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

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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;

2 **Abstract:**

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

22

23 **Introduction**

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

38 Milk is a complex food, a unique package of many nutrients such as calcium, magnesium,
39 iodine, phosphorus, vitamin B₁₂, pantothenic acid, riboflavin, high quality protein, peptides,
40 and oligosaccharides. In the human body these bioactive components may interact with each
41 other and exert synergistic effects, making it difficult to assign the specific health effect of a
42 single component. Bovine milk, which is widely consumed around the world, contains
43 approximately 32-34 g/L protein of which 80% (w/w) is casein and 20% (w/w) is whey
44 protein. Both milk proteins consist of smaller protein fractions such as casein - alpha-s1,
45 alpha-s2, beta and kappa-casein, and whey - beta-lactoglobulin, alpha-lactalbumin,
46 lactoferrin, immunoglobulins, serum albumin, glycomacropeptide, enzymes and growth
47 factors. Milk proteins are considered to be high quality proteins. Whey protein is rich in
48 branched-chain amino acids (BCAA) such as leucine, isoleucine and valine, whilst casein
49 contains more histidine, methionine, phenylalanine, proline, serine, tyrosine and valine. It is
50 well established that casein and whey have differential effects on gastric emptying and
51 kinetics of digestion and absorption⁽⁷⁾. Intact micellar casein clots in the stomach due to the
52 low pH, and is, therefore, digested more slowly, which results in a prolonged and more
53 sustained AA release. In contrast, intact whey (which is acid soluble) or hydrolysed whey and
54 casein are absorbed more rapidly, with a slower AA release and half-life⁽⁷⁾. It is, however, of
55 note that micellar casein is different from Ca or Na caseinate (micellar casein is acidified and

56 neutralised with alkali e.g. NaOH or Ca(OH)₂ in order to form caseinate), as the latter are
57 soluble and thus may show similarities to whey in terms of digestion rates^(8, 9). As a result of
58 their different inherent AA compositions leading to distinct absorption and kinetic behaviour,
59 they may also have differential effects on human health.

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

63

64 **Comprehensive literature search**

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

73

74 **Blood pressure**

75 Cardiovascular diseases (CVD) remain the leading cause of death in most countries
76 worldwide. In the UK there has been a significant decrease in death rates since 1961, and due
77 to a combination of better healthcare and preventative strategies, in 2012 CVD became the
78 second main cause of death (CVD caused 28% of all death and cancer 29%)⁽¹⁰⁾.
79 Approximately seven million people live with CVD in the UK which costs £19 billion each
80 year (including premature death, lost productivity, hospital treatment, prescriptions) resulting
81 in a significant economic burden⁽¹⁰⁾. Premature death from CVD can be prevented by
82 improving modifiable risk factors. For example, it has been estimated that in the general
83 population increasing physical activity, smoking cessation and dietary changes can lead to
84 50%, 20-30% and 15-40% mortality risk reduction, respectively⁽¹¹⁾.

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

91

92 *Long-term studies on blood pressure*

93 We have recently reviewed the evidence from RCTs on the antihypertensive effects of milk
94 proteins and peptides⁽¹³⁾. For that review we systematically searched and reviewed the
95 literature until December 2012. There was an imbalance in the literature as more RCTs were
96 conducted using mainly one type of casein-derived peptides, called lactotriptides (LTP).
97 We, therefore conducted an updated meta-analysis on the impact of LTP on BP⁽¹⁴⁾, which
98 included all available and relevant RCTs and detailed subgroup and regression analyses which
99 were somewhat limited in previous meta-analyses in this area⁽¹⁵⁻¹⁸⁾. We found a small, but
100 significant reduction in both SBP (-2.95 mmHg (95% CI: -4.17, -1.73; $p < 0.001$)) and
101 DBP (-1.51 mmHg (95% CI: -2.21, -0.80; $p < 0.001$)) after four weeks of LTP
102 supplementation in pre- and hypertensive populations. Since there was a statistically
103 significant heterogeneity of treatment effects across studies, sub-group analyses were
104 performed. These analyses suggested differences in countries where RCTs were conducted:
105 Japanese studies reported significantly greater BP-lowering effect of LTP (-5.54 mmHg for
106 SBP; and -3.01 mmHg for DBP), compared with European studies (-1.36 mmHg for SBP; and
107 -0.83 mmHg for DBP; $p=0.002$ for SBP and <0.001 for DBP). This was confirmed in a recent
108 meta-analysis which focused on Asian RCT only. However it only assessed SBP and the
109 authors reported a very similar reduction of -5.63 mmHg in SBP as we found⁽¹⁹⁾. There may
110 be several explanations for this observation. Firstly Japanese diets contains less milk and
111 dairy products than European diets, therefore consumption of milk proteins may have a
112 greater overall impact when compared to population that consume these proteins more
113 regularly and in higher quantities⁽²⁰⁾. Furthermore there are reported ethnic differences in the
114 response to drug administration, BP-lowering in particular⁽²¹⁾ which could impact on the
115 response to these bioactive proteins and finally differences in response may have resulted
116 from different spatial conformations (cis/trans) of LTP used in the studies, due to production

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

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

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

150 The authors acknowledged several limitations of the study, including difficulties in
151 recruitment, changes in the research protocol after study commencement and not controlling
152 for the extra energy intake that 1 litre/day treatment drinks provided, which led to an increase
153 in weight in those in the treatment groups compared to a loss in the control group which
154 consumed water. Therefore due to these limitations it was difficult to draw firm conclusions
155 from these data. A study of Figueroa *et al.* examined the effects of both whey and casein on
156 BP and vascular function combined with exercise training in obese, hypertensive women⁽³⁶⁾.
157 In their 4-week trial, participants were assigned to consume 30 g casein, whey or 34 g of
158 maltodextrin (control) and perform resistance and endurance exercises 3 days/week under a
159 qualified instructor's supervision. They reported significant reduction in both brachial and
160 aortic SBP in both whey and casein groups compared to control, although this was not
161 observed for DBP. The exercise training did not have additional effects on BP or arterial
162 function, owing the beneficial effect on the cardiovascular system to the milk proteins (Table
163 1.).

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

167

168 ***Long-term studies on blood pressure***

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

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

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

183

184 **Vascular function**

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

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

204

205 ***Long-term studies on vascular function***

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

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

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

223

224 ***Short-term studies on vascular function***

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

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

242 endothelial-derived mediators⁽⁵⁸⁾. Therefore it is important to determine the effect on other
243 mediators of risk that may indirectly affect BP.

244

245 **Glycaemic control**

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

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

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

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

303

304 ***Short-term studies on glycaemic control***

305

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

321

322 ***Long-term studies on glycaemic control***

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

335

336 **Lipid metabolism**

337 *Short-term studies on lipids*

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

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

357

358 *Long-term studies on lipids*

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

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

396

397 **Inflammation and oxidative stress**

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

402 ***Long-term studies on inflammation and oxidative stress***

403 A recent meta-analysis evaluated the effects of chronic consumption of whey protein and
404 hydrolysate on C-reactive protein (CRP), a systemic inflammatory marker⁽¹³³⁾. Nine RCTs
405 were included which showed a small, non-significant reduction in CRP 0.42mg/L (95% CI
406 -0.96, 0.13). Sub-group analyses suggested that >20 g/day may be more effective, and elevated
407 baseline CRP level (≥ 3 mg/L) could be more responsive to whey or whey peptides
408 consumption⁽¹³³⁾. Similarly, Arnberg *et al.* reported no change in CRP in adolescence after whey,
409 casein or skim milk consumption for 12 weeks⁽³⁵⁾.

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

418

419 ***Long-term studies on inflammation and oxidative stress***

420 Pal and Ellis, also reported no change in IL-6, IL-8 and TNF- α in a postprandial study
421 investigating whey and casein⁽³²⁾. Likewise, a whey-derived peptide, NOP-47, also failed to
422 change the level of serum cytokines (TNF- α , IK-6, IL-8, monocyte chemoattractant protein-1,
423 vascular endothelial growth factor, soluble E-selectin, soluble vascular cell adhesion
424 molecule-1) and chemokines⁽⁵⁶⁾. However consumption of a cake containing whey protein
425 after exhaustive cycling in nine subjects reported reduced levels of CRP and IL-6 by 46% and
426 50%, respectively⁽¹³⁶⁾. Holmer-Jensen *et al.* assessed the postprandial effects of whey protein,
427 casein, gluten and cod on low-grade inflammatory markers (monocyte chemotactic protein-1
428 (MCP-1), CC chemokine ligand-5 (CCL5/RANTES)) in conjunction with a high fat meal⁽¹³⁷⁾.

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

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

437

438 **Conclusion and implication for future studies**

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

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

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

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

469

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475

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480

481 **Authorship**

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

484

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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 <i>et al.</i> ⁽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 <i>et al.</i> ⁽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 <i>et al.</i> ⁽³⁶⁾	Obese women (33)	4 weeks	Casein, whey protein	Carbohydrate	↓bSBP and aSBP in casein and whey groups
SHORT-TERM					
Teunissen-Beekman <i>et al.</i> ⁽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 <i>et al.</i> ⁽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 <i>et al.</i> ⁽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 <i>et al.</i> ⁽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 <i>et al.</i> ⁽⁷⁵⁾	Healthy (6)	120 mins	HC (36 g)	Intact casein	↑GIP
Hall <i>et al.</i> ⁽⁸²⁾	Healthy (9)	180 mins	WP (48 g)	Casein	↑GLP-1
Veldhorst <i>et al.</i> ⁽⁸³⁾	Healthy (25)	180 mins	WP (10 and 25%)	Casein, soy	↑GLP-1
Petersen <i>et al.</i> ⁽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 <i>et al.</i> ⁽⁹²⁾	Healthy (10)	230 mins	WP as pre-meal (10-20 g)	Glucose, water	↓Glucose response, ↑GLP-1, ↑GIP
Akhavan <i>et al.</i> ⁽⁹³⁾	Healthy (16/21)	170 mins	WP as pre-meal (10-40 g)	Water	↓Glucose response
Acheson <i>et al.</i> ⁽⁹⁴⁾	Healthy (23)	330 mins	WPI (50 % of diet)	Casein, soy, glucose	↑Insulin response
Morifuji <i>et al.</i> ⁽⁹⁵⁾	Healthy (10)	120 mins	WPH (86,9%)	WP, soy, soy hydrolysate	↑Insulin response
Nilsson <i>et al.</i> ⁽⁹⁷⁾	Healthy (12)	120 mins	WP (18 g)	Glucose, amino acids	↔GLP-1
Holmer-Jensen <i>et al.</i> ⁽⁹⁸⁾	Obese (11)	480 mins	WPI + fat-rich meal (45 g)	Casein and gluten	↓GIP
Holmer-Jensen <i>et al.</i> ⁽⁹⁹⁾	Obese (12)	480 mins	WPI + fat-rich meal (45 g)	WP specific fractions	↔GLP-1
Frid <i>et al.</i> ⁽¹⁰⁰⁾	T2D (14)	240 mins	WP (27.6 g)	Ham (96 g) + lactose (5.3 g)	↓Glucose response, ↑Insulin response
Ma <i>et al.</i> ⁽¹⁰¹⁾	T2D (8)	300 mins	WP as pre-meal (55 g)	WP in main meal	↑Insulin and incretin response
Ma <i>et al.</i> ⁽¹⁰²⁾	T2D (7)	240 mins	WPI (25 g)	'diet' drink	↓Glucose response
Mortensen <i>et al.</i> ⁽¹⁰³⁾	T2D (12)	480 mins	WPI + fat-rich meal (45 g)	Casein, gluten, cod	↔GLP-1, ↓GIP
Mortensen <i>et al.</i> ⁽¹⁰⁴⁾	T2D (12)	480 mins	WPI + fat-rich meal (45 g)	WP specific fractions	↔GLP-1
Jonker <i>et al.</i> ⁽¹⁰⁵⁾	T2D (13)	250 mins	CH (12 g)	CH (0 g)	↑Insulin response

Geerts <i>et al.</i> ⁽¹⁰⁶⁾	T2D (36)	240 mins	CH (12 g)	Intact casein	↓Glucose response
LONG-TERM					
Pal <i>et al.</i> ⁽⁹⁶⁾	Overweight and obese (70)	12 weeks	WPI (2x27 g/d)	Glucose	↑Fasting insulin + HOMA-IR
Ma <i>et al.</i> ⁽¹⁰²⁾	T2D (7)	4 weeks	WPI (25 g)	'diet' drink	↓Glucose response
Gouni-Berthold <i>et al.</i> ⁽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 diabetes; 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 <i>et al.</i> ⁽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 <i>et al.</i> ⁽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 <i>et al.</i> ⁽⁹⁹⁾	Obese (12)	480 mins	WPI + fat-rich meal (45 g)	WP specific fractions	↔TAG response
Mortensen <i>et al.</i> ⁽¹⁰³⁾	T2D (12)	480 mins	WPI + fat-rich meal (45 g)	Casein, gluten, cod	↓TAG response, ↓FFA
Mortensen <i>et al.</i> ⁽¹⁰⁴⁾	T2D (12)	480 mins	WPI + fat-rich meal (45 g)	WP specific fractions	↔TAG response
LONG-TERM					
Pal <i>et al.</i> ⁽⁹⁶⁾	Overweight and obese (70)	12 weeks	WPI (2x27 g/d)	Glucose	↓Fasting TAG, ↓TC, ↓LDL-c
Weisse <i>et al.</i> ⁽¹¹⁹⁾	Hyper-cholesterolemic (43)	6 weeks	Casein (35 g/d)	Baseline	↓TC
Claessens <i>et al.</i> ⁽¹¹⁸⁾	Obese (48)	12 weeks	WP (2x25 g/d)	Casein	↔fasting lipids
Petyaev <i>et al.</i> ⁽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 <i>et al.</i> ⁽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-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MS; metabolic syndrome; T2D, type-2 diabetes; 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 <i>et al.</i> ⁽¹³⁴⁾	COPD (36)	12 weeks	WP (20 g)	0 g WP	↓CRP, ↓IL-6, ↓IL-8, ↓TNF-α
Bharadwaj <i>et al.</i> ⁽¹³⁵⁾	Post-menopausal women (38)	24 weeks	Ribonuclease-enriched lactoferrin (2 × 125 mg/d)	Placebo	↓IL-6, ↓TNF-α
Arnberg <i>et al.</i> ⁽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 <i>et al.</i> ⁽⁴⁶⁾	Mild hypertensives (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 <i>et al.</i> ⁽⁵⁶⁾	Healthy (20)	120 mins	Whey-derived peptide (NOP-47, 5 g)	Placebo	↔CRP, ↔IL-6, ↔IL-8, ↔TNF-α
Kerasioti <i>et al.</i> ⁽¹³⁶⁾	Healthy men (9)	48 h	WP (0.26 g protein/kg BW/h)	Placebo	↓CRP, ↓IL-6, ↑IL-10
Holmer-Jensen <i>et al.</i> ⁽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-Proline; Whey MPM, whey malleable protein matrix; WP, whey protein; WPH, whey protein hydrolysate; WPI, whey protein isolate.