hypertensive groups[14].

During our systematic literature search[13] we found that there were very few studies investigating the BP-lowering effects of other casein-derived peptides in humans[23-27]. Furthermore these studies were limited, used different types of peptides and were often uncontrolled with poor methodological and study design. Due to these inconsistencies in study design, it was impossible to compare these data and no firm conclusion could be drawn on the antihypertensive effects of casein-derived peptides. Similarly, we found a limited number of RCTs conducted using intact whey or whey-derived peptides assessing their antihypertensive effects in humans[28-33]. These trials seems to be of higher quality than studies on casein-derived peptides, however the findings of these studies were also inconsistent[13].

Since our review, published in 2013, three new studies which assessed the effects of milk proteins on BP as primary outcome were published. Petyaev *et al.*[34] examined the impacts of whey protein embedded in a protective lycopene matrix, a new proprietary formulation, so called whey protein lycosome, in a pilot study. Authors hypothesised that this formulation would protect whey protein from gastrointestinal degradation which would increase the bioavailability of the protein, and thus reduce the need for a high dose. They administered 70 mg of whey protein along with 7 mg of lycopene in the form of a capsule (WPL) and compared this to whey protein (70 mg) and lycopene (7 mg) separately (taken once a day for a month). A significant decrease in BP (-7 mmHg in SBP and -4 mmHg in DBP, $p<0.05$) in the WPL group was reported compared to baseline only and no effect relative to the whey and lycopene given separately. Due to the nature of this pilot study, there was no information on blinding, the sample size was small (10/treatment group) and due to the limited statistical analysis further investigation is needed to evaluate the potential antihypertensive effect of WPL. Another RCT was conducted in overweight and obese adolescents (aged 12-15 years), who were asked to consume 1 litre/day of either water, skimmed milk, whey or casein (milk-based treatment drink contained 35 g/L protein) for 12 weeks[35]. A decrease in brachial and central aortic DBP compared to baseline and control group (consuming water) was observed, whereas whey protein appeared to increase brachial and central aortic SBP, and central DBP.

The authors acknowledged several limitations of the study, including difficulties in recruitment, changes in the research protocol after study commencement and not controlling for the extra energy intake that 1 litre/day treatment drinks provided, which led to an increase in weight in those in the treatment groups compared to a loss in the control group which consumed water. Therefore due to these limitations it was difficult to draw firm conclusions from these data. A study of Figueroa *et al.* examined the effects of both whey and casein on BP and vascular function combined with exercise training in obese, hypertensive women[36]. In their 4-week trial, participants were assigned to consume 30 g casein, whey or 34 g of maltodextrin (control) and perform resistance and endurance exercises 3 days/week under a qualified instructor's supervision. They reported significant reduction in both brachial and aortic SBP in both whey and casein groups compared to control, although this was not observed for DBP. The exercise training did not have additional effects on BP or arterial function, owing the beneficial effect on the cardiovascular system to the milk proteins (Table 1.).

In summary, emerging evidence suggest that milk protein consumption for at least four weeks may result in small blood pressure lowering, however further well controlled studies involving 24-hour ambulatory blood pressure monitor should be performed for confirmation.

Long-term studies on blood pressure

According to a typical Western eating pattern, people spend up to 18h/day in a postprandial state consuming three or more meals daily. Furthermore elevated postprandial lipeamia, glycaemia and inflammation have been linked with increased risk for chronic disease development including diabetes and CVD[37-39]. Therefore dietary strategies that attenuate the postprandial metabolic disturbance are urgently required.

To date only two studies have evaluated the acute effects of milk proteins on BP. Pal and Ellis compared 45 g whey protein isolate, 45 g Na-caseinate with 45 g glucose in conjunction with a breakfast in normotensive overweight and obese women[32] but found no effect of treatment. A more recent study compared the postprandial effects of several dietary proteins (milk protein, pea protein and egg-white) and carbohydrate-rich meals on BP-related responses[40]. Although the authors failed to specify the specific type of milk protein isolate used, its BP-lowering effect was not significantly different to pea protein, although both milk and pea

protein were significantly lower than egg-white ($p \leq 0.01$) (Table 1.). The lack of evidence on the acute BP effects of milk proteins warrants further research .

Vascular function

Vascular dysfunction is often used as an umbrella term for abnormalities of the vascular system, such as endothelial dysfunction and arterial stiffness[41]. The endothelium, the inner layer of cells of the vasculature, plays a key regulatory role in the vascular system. Any disturbance in endothelial function, such as increased permeability, reduced vasodilation and activation of thrombotic and inflammatory pathways, can lead to atherosclerotic development[42]. Due to the central role of the endothelium in the development of atherosclerosis, several non-invasive methods have been developed to assess endothelial dysfunction. Nitric oxide plays a primary role in the control of vascular function and which is produced by the endothelium. Flow-mediated dilation (FMD) is considered to be the 'gold standard' method of assessing endothelial function and may surpass the predictive value of traditional risk factors such as smoking, elevated cholesterol level in predicting cardiovascular events in patients with established cardiovascular disease[43]. However it is of note that this technique requires extensive training and is operator dependent, which may limit its value.

Arterial stiffness is a measure of arterial elasticity which is the ability to expand and contract along with cardiac pulsation and relaxation. CVD risk factors such as ageing, hypertension, smoking and diet have been shown to have a detrimental effect on arterial distensibility, inducing an imbalance between the synthesis and degradation of elastin and type 1 and 3 collagen[44]. Pulse wave velocity (PWV) is considered to be the 'gold-standard' to measure arterial stiffness and has a substantial predictive value for CVD events[45].

Long-term studies on vascular function

Our previous review also evaluated the health effects of milk proteins and/or their peptides on vascular function[13]. In brief, we identified nine chronic RCTs[33, 46-53], of which eight used lactotripeptides[46-54] and one trial used intact casein and whey[33]. These studies were diverse in several aspects of methodologies such as design, length and dose of treatment, subject characteristics and measures of vascular function, and most importantly type of milk proteins

used. Due to this heterogeneity, it is not possible to draw firm conclusions on the relative effects of milk proteins on the vascular function.

We have identified three further RCTs: Petyaev *et al.* examined the impacts of WPL not only on BP, but vascular reactivity, using FMD[34]. They reported statistically significant improvements in FMD in the WPL group only (+2.6 %, $p<0.05$) compared to baseline. Arnberg *et al.* also evaluated the effects of intact whey, casein and semi-skimmed milk on arterial stiffness using PWV, however failed to show any changes in vascular function[35]. However Figueroa and colleagues reported favourable changes in augmentation index (AI: a measure of arterial stiffness) and brachial-PWV in both whey and casein groups combined with exercise, compared to the control group. It is of note that the randomisation may not have been adequate as the baseline values for both BP and arterial stiffness were different than the whey and casein groups which may have confounded the study (Table 2.).

Short-term studies on vascular function

Only four RCTs were conducted to evaluate the effects of milk proteins on vascular function in a postprandial setting[32, 54-56]. Pal and Ellis failed to show any acute effects of whey and casein ingestion with a meal in normotensive obese postmenopausal women on arterial stiffness measured by pulse wave analysis[32]. Likewise, Turpeinen *et al.* also did not observe any statistically significant change in arterial stiffness measured by PWV after acute ingestion of 25 mg lactotripeptides with 2 g plant sterol ester mixed in a milk drink in mildly hypertensive subjects[54]. However Ballard and colleagues reported significant improvements in arterial reactivity assessed by FMD (+4.3 %) at 120 min after ingestion compared with placebo corresponding time point, ($p<0.05$) in mildly hypertensive, overweight individuals after whey hydrolysate (5 g NOP-47) ingestion with water[55]. Mariotti *et al.* failed to report any significant effects of casein, whey or α-lactalbumin enriched whey protein on digital volume pulse (a measure of arterial stiffness)[57] (Table 2.).

Intriguingly, BP-lowering effects of milk proteins were not associated with changes in vascular function in the reviewed RCTs[13] which is confirmed by emerging evidence on the relationship between BP and arterial stiffness. This suggests that the interaction between BP and arterial stiffness may be bi-directional[58, 59] via complex interactions between different pathways such as inflammatory[60, 61], hormonal (e.g. leptin, insulin)[61-63] and disturbance in

endothelial-derived mediators[58]. Therefore it is important to determine the effect on other mediators of risk that may indirectly affect BP.

Glycaemic control

Insulin has a range of biological actions within the human body[64], not only has it a key regulatory role in metabolic energy disposal and storage in tissues, but it is responsible for cell growth and development[65], ion transport[66], and sympathetic nervous system activity[67]. In addition, insulin has haemodynamic activities such as increasing blood flow and cardiac output, probably via increased NO production[64]. Giugliano *et al.* demonstrated insulin release after an intravenous infusion of L-arginine resulted in improvements in FMD[68]. However Gates *et al.* showed an insulin-independent vasodilation after L-arginine administration[69]. Similarly, Ballard and colleagues reported an insulin-independent FMD improvement in response to the acute ingestion of a whey-derived peptide, NOP-47[55].

It is well established that food proteins and more specifically AAs acutely stimulate insulin secretion[70] with several AAs possessing direct insulinotropic effects[71, 72]. Both whey and casein appear to increase insulin secretion, however to different extents[73]. This may be due to their effect on gastric emptying, absorption and kinetics, since the insulin responses seemed to correlate with the increase in plasma AA concentration after protein ingestion[74]. Likewise, hydrolysates appear to increase insulin production more than intact proteins[75].

It is not yet known how milk proteins exert their beneficial effects on glucose homeostasis, however, BCAAs, in particular, leucine, isoleucine, valine, lysine and threonine are shown to act as insulin secretagogues (inducing insulin secretion from pancreatic β-cells), with leucine reportedly having the greatest insulinotopic effect acutely[76]. This may be via the regulation of both ATP production (by metabolic oxidation and allosteric activation of glutamate dehydrogenase) and K_{ATP} activity[77]. Similarly, BCAA and particularly leucine, has been reported to activate the mammalian rapamycin (mTOR) pathway resulting in a higher incretin hormone (insulin, glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP)) synthesis[77, 78]. GIP is also known as glucose-dependent insulinotropic peptide, synthesised by K cells found in the mucosa of the duodenum and jejunum in response to food ingestion, which may subsequently further induce insulin production[79]. While the effect of GIP appears to be more pronounced at normoglycaemic levels, GLP-1 is more active during

hyperglycaemia[79]. Jakubowitz and Froy showed that whey protein drink increased GIP response (+80%) in healthy adults, yet a mixture of BBCA mimicking the supply of AA in whey protein, failed to exert the same effect[80]. Therefore they suggested that certain bioactive peptides and/or AAs deriving from whey protein during digestion may be responsible for this action[80]. GLP-1 is a potent antihyperglycemic hormone secreted by intestinal L cells[79]. Interestingly, it has been shown to possess cardioprotective effects, which may be further complemented by natriuretic and antioxidative stress on the kidneys leading to beneficial impacts on BP and vasculature[81]. This warrants further consideration in future research when the effects of milk proteins are assessed on the cardiovascular system. Additionally, GLP-1 was more pronounced in healthy subjects after whey consumption compared to casein or soya, however after 2 hours of ingestion the concertation of the hormone decreased, while it continued to increase after casein[80, 82, 83]. This may be explained by the different plasma kinetics of milk proteins. Two enzyme inhibitory peptides deriving from milk proteins have been associated with the beneficial effects on the glucose homeostasis: dipeptidyl peptidase-IV (DPP-IV) enzyme inhibitors and alpha-glucosidase (AG) enzyme inhibitors. Although DPP-IV plays several roles in different physiological processes, it has a distinct effect on glucose homeostasis by degrading incretin hormones: GLP-1 and GIP[84]. Whereas there is a definite lack of human studies examining the effects of DPP-IV inhibitory peptides deriving from milk proteins; some *in silico* (computer-aided), *in vitro* and limited animal studies suggesting a potential role in controlling glucose metabolism. Lacroix and Li-Chan proposed that casein appears to be a better source of DPP-IV inhibitory peptides than whey protein[85]. However, *in vitro* and *in vivo* studies suggest that whey protein may be equal or a better source of these inhibitory peptides (for review see[;86]). The AG enzyme is found in the brush border of the enterocytes in the small intestine and is responsible for the synthesis and breakdown of carbohydrate by cleaving glycosidic bonds in complex carbohydrates to produce monosaccharides. A potential therapy in type 2 diabetic patients could be to reduce the absorption of glucose by carbohydrate hydrolysing enzymes such as AG, which may also enhance and promote GLP-1 secretion[87]. A very limited number of *in vitro* studies demonstrated that AG inhibitory peptides may be derived from whey protein[88, 89]. This clearly warrants further research.

Short-term studies on glycaemic control

Milk proteins have been extensively investigated for their insulinotropic and glucose-lowering effects in healthy subjects[73, 75, 82, 83, 90-99] and to a limited extent in individuals with suboptimal glucose control[100-106]. The dose varied significantly between studies from as little as 10 g[92, 105, 106] to 51 g[91]. Milk proteins were administered on their own or with a meal or even served as pre-meals. Current evidence on the effects of whey protein on glucose control appears to be more promising than casein, furthermore it has been proposed that whey protein may be as effective at inducing insulin secretion as medication (sulfonylureas) prescribed for management of hyperglycaemia in type 2 diabetic patients[80, 107] (Table 3.). Thus providing a rationale for individuals with impaired glucose control or for patients with T2DM (type 2 diabetes mellitus) to consume whey protein prior to or with meals to control postprandial glucose metabolism. Future studies should examine the minimum dose at which whey protein exerts beneficial effects. Similarly due to the different timeframe by which milk proteins have an effect, longer postprandial trials (e.g. 24h) may provide important information on how casein could improve hyperglycaemia in individuals characterised by insulin resistance but with functional β-cells.

Long-term studies on glycaemic control

To best of our knowledge, only three studies have investigated the chronic supplementation of milk proteins, rather than milk or dairy products, on glycaemic control. Pal *et al.* examined the effects of whey and casein (2 x 27g/day for 12 weeks) in overweight and obese subjects[96]. Most subjects had borderline impaired glucose tolerance at baseline, but at the end of the intervention a reduced fasting insulin concentration was observed in the whey protein group compared with the control group (glucose), although no change in fasting glucose was reported. In another study, a whey fermentation product (malleable protein matrix, MPM) decreased fasting plasma glucose concentration after three months supplementation compared to the control group, which was more pronounced in individuals with impaired fasting glucose at baseline[108]. An acute-in-chronic study also reported a decrease in postprandial glucose response in whey group, which remained unchanged after the four-week supplementation period[102] (Table 3.).

Lipid metabolism

Short-term studies on lipids

Postprandial triacylglycerolaemia has been associated with markers of early atherosclerosis such as endothelial dysfunction and carotid media thickness[109, 110] and is strongly influenced by the composition of a meal: including the quality and quantity of fat[111, 112] and carbohydrate[113, 114]. In theory due to the insulinogenic effects of milk proteins, their consumption would be predicted to attenuate postprandial lipaemia, as insulin has an inhibitory effect on hormone-sensitive lipase and hepatic release of free fatty acid (FFA) and stimulatory effect on lipoprotein lipase which hydrolyses triacylglycerol for metabolism or storage. However evidence from postprandial RCT is limited. Postprandial investigations reported decrease in triacylglycerols (TAG) after both whey and casein ingestion in combination with a fat-rich meal in obese[98] and individuals with T2DM[103, 115], but showed no effect on TAG after acute consumption of whey protein[99, 104]. Free fatty acid also decreased after whey and casein ingestion in obese[99] and T2DM patients[104]. It is of note that parameters of lipid metabolism such as low- and high-density lipoproteins and total cholesterol remain stable acutely[116, 117].

Recently an acute study reported that casein with a high fat, high energy meal, compared to whey protein and α-lactalbumin enriched whey protein, significantly reduced postprandial TAG and had a marked effect of chylomicron kinetics[57]. This could be due to the different physicochemical makeup of casein and whey protein, as casein forms a gel in the stomach influencing the rate of absorption and gastric emptying (Table 4.).

Long-term studies on lipids

To date, five chronic RCT, which examined the lipid lowering effects of milk proteins, have been identified. Three month supplementation of whey (2 x 25 g/day) and casein (2 x 25 g/day) during an ad libitum weight regain diet after substantial diet-induced weight loss in healthy obese subjects resulted in no change in plasma lipids[118]. However whey protein isolate (2 x 27 g/day) significantly reduced fasting TAG, total cholesterol and LDL-cholesterol after three months in overweight, obese individuals[96]. Another three month supplementation study with MPM (15 g/day protein in two daily servings of 150g yoghurt) reduced fasting TAG, which was more pronounced in subjects with elevated baseline

TAG[108]. In a six week study casein (35 g/day) also reduced total cholesterol in hypercholesterolemic subjects[119]. Petyaev *et al.* reported a decrease in LDL-cholesterol, TAG and TC in their pilot study[34] (Table 4.). The limited evidence suggests that milk proteins have a beneficial impact on fasted lipids, although further studies are required. However it is not clear as to possible mechanisms of action although insulin may play a role. *In vitro* studies suggest that milk proteins and BCAA inhibit expression of genes involved in intestinal fatty acid and cholesterol absorption and synthesis[120]. Whey has been shown to induce urinary excretion of tricarboxylic acid cycle (TCA) compounds such as citric acid and succinic acid in rats, which are substrates for lipogenesis, suggesting an increased catabolic state (e.g. lipolysis) and reduced lipid accretion compared to casein[121]. This could be a possible mechanism of lipid reduction. Similarly, in another metabolic study conducted in humans, cheese (casein) appeared to induce lowering of urinary citrate[122], which suggests that cheese consumption affects the TCA cycle. Additionally, microbiota-related metabolite, hippuric acid was significantly higher in the cheese group, than in the milk, implying a stimulation of gut bacteria activity. The enhanced bacterial activity also resulted in higher short-chain fatty acids (SCFA)[122], which have been proposed as key regulatory metabolites in lipid metabolism[123]. This effect may be due to the cheese matrix rather than the casein per se. An *in vivo* study proposed another potential mechanism of action through decreased lipid infiltration into the liver in rats with non-alcoholic fatty liver[124]. Another possible putative mechanism is increased fat oxidation. Lorenzen *et al.* demonstrated an increased lipid oxidation after acute casein consumption compared to whey[125]. They speculated that it may be due to lower insulin secretion after casein consumption relative to whey since insulin downregulates lipid oxidation. However insulin was not measured in the study and this mechanism could not be confirmed. The same research group examined the effects of dairy Ca on lipid metabolism in conjunction with a low and high fat diet during 10 days[126]. They found that dairy Ca attenuates the increase in total and LDL-cholesterol, without affecting the rise in HDL-cholesterol. This observed phenomenon may be due to the formation of insoluble Ca-fatty acid soaps and/or the production of hydrophobe aggregation with bile and with other fatty acids[126-128].

Inflammation and oxidative stress

Inflammation and oxidative stress are chronic conditions which contribute to many diseases such as obesity[129], T2DM[130] and CVD[131]. Different dietary components have an impact on low-grade inflammation[132], however there is a lack of RCTs evaluating the acute and chronic consumption of milk proteins on inflammation or oxidative stress with inconsistent outcomes.

Long-term studies on inflammation and oxidative stress

A recent meta-analysis evaluated the effects of chronic consumption of whey protein and hydrolysate on C-reactive protein (CRP), a systemic inflammatory marker[133]. Nine RCTs were included which showed a small, non-significant reduction in CRP 0.42mg/L (95% CI −0.96, 0.13). Sub-group analyses suggested that >20 g/day may be more effective, and elevated baseline CRP level (≥3 mg/L) could be more responsive to whey or whey peptides consumption[133]. Similarly, Arnberg *et al.* reported no change in CRP in adolescence after whey, casein or skim milk consumption for 12 weeks[35].

Interleukin (IL)-6, IL-8 and tumour necrosis factor (TNF)-α are also recognised inflammatory markers, which induce CRP. Pal and Ellis failed to observe significant changes in these inflammatory markers (2 x 27g whey or casein or glucose for 12 weeks) in overweight individuals[33]. However Sugawara *et al.* reported decreased level of IL-6, IL-8 and TNF-α in patients with chronic obstructive pulmonary disease after whey intervention compared with control group[134]. Likewise, IL-6 and TNF-α were decreased after lactoferrin consumption for six months in postmenopausal women[135]. Similarly Hirota *et al.* reported decreased levels of TNF-α in mildly hypertensive subjects fed with the casein-derived lactotripeptides[46] (Table 5.).

Long-term studies on inflammation and oxidative stress

Pal and Ellis, also reported no change in IL-6, IL-8 and TNF-α in a postprandial study investigating whey and casein[32]. Likewise, a whey-derived peptide, NOP-47, also failed to change the level of serum cytokines (TNF-α, IK-6, IL-8, monocyte chemoattractant protein-1, vascular endothelial growth factor, soluble E-selectin, soluble vascular cell adhesion molecule-1) and chemokines[56]. However consumption of a cake containing whey protein after exhaustive cycling in nine subjects reported reduced levels of CRP and IL-6 by 46% and 50%, respectively[136]. Holmer-Jensen *et al.* assessed the postprandial effects of whey protein, casein, gluten and cod on low-grade inflammatory markers (monocyte chemotactic protein-1 (MCP-1), CC chemokine ligand-5 (CCL5/RANTES)) in conjunction with a high fat meal[137].

They reported that all meals increased CCL//RANTES, however the smallest increase was observed after the whey protein meal. MCP-1 was initially suppressed after all meals, and the meal containing whey protein induced the smallest overall postprandial suppression[137] (Table 5.).

The mechanism of action of milk proteins on oxidative stress and inflammation are unclear but Ca may supresses the pro-inflammatory and reactive oxygen species production *in vitro*[138]. Interestingly, the milk protein-derived inhibitors of the angiotensin-I-converting enzyme may also be involved in the anti-inflammatory process[139].

Conclusion and implication for future studies

Taken together, there is a growing number of RCTs which suggest that casein and whey protein may have a role in cardiometabolic health. Studies focussed on reducing chronic disease risk factors such as hypertension and dysregulated lipid/glucose metabolism by non-pharmacological, dietary strategies will have significant implications not only for social and economic welfare, but for the healthcare system.

Due to the different physicochemical makeup of casein and whey protein, they may exert differential effects *in vivo* in humans. Notably, manufacturing may play a significant role in the physiological effects of milk proteins, however future studies should investigate which processing method results in more bioactive effects. There is inconclusive evidence on the relative impacts of milk proteins on diurnal BP and vascular function, yet there appears to be strong evidence on the insulinotropic impacts of dairy proteins, owing to the specific AA composition such as BCAA. They also appear to play a beneficial role in lipid homeostasis (Table 1.). Nevertheless the mechanism underlying the action of dairy proteins on the cardiometabolic health warrants further research.

The incorporation of a meal enriched with protein in the habitual diet may result in the improvement of cardiometabolic health as well as the prevention of developing cardiometabolic diseases. Additionally, in contrast with pharmacological antihypertensive treatments, food-derived proteins have not been shown to cause any side-effects or hypotension, making them safe to consume by individuals with a variety of other disease conditions. After careful consideration of the available evidence and knowledge gaps, we have conducted two double-blind, controlled, cross-over studies aiming to compare the

chronic (n=38) and postprandial (n=27) impacts of whey protein isolate (2 x 28 g) and Ca-caseinate (2 x 28 g) with control (2 x 26 g, maltodextrin) on vascular function, BP, markers of insulin resistance, lipid metabolism and inflammatory status in men and women with mild hypertension (≥120/80 mmHg). These studies aim to provide valuable information on the relative effects of milk proteins on blood pressure and on detailed aspects of vascular function compared with maltodextrin. These trials will further our knowledge of whether milk proteins have significant influences as health-promoting food components and whether the public as well as the food industry could benefit from it. The results from these studies are likely to be available in mid-2016.

Financial support

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. AAF is supported by a UK Biotechnology and Biological Sciences Research Council (BBSRC) studentship. The human trials were financially supported by BBSRC and Volac Int. Ltd.

Declaration of interest

JAL and DIG have previously received funding for research from AHDB Dairy. JAL and DIG have acted as an advisor to the Dairy Council. JAL and DIG have received 'in kind' foods from Arla for an MRC funded study.

Authorship

AAF conceived and wrote the manuscript. All authors critically reviewed and approved the final version of the manuscript

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Table 1. Impacts of milk proteins on blood pressure.

Reference	Subjects (n)	Study design and duration	Treatment (g)	Comparison	Treatment effect
LONG-TERM					
Petyaev *et al.*[34]	Prehypertensive (40)	Pilot, 4 weeks	Whey protein isolate (70 mg) embedded into lycopene micelles (7 mg)	Whey protein isolate, lycopene and placebo	↓BP
Arnberg *et al.*[35]	Overweight adolescents (193)	12 weeks	Casein (35g/L), whey protein (35g/L) and skimmed milk (1 litre)	Water, pretest control group	↓bBP and cDBP in casein group, ↑cDBP, bSBP and cSBP in whey group
Figueroa *et al.*[36]	Obese women (33)	4 weeks	Casein, whey protein	Carbohydrate	↓bSBP and aSBP in casein and whey groups
SHORT-TERM					
Teunissen-Beekman *et al.*[40]	Overweight or obese (48)	240 mins	Milk protein, pea protein, egg-white protein	Maltodextrin	↓BP milk and pea protein groups compared to egg-white protein group

↑, Increase; ↓, Decrease; BP, blood pressure; bBP, brachial blood pressure; cBP, central blood pressure; DBP; diastolic blood pressure; SBP, systolic blood pressure

Table 2. Impacts of milk proteins on vascular function

Reference	Subjects (n)	Study design and duration	Treatment (g)	Comparison	Treatment effect
LONG-TERM					
Petyaev *et al.*[34]	Prehypertensive (40)	Pilot, 4 weeks	Whey protein isolate (70 mg) embedded into lycopene micelles (7 mg)	Whey protein isolate, lycopene and placebo	↑FMD
Arnberg *et al.*[35]	Overweight adolescents (193)	12 weeks	Casein (35g/L), whey protein (35g/L) and skimmed milk (1 litre)	Water, pretest control group	↔
SHORT-TERM					
Mariott[57]	Overweight men (10)	360 mins	Casein	Whey protein isolate, α-lactalbumin-enriched whey protein	↔

FMD, flow-mediated dilation, ↑, Increase; ↔, no effect

Table 3. Impacts of milk proteins on glycaemic control.

Reference	Subjects (n)	Study design and duration	Treatment (g)	Comparison	Treatment effect
SHORT-TERM					
Nilsson *et al.*[73]	Healthy (12)	120 mins	WP (18.2 g)	White-wheat bread, milk, cod, cheese, gluten-low, gluten-high	↑Insulin response, ↑GIP, ↔GLP-1
Calbet *et al.*[75]	Healthy (6)	120 mins	HC (36 g)	Intact casein	↑GIP
Hall *et al.*[82]	Healthy (9)	180 mins	WP (48 g)	Casein	↑GLP-1
Veldhorst *et al.*[83]	Healthy (25)	180 mins	WP (10 and 25%)	Casein, soy	↑GLP-1
Petersen *et al.*[90]	Healthy (10)	120 mins	WP (20 g)	Glucose	↓Glucose response
Pal and Ellis[91]	Healthy men (22)	240 mins	WP (50.8 g)	Turkey, egg, tuna	↓Glucose response, ↑Insulin response
Akhavan *et al.*[92]	Healthy (10)	230 mins	WP as pre-meal (10-20 g)	Glucose, water	↓Glucose response, ↑GLP-1, ↑GIP
Akhavan *et al.*[93]	Healthy (16/21)	170 mins	WP as pre-meal (10-40 g)	Water	↓Glucose response
Acheson *et al.*[94]	Healthy (23)	330 mins	WPI (50 % of diet)	Casein, soy, glucose	↑Insulin response
Morifuji *et al.*[95]	Healthy (10)	120 mins	WPH (86,9%)	WP, soy, soy hydrolysate	↑Insulin response
Nilsson *et al.*[97]	Healthy (12)	120 mins	WP (18 g)	Glucose, amino acids	↔GLP-1
Holmer-Jensen *et al.*[98]	Obese (11)	480 mins	WPI + fat-rich meal (45 g)	Casein and gluten	↓GIP
Holmer-Jensen *et al.*[99]	Obese (12)	480 mins	WPI + fat-rich meal (45 g)	WP specific fractions	↔GLP-1
Frid *et al.*[100]	T2D (14)	240 mins	WP (27.6 g)	Ham (96 g) + lactose (5.3 g)	↓Glucose response, ↑Insulin response
Ma *et al.*[101]	T2D (8)	300 mins	WP as pre-meal (55 g)	WP in main meal	↑Insulin and incretin response
Ma *et al.*[102]	T2D (7)	240 mins	WPI (25 g)	'diet' drink	↓Glucose response
Mortensen *et al.*[103]	T2D (12)	480 mins	WPI + fat-rich meal (45 g)	Casein, gluten, cod	↔GLP-1, ↓GIP
Mortensen *et al.*[104]	T2D (12)	480 mins	WPI + fat-rich meal (45 g)	WP specific fractions	↔GLP-1
Jonker *et al.*[105]	T2D (13)	250 mins	CH (12 g)	CH (0 g)	↑Insulin response

Geerts *et al.*[106]	T2D (36)	240 mins	CH (12 g)	Intact casein	↓Glucose response
LONG-TERM					
Pal *et al.*[96]	Overweight and obese (70)	12 weeks	WPI (2x27 g/d)	Glucose	↑Fasting insulin + HOMA-IR
Ma *et al.*[102]	T2D (7)	4 weeks	WPI (25 g)	'diet' drink	↓Glucose response
Gouni-Berthold *et al.*[108]	MS (180)	12 weeks	Whey MPM (15.3g)	Placebo	↓Glucose response

↑, Increase; ↓, Decrease; ↔, no effect; CH, casein hydrolysate; D, day; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; HC; hydrolysed casein; HOMA-IR, homeostasis model assessment of insulin resistance; MS; metabolic syndrome; T2D, type-2 diebetes; Whey MPM, whey malleable protein matrix; WP, whey protein; WPH, whey protein hydrolysate;WPI, whey protein isolate.

Table 4. Impacts of milk proteins on lipid metabolism.

Reference	Subjects (n)	Study design and duration	Treatment (g)	Comparison	Treatment effect
SHORT-TERM					
Brader *et al.*[115]	T2D (11)	480 mins	Casein combined with carbohydrates and a fat-rich meal (45 g)	Control meal, control meal+carbohydrate, control meal+casein	↓TAG concentration in chylomicron-rich fraction
Holmer-Jensen *et al.*[98]	Obese (11)	480 mins	WPI + fat-rich meal (45 g)	Cod and gluten	↓TAG response, ↓TAG concentration in chylomicron-rich fraction, ↓FFA
Holmer-Jensen *et al.*[99]	Obese (12)	480 mins	WPI + fat-rich meal (45 g)	WP specific fractions	↔TAG response
Mortensen *et al.*[103]	T2D (12)	480 mins	WPI + fat-rich meal (45 g)	Casein, gluten, cod	↓TAG response, ↓FFA
Mortensen *et al.*[104]	T2D (12)	480 mins	WPI + fat-rich meal (45 g)	WP specific fractions	↔TAG response
LONG-TERM					
Pal *et al.*[96]	Overweight and obese (70)	12 weeks	WPI (2x27 g/d)	Glucose	↓Fasting TAG, ↓TC, ↓LDL-c
Weisse *et al.*[119]	Hyper-cholesterolemic (43)	6 weeks	Casein (35 g/d)	Baseline	↓TC
Claessens *et al.*[118]	Obese (48)	12 weeks	WP (2x25 g/d)	Casein	↔fasting lipids
Petyaev *et al.*[34]	Prehypertensive (40)	Pilot, 4 weeks	Whey protein isolate (70 mg) embedded into lycopene micelles (7 mg)	Whey protein isolate, lycopene and placebo	↓TC, ↓TAG, ↓LDL-c, ↑HDL
Gouni-Berthold *et al.*[108]	MS (180)	12 weeks	Whey MPM (15.3g)	Placebo	↓TAG

↑, Increase; ↓, Decrease; ↔, no effect; CH, casein hydrolysate; D, day; FFA, free fatty acids; HC; hydrolysed casein; HDL-c, high-denisty lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MS; metabolic syndrome; T2D, type-2 diebetes; TAG, triacylglycerol; TC, total cholesterol; Whey MPM, whey malleable protein matrix; WP, whey protein; WPH, whey protein hydrolysate;WPI, whey protein isolate.

Table 5. Impacts of milk proteins on inflammation and oxidative stress.

Reference	Subjects (n)	Study design and duration	Treatment (g)	Comparison	Treatment effect
LONG-TERM					
Sugawara *et al.*[134]	COPD (36)	12 weeks	WP (20 g)	0 g WP	↓CRP, ↓IL-6,↓IL-8, ↓TNF-α
Bharadwaj *et al.*[135]	Post-menopausal women (38)	24 weeks	Ribonuclease-enriched lactoferrin (2 × 125 mg/d)	Placebo	↓IL-6, ↓TNF-α
Arnberg *et al.*[35]	Overweight adolescents (193)	12 weeks	Casein (35g/L), whey protein (35g/L)	Water, pretest control group	↑CRP
Pal and Ellis[33]	Overweight (70)	12 weeks	WPI (54 g), Casein (54 g)	Glucose	↔CRP, ↔IL-6, ↔TNF-α
Hirota *et al.*[46]	Mild hyper-tensives (25)	1 week	VPP (3.42 mg), IPP (3.87 mg)	Baseline	↔CRP, ↓TNF-α
SHORT-TERM					
Pal and Ellis[32]	Overweight postmenopausal women (20)	480 mins	WPI (45 g), Casein (45 g)	Glucose	↔CRP, ↔IL-6, ↔TNF-α
Ballard *et al.*[56]	Healthy (20)	120 mins	Whey-derived peptide (NOP-47, 5 g)	Placebo	↔CRP, ↔IL-6, ↔IL-8, ↔TNF-α
Kerasioti *et al.*[136]	Healthy men (9)	48 h	WP (0.26 g protein/kg BW/h)	Placebo	↓CRP, ↓IL-6, ↑IL-10
Holmer-Jensen *et al.*[137]	Obese (11)	240 mins	WP + high-fat meal	Casein, cod and gluten + high-fat meal	↓CCL5/RANTES, ↑MCP-1

↑, Increase; ↓, Decrease; ↔, no effect; BW, body weight; CCL, CC chemokine ligand-5; CH, casein hydrolysate; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; D, day; IL, interleukin; IPP, Isoleucine-Proline-Proline; MCP-1, monocyte chemotactic protein-1; TNF, tumor necrosis factor; VPP, Valine-Proline-Proine; Whey MPM, whey malleable protein matrix; WP, whey protein; WPH, whey protein hydrolysate;WPI, whey protein isolate.

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